World J Biol Psychiatry (2001) 2, 54 - 57

Editorial

Genes for Human Personality Traits: "Endophenotypes" of Psychiatric Disorders?

A generation ago a paradigm shift occurred in psychiatry. The idea that psychopathology in an individual reflected the outcome of untoward early childhood experiences was replaced by the idea that psychiatric illnesses are caused by chemical aberrations due to faulty genes interacting with adverse experience throughout the lifespan. This paradigm shift appeared to return psychiatry to the bosom of medicine and to mark a great divide between psychiatry and psychology. Variations in normal personality belonged to the field of psychology; psychiatric illnesses were clinical conditions within the purview of medicine.

At the beginning of the twenty-first century, we have ample proof in hand that mental illnesses are partly genetic. Concordance rates around 50% for schizophrenia and bipolar disorder in monozygotic twins compared to baseline population rates around 1% leave little room for doubt that there is an important genetic component to these illnesses. Yet the search for a single major gene has frustrated even genome-wide linkage approaches.

The question that immediately presents itself is: what is the nature of genes that have common alleles (so that they must often confer genetic advantage) which in certain combinations can lead to serious illness? For diabetes a reasonable and testable answer would be: genes for carbohydrate metabolism. For certain kinds of dwarfism it might be: genes affecting height. We propose that for mental illnesses a plausible answer is: genes for normal personality traits.

Twin studies of human personality traits in tens of thousands of twin-pairs have convincingly shown that inter-individual differences in characteristics such as sociability and neuroticism are approximately 50% due to differences in genes (Loehlin 1992; Plomin 1990; Plomin et al 1997). The mechanisms of action of such genes (and the environment) are complex and non-linear, but nevertheless amenable to scientific study. We suggest that some of the genes affecting personality may be heuristic "endophenotypes" for classic psychiatric disorders.

The term endophenotype was used by Gottesman (1991) to describe a trait that may be intermediate on the chain of causality from genes to diseases. Some family relatives of affected patients also carry the endophenotype, although not the disease phenotype. The increased penetrance of the endophenotype, and its closer relationship to the gene than that of the phenotype proper, are expected to help genetic studies.

As an example, cholesterol levels can serve as endophenotypes for myocardial infarction. Apolipoprotein E (ApoE) is a lipid-transport protein. Different alleles of the ApoE gene are associated with different cholesterol levels, and these in turn are associated with different risks for myocardial infarction. But numerous other factors also influence the risk for myocardial infarction. In a sense the ApoE gene is a gene "for" myocardial infarction, but the relationship is closer, and therefore easier to discover, when we consider it a gene for cholesterol levels. Furthermore, we can include all family members in our analysis of this relationship, or at least all those with high cholesterol levels, not just those with myocardial infarction.

Examples of potential endophenotypes in psychiatry include abnormalities of eye-tracking movements (Holzman et al 1988) and the P50 evoked potential (Freedman et al 1997) in schizophrenic patients and their relatives. A majority of schizophrenic patients, and 45% of their first-degree relatives, show abnormal eye movements, especially during smooth pursuit, on electro-optical recordings. A family study of discordant twins was incompatible with simple Mendelian transmission of schizophrenia; however, when the assessment included schizophrenia and abnormal eye movements, this phenotype exhibited a pattern consistent with autosomal dominant transmission. Plainly, the combination of a gene for this characteristic and another gene(s), which together may lead to outright illness, may exhibit a more complicated transmission pattern. However, the simple inheritance of the endophenotype may permit rapid identification of at least one risk gene for schizophrenia.

Our hypothesis is that personality traits may be heuristic endophenotypes for psychiatric geneticists. Let us imagine that a certain allele of an "introversion-extraversion" gene increases an individual's tendency to prefer to be alone by 10% compared to the commonest allele, and a rarer allele increases it by 20%. Most individuals with these alleles will still have introversion scores within the normal range, but an occasional individual who is homozygotic for the rarest allele might be diagnosed with social phobia. An individual who inherits two of these introversion alleles ***and*** an allele that increases the risk for psychopathology in general, may be more likely to have schizoid personality disorder. Now consider an individual with this genotype who also inherits a gene that contributes to unconventional thinking; he may be more liable to schizotypal personality disorder. Another individual with two of the genes affecting introversion, plus the gene affecting eccentricity, plus a gene that increases adventurousness, might become an intrepid explorer; his brother might develop schizophrenia. At the biochemical level a minor change in the dopamine transporter, reducing the amount of dopamine reuptake, might have striking consequences when paired with a minor change in a mono-amine oxidase enzyme responsible for dopamine degradation. The biochemical variants in the brain and the phenotypic personality variants might be two aspects of the same phenomenon, much as has been proposed as a general solution to the "mind-body problem" (Feigl 1967). Cloninger has presented a detailed model (Cloninger 1987) of how various combinations of extreme personality traits may lead on to personality disorders. We extend this hypothesis to suggest that major psychiatric illnesses may result from non-linear combinations of genetic-biochemical polymorphisms whose phenotype is expressed as personality traits.

We previously reported an association between a human personality trait called "novelty seeking" and a dopamine D4 receptor exon III polymorphism (D4DR) (Benjamin et al 1996; Ebstein et al 1996). The thinking behind the search for genes that might influence personality traits (Benjamin et al 1993) was not limited to the desire to advance our understanding of normal personality alone; we in fact hypothesized (Belmaker and Biederman 1994) that such genes, once discovered, might yield new insights into the genetics and pathological chemistry of psychiatric disorders.

This idea, that individual genes might influence personality traits and psychopathology, would appear to be partly supported thus far by the "saga" of the D4DR polymorphism (Ebstein and Belmaker 1997). The initial reports of an association between D4DR and novelty seeking were followed by attempts at replication; more relevant for our present purpose is that they were also followed by reports of associations between D4DR and attention-deficit hyperactivity disorder (ADHD) in children (LaHoste et al 1997), heroin abuse (Kotler et al 1997) and Tourette's syndrome (Grice et al 1996). "Novelty seeking", a factor on the Tridimensional Personality Questionnaire (Cloninger 1987), refers to a cluster of risk-taking, distractible, impulsive and fickle behaviours. This behavioural tendency bears some similarity to some features of ADHD and perhaps also to experiments with drug-taking and Tourette's syndrome; these reported associations have been replicated, particularly for a large majority of studies of D4DR in ADHD (see Farone et al 1999). These associations encourage us to look afresh at our current understanding of the psychological substrates of these phenotypes (e.g. what is common to ADHD and novelty seeking?). Thus genetics and psychology can enrich each other just as genetics and physiology enrich each other in other disciplines.

A further contribution of replicable behavioural findings with any gene is that such a gene can provide the first clue on a trail ultimately leading to gene-gene combinations with large effect sizes on behavioural traits, the kind of effect size that would allow for true prediction in clinical psychiatry and psychology. Just as each of the putative genes "for" schizophrenia, manic-depression and so on probably has a small effect size (or none at all) when it acts alone, the same is true of the "personality" genes reported so far. D4DR, for example, explained only 4% of the variance in novelty seeking in the initial reports.

We (Benjamin et al 2000; Ebstein et al 1997) and others (Noble et al 1998) have lately begun to study the interaction component of analysis of variance (ANOVA) of large genetic studies of personality.

Entering two or more genetic polymorphisms as independent variables allows one to test for interactions between these genes. "Interaction" in this context refers to results beyond those predicted by simply summing the effects of two or more genes. Examples include synergistic amplification of the effect of a particular allele of one gene by a particular allele of a second gene, and "permissive" effects, i.e. one gene cannot be expressed at all unless a particular allele of another gene is present. In studies of new-born babies (Ebstein et al 1998) and very young children (Auerbach et al 1999), longer variants of the dopamine D4 receptor exon III polymorphism (DRD4) increased approach type behaviours only in the absence of short variants of the serotonin transporter promoter linked polymorphism (5-HTTLPR). This finding prompted the re-examination of adult subjects previously typed for DRD4, and similar results were found in the adults (Benjamin et al 2000).

A D4DR-serotonin-2C receptor polymorphism interaction affected the personality trait of "reward dependence" by about ten standard errors of the mean in a preliminary analysis (Ebstein et al 1997), and this interaction, with a smaller effect size, was later replicated (Kuhn et al 1999). Such an interaction would not have been sought without the prior reports of the D4DR association.

One of the important achievements of biological psychiatry over the past generation has been the reduction of guilt among family members of the mentally ill. The concept of biological causes opened up the option of a guilt-free medical model of psychiatric illness. Without losing this gain, we must allow the model to become more complex. The role of diet in heart disease, and of sun exposure in skin cancer, does not prevent insurance coverage of these illnesses, nor appropriate caring and sympathy for the sick victims. Similarly, mental illnesses may be related to pre-morbid personality in a complex and non-linear way. Such relationships do not preclude psychiatry's inclusion in the medical model, nor should the medical model prevent our research from considering personality variables in the aetiology of major mental illnesses.

Jonathan Benjamin
Richard P Ebstein
Robert H Belmaker

Correspondence:
Robert H Belmaker, M.D.
Beer-Sheba Mental Health Center
PO Box 4600
Beer-Sheba
Israel
Tel: +972 8 640 16202
Fax: +972 8 640 1621
E-mail: belmaker@bgumail.bgu.ac.il

References

Auerbach J, Geller V, Lezer S, Shinwell E, Belmaker R, Levine J, Ebstein R (1999) Dopamine D4 receptor (D4DR) and serotonin transporter promoter (5-HTTLPR) polymorphisms in the determination of temperament in 2-month-old infants. Mol Psychiatr 4: 369-373.

Belmaker R, Biederman J (1994) Genetic markers, temperament and psychopathology. Biol Psychiatry 36: 71-72.

Benjamin J, Press J, Maoz B, Belmaker R (1993) Linkage of a normal personality trait to the color-blindness gene. Biol Psychiatry 34: 581-583.

Benjamin J, Li L, Patterson C, Greenberg B, Murphy D, Hamer D (1996) Population and familial association between the D4 dopamine receptor and measures of Novelty Seeking. Nat Genet 12: 81-84.

Benjamin J, Osher Y, Kotler M (2000) Association between tridimensional personality questionnaire (TPQ) traits and three functional polymorphisms: dopamine receptor D4 (DRD4), serotonin transporter promoter region (5-HTTLPR) and catechol O-methyltransferase (COMT). Mol Psychiatr 5: 96-100.

Cloninger C (1987) A systematic method for clinical description and classification of personality variants: A proposal. Arch Gen Psychiatry 44: 573-588.

Ebstein R, Belmaker R (1997) Saga of an adventure gene: Novelty seeking, substance abuse and the dopamine D4 receptor (D4DR) exon III repeat polymorphism. Mol Psychiatr 2: 381-384.

Ebstein R, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett E, Nemanov L, Katz M, Belmaker R (1996) D4DR exon III polymorphism associated with the personality trait of Novelty Seeking in normal human volunteers. Nat Genet 12: 78-80.

Ebstein R, Segman R, Benjamin J, Novick O, Osher Y, Nemanov L, Belmaker R (1997) 5-HT2C (HTR2C) serotonin receptor gene polymorphism associated with the human personality trait of reward dependence: Interaction with dopamine D4 receptor (D4DR) and dopamine D3 receptor (D3DR) polymorphisms. Am J Med Genet (Neuropsychiatr Genet) 74: 65-72.

Ebstein R, Levine J, Geller V, Auerbach J, Gritsenko I, Belmaker R (1998) Dopamine D4 receptor and serotonin transporter promoter in the determination of neonatal temperament: Novelty seeking in two-week-old infants. Mol Psychiatr 3: 238-246.

Faraone S, Biederman J, Weiffenbach B, Keith T, Chu M, Weaver A, Spencer T, Wilens T, Frazier J, Cleves M, Sakai J (1999) Dopamine D4 gene 7-repeat allele and attention deficit hyperactivity disorder. Am J Psychiatry 156: 768-770.

Feigl H (1967) The 'mental' and the 'physical'. University of Minnesota Press, Minneapolis.

Freedman R, Coon H, Myles-Worsley M (1997) Linkage of a neurophysiological deficit in schizophenia to a chromosome 15 locus. Proc Natl Acad Sci (USA) 94: 587-592.

Gottesman II (1991) Schizophrenia Genesis: The origins of madness. WH Freeman and Co, New York.

Grice D, Leckman J, Pauls D, Kurlan R, Kidd K, Pakstis A, Chang F, Buxbaum J, Cohen D, Gelertner J (1996) Linkage disequilibrium between an allele of the dopamine D4 locus and Tourette syndrome, by the transmission disequilibrium test. Am J Hum Genet 59: 644-652.

Holzman P, Kringlen E, Matthysse S, Flanagan S, Lipton R, Cramer G, Levin S, Lange K, Levy D (1988) A single dominant gene can account for eye tracking dysfunctions and schizophrenia in offspring of discordant twins. Arch Gen Psychiatry 45: 641-647.

Kotler M, Cohen H, Segman R, Gritsenko I, Nemanov L, Lerer B, Kramer I, Zer-Zion M, Kletz I, Ebstein R (1997) Excess dopamine D4 receptor (D4DR) exon III seven repeat allele in opioid-dependent subjects. Mol Psychiatr 2: 251-254.

Kuhn K-U, Meyer K, Nothen M, Gansicke M, Papassotiropoulos A, Maier W (1999) Allelic variants of dopamine recceptor D4 (DRD4) and serotonin receptor 5HT2c (HTR2c) and temperament factors: replication tests. Am J Med Genet (Neuropsychiatr Genet) 88: 168-172.

LaHoste G, Swanson J, Wigal S, Glabe C, Wigal T, King N, Kennedy J (1997) Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatr 1: 121-124.

Loehlin J (1992) Genes and Environment in Personality Development. Sage, Newbury Park, Ca.

Noble E, Oskaragoz T, Ritchie T, Zhang X, Belin T, Sparkes R (1998) D2 and D4 dopamine receptor polymorphisms and personality. Am J Med Genet (Neuropsychiatr Genet) 81: 257-267.

Plomin R (1990) The role of inheritance in behavior. Science 248: 183-188.

Plomin R, De Fries J, McClearn G, Rutter M (1997) Behavioral Genetics. 3 ed. Freeman, New York.

World J Biol Psychiatry (2001) 2, 59 - 69

REVIEW/MINI-REVIEW ▸

Thyroid Hormone, Neural Tissue and Mood Modulation

Michael Bauer [1,2], Peter C. Whybrow [1]

[1] Neuropsychiatric Institute & Hospital, Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles (UCLA), Los Angeles, CA, USA

[2] Psychiatrische Klinik und Poliklinik, Universitätsklinikum Benjamin Franklin, Freie Universität Berlin, Berlin, Germany

Summary

The successful treatment of affective disorders with thyroid hormone exemplifies the suggested interrelationship between endocrine and neuronal systems in these disorders. Thyroid hormones have a profound influence on behaviour and appear to be capable of modulating the phenotypic expression of major affective illness. Specifically, there is good evidence that triiodothyronine (T_3) may accelerate the antidepressant response to tricylic antidepressants, and some studies suggest that T_3 may augment the therapeutic response to antidepressants in refractory depressed patients. Open studies have also indicated that adjunctive supraphysiological doses of thyroxine (T_4) can ameliorate depressive symptomatology and help stabilize the long-term course of illness in bipolar and unipolar patients, especially women refractory to standard medications.

Despite acceptance of the essential role of thyroid hormone on brain maturation and differentiation, and the clinical and therapeutic observations in association with mood disorders, the molecular action that may underlie the mood-modulating properties of thyroid hormone in the adult brain has only recently become the focus of research. The identification of nuclear T_3 receptors, the region-specific expression of deiodinase isoenzymes and the molecular analyses of thyroid-responsive genes in the adult brain have provided the biological bases for a better understanding of thyroid hormone action in mature neurons. Also the influence of thyroid hormones on the putative neurotransmitter systems that regulate mood and behaviour, serotonin and norepinephrine, may be helpful in explaining their mood-modulating effects.

Key words: *thyroid hormone, affective disorder, augmentation, neural tissue.*

Correspondence:
Michael Bauer, M.D., Ph.D.
Neuropsychiatric Institute & Hospital
Department of Psychiatry and
Biobehavioral Sciences
University of California Los Angeles (UCLA)
300 UCLA Medical Plaza, Suite 2330
Los Angeles, CA 90095
Tel: +1 310 825 4908
Fax: +1 310 206 4310
E-mail: mjbauer@mednet.ucla.edu

The thyroid system, behaviour and affective illness

Diseases affecting the thyroid gland are frequently associated with significant neuropsychiatric disturbances (Whybrow and Bauer 2000a,b). The most common psychiatric symptoms associated with thyroid disorders are depression, cognitive dysfunction and anxiety. In severe forms of hypothyroidism (myxedema), even psychotic and delusional symptoms may occur and the syndrome may mimic melancholic depression and dementia (Treadway et al 1967). The reversible nature of the psychiatric symptoms after treatment of the thyroid disorder indicates that they are secondary to the hormonal abnormality. The majority of patients who experience mood, cognitive and psychotic changes due to thyroid dysfunction will return to normal with treatment (Whybrow et al 1969). However, response is not uniform and differences may be due to other psychiatric illnesses or the duration or severity of the thyroid disorder. In some patients, neuropsychiatric sequelae may persist in spite of a return to euthyroid status, indicating irreversible central nervous system (CNS) damage caused by the endocrine disorder (Bauer and Whybrow In Press).

These observations have stimulated psychiatric research into possible links between thyroid hormone homeostasis and affective illness during the past three decades. Although most patients afflicted by a mood disorder do not have overt biochemical evidence of hypothyroidism, they do share numerous clinical stigmata with the endocrine disorder. The detected biochemical and endocrine abnormalities in the hypothalamic-pituitary-thyroid (HPT) axis in primary affective illness, e.g. a blunted thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) injection, are more subtle and findings are contradictory in some instances (Loosen 1985; Bauer and Whybrow 1988; Baumgartner et al 1988; Haggerty et al 1993).

Early research focused upon the therapeutic effects of thyroid hormones in the treatment of affective illness. Research on thyroid-neural interactions led to the initial hypothesis that thyroid hormones play an important role in modulating catecholamine neurotransmission

(Whybrow and Prange 1981). This hypothesis has since been modified to extend the modulating influence of thyroid hormone to other neurotransmitters, e.g. serotonin, and to intracellular molecular mechanisms.

After a brief introduction to thyroid physiology, this article reviews the studies that have examined the role of thyroid axis hormones in the treatment of affective (mood) disorders, and discusses some of the clinically relevant associations between the thyroid and neural systems that are putatively involved in the modulation of mood.

Thyroid hormone metabolism in the periphery and the brain

The thyroid gland produces two thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), which display significant differences in their metabolic pathways, biological activity, and elimination half-life (Larsen et al 1998). T_4, the major secretion product of the thyroid gland, is converted to its biologically active metabolite, T_3, by widely distributed enzymes called iodothyronine 5′ monodeiodinases (deiodinases). After release into the general circulation, thyroid hormones are necessary for the regulation of various metabolic functions and homeostasis in all body tissues throughout life. In addition, T_3 and T_4 exert negative feedback on thyroid hormone release at pituitary and hypothalamic levels (Larsen et al 1998).

From animal studies it is well established that the brain thyroid economy is tightly regulated and largely independent of peripheral metabolic shifts in thyroid function (Dratman et al 1983). In contrast to most peripheral tissues, which take up T_3 directly from the blood, the brain appears to regulate its interstitial levels of T_3 by local deiodination of T_4 (Crantz et al 1982). Thus, the brain is significantly dependent upon the uptake of T_4 from the circulation, with local enzymatic deiodination of T_4 being the major source of nuclear T_3 in the cerebral cortex (Leonard and Koehrle 2000). Studies indicate that more than 70% of the T_3 that is bound to intranuclear receptors in the brain is locally derived from T_4 by deiodination (Crantz et al 1982). The process of deiodination is different in the adult brain from that in peripheral tissues. Specifically, the type II (D2) and type III (D3) deiodinases catalyze these metabolic processes in spatially distinct patterns in the CNS and appear to be segregated into specific cell types (St. Germain and Galton 1997). D2 is expressed primarily in the brain and anterior pituitary gland where it metabolizes T_4 to the active thyroid hormone form, T_3. The activity of D2 in distinct regions of the brain varies widely, with the highest levels found in cortical areas and lower levels in the midbrain, pons, hypothalamus and brainstem (van Doorn et al 1985). In rat brain D2 is expressed in neurons, in particular in the nerve terminals, but also in astrocytes (Leonard 1988).

Hormones of the HPT system in the treatment of mood disorders

The administration of thyroid hormone as a treatment in modern psychiatry has existed since early in the 20th century. Norwegian physicians were the first to use hypermetabolic doses of desiccated sheep thyroid gland to treat successfully patients with cyclic mood disorders and periodic catatonia (Gjessing 1938). Since the identification of T_3 and T_4 as the principal thyroid hormones in the 1950s, and their subsequent synthesis, plus the discovery of TRH and TSH, the effect of these hormones alone and in combination with standard psychotropic drugs in the treatment of mood disorders has been studied repeatedly.

Treatment with TRH and TSH

Shortly after the identification and purification of TRH from sheep hypothalami in the late 1960s, two initial reports suggested that administration of 500 μg intravenously produced rapid (within hours) antidepressant effects that persisted for up to three days (Kastin et al 1972; Prange et al 1972). However, several attempts to replicate this finding, including controlled double-blind studies using doses up to 1000 μg intravenously, showed inconsistent results (Stein and Avni 1988; Sattin 1998). To date, different routes of TRH administration (oral, intravenous, subcutaneous, intrathecal) have been applied in major depression.

Recent studies have shown promising antidepressant effects for TRH by intrathecal infusion (Marangell et al 1997a) and longer-term intravenous or subcutaneous injection (Callahan et al 1997). Beside the mood-elevating effects of TRH, some other interesting observations have emerged from these studies, suggestive of increased likelihood of response to TRH infusion in women and in depressed patients with a history of bipolar disorder (Frye et al 1999).

One placebo-controlled study in 30 depressed subjects reported a beneficial acceleration effect of TSH administered intramuscularly when given in addition to a tricyclic antidepressant (Prange et al 1970). A high proportion (89%) of subjects responded in the group that had received imipramine and TSH, compared to only 44% of those given imipramine and placebo. While the authors concluded that the thyroid stimulation caused by TSH was most likely to be the reason for the therapeutic effects, they did not rule out that TSH may exert a direct behavioural effect as well. To date, the findings from this study have not been replicated or pursued by other authors.

Treatment with thyroid hormones alone

Although it is well established that symptoms of depression that occur in hypothyroid conditions usually resolve after the euthyroid status has been restored, treatment effects with thyroid hormones alone, without the concomitant use of standard psychiatric medications, have only rarely been studied in mood disorders. The initial reports in the late 1950s were case series with inconclusive results (Flach et al 1958; Feldmesser-Reiss 1958). In a later study, Wilson et al (1974) compared up to 62.5 μg/d T_3 alone with imipramine in depressed patients in a double-blind study. At a dose of 50 μg/d, T_3 alone was as effective as imipramine. However, later in the study, when T_3 doses reached 62.5 μg/d, patients showed mild thyrotoxicity, and the study was terminated. Therefore, the study left unanswered the question whether T_3 alone in doses of 50 μg or less might prove a sufficient treatment for depression (Prange et al 1976). Okuno and Nakayasu (1988) administered 50 to 100 μg/d of T_4 alone for two weeks to patients with primary major depressive disorder without apparent thyroid dysfunction; the average effects were modest, although some patients improved markedly.

In summary, there is no systematic research on the question whether thyroid hormones alone are an effective treatment for patients with primary mood disorders.

Thyroid hormone supplementation in the treatment of mood disorders

An attempt was made to identify all reports on the use of thyroid hormone supplementation in the treatment of mood disorders. A computer-aided search of the National Library of Medicine MEDLINE database from 1966 to December 2000 using the subject headings thyroid hormones, triiodothyronine, thyroxine, affective disorders and depression was performed, supplemented by the bibliographies of reports identified. We reviewed only those studies which included six or more patients.

The use of synthetic thyroid hormones, T_3 and T_4, as supplementary agents in affective disorders has a long history, with the first reports published in the late 1960s (Prange et al 1969). Three groups of studies on the technique of thyroid supplementation (potentation) of antidepressant or mood stabilizing drugs must be distinguished. The first group, the *acceleration* studies, involves the use of supplementation with thyroid hormone at the initiation of an antidepressant trial to speed up time to response. The second group, the *augmentation* studies, includes the supplementation with thyroid hormone after a 4- to 6-week trial of an antidepressant has failed or resulted in a partial antidepressant response. A third group of studies uses supplementation with thyroid hormone to prevent future episodes in recurrent mood disorders, the *maintenance* (prophylactic) studies.

Studies with triiodothyronine (T_3)

• Acceleration studies

Prange et al (1969) were the first to investigate the immediate addition of thyroid hormone to speed up antidepressant treatment response. Despite this study, and other controlled studies with a positive outcome in the early 1970s which followed the initial report by Prange, the thyroid hormone acceleration paradigm has received less attention in the past 25 years. To date, seven placebo-controlled studies have been published, five of which showed a positive acceleration outcome (Table 1). A recent meta-analysis examined whether evidence exists to support the clinical efficacy of thyroid hormone acceleration (Altshuler et al In Press). Five of six double-blind, placebo-controlled studies included in the meta-analysis found that the addition of T_3 had a statistically significant effect on the time to response compared with the effects of placebo. Results of this meta-analysis support an acceleration of antidepressant response when adjunctive T_3 is included early in antidepressant treatment; it also revealed that women may be more likely than men to benefit from the addition of T_3. Although some of the placebo-controlled studies had some methodological limitations, they were homogeneous with respect to the type of antidepressant (all TCAs, five of six studies used imipramine), the dose of T_3 and the rating scale used to measure outcome (HAMD). Unfortunately, no T_3 acceleration studies have been performed to date with the selective serotonin reuptake inhibitors (SSRIs). Thus, further studies to assess the efficacy of T_3 acceleration with the newer antidepressants and to evaluate the use of T_3 as an acceleration agent in women are warranted.

• Augmentation studies

Studies assessing the effects of thyroid hormones in treatment-resistant depression have largely focused on T_3 as the augmenting thyroid hormone. Numerous case series and at least 13 prospective trials (nine open and four controlled double-blind studies) have evaluated the use of T_3 (most studies have used 20 to 50 μg/d) to potentiate the response to tricyclic antidepressants in non-responders to treatment (Table 2). The open studies consistently showed that about 50% of TCA non-responders are converted to responders within two to three weeks after the addition of T_3. However, the controlled double-blind studies (Goodwin et al 1982; Gitlin et al 1987; Joffe and Singer 1990; Joffe et al 1993b) are only partially supportive of the data given in the open studies. The largest placebo-controlled study in 33 unipolar depressed outpatients (11 women, 22 men) displayed significant improvement with T_3 compared to placebo after two

Table 1

Results of double-blind, placebo-controlled T_3 acceleration studies[a]

Author, Year	Subjects	Study Group Size N (F/M)	Day T_3 Added	No. of Days Assessed Post-Treatment[b]	T_3 Dose (μg/d)	Comedication Antidepressant (mg/d)	Acceleration Outcome
Prange et al 1969	"Retarded" depression	20 (16/4)	5	28	25	IMI 150	+
Wilson et al 1970	"Nonretarded" UP	20 (16/4)	5	28	25	IMI 150	+
Coppen et al 1972	UP, BD	15 (8/7)	1	28	25	IMI 150	+
Feighner et al 1972	Primary depression	21 (15/6)	1	22	25	IMI 200	-
Wheatley 1972	Neurotic depression	30 (21/9)	1	21	20	AMI 100	+
Wilson et al 1974	UP	19 (19/0)	3	28	25, ↑ to 62.5 (day 7)	IMI 150	+
Steiner et al 1978	UP, BD	8 (8/0)	1	35	25	IMI 150	-

[a] Adapted from Altshuler et al

[b] Change in depression severity assessed with HAMD

Abbreviations: AMI=amitriptyline; BD=bipolar disorder, depressed; HAM-D=Hamilton Rating Scale for Depression (Hamilton 1960); IMI=imipramine; TCA= tricyclic antidepressant; T_3=triiodothyronine; UP=unipolar depression

Table 2

Results of open and controlled triiodothyronine (T_3) augmentation studies

Author, Year	Subjects	Study Group Size N (F/M)	Design	Duration (days)	T_3 Dose (μg/d)	Antidepressant	Outcome No. of Responder (%)
Earle 1970	"Retarded" depression	25 (22/3)	Open	n.s.	25	TCA	14 (56)
Ogura et al 1974	Mixed diagnoses	44 (22/22)	Open	7-126	20-30	TCA	29 (66)
Banki 1975	UP, BD	96 (96/0)	Open	10	20-40	TCA	39 (75)
Banki 1977	UP, BD	33 (33/0)	Historical controls	7	20-40	AMI	23 (70)
Tsutsui et al 1979	Depression, n.s.	11 (1/10)	Open	14-56	5-25	TCA	10 (91)
Goodwin et al 1982	UP, BD	12 (6/6)	DB	26-112	25-50	AMI, IMI	8 (67)
Schwarcz et al 1984	UP	8 (4/4)	Open	28	25-50	DMI	4 (50)
Targum et al 1984	UP	21 (14/7)	Open	21	25 or T_4 100	Mixed	7 (33)
Gitlin et al 1987	UP	16 (7/9)	RA, DB, P, X	14	25	IMI	T_3=placebo
Thase et al 1989	UP	20 (15/7)	Open	28	25	IMI	5 (25)
Joffe & Singer 1990	UP	38 (14/24)	DB vs. T_4 (150 μg)	21	37.5	DMI, IMI	T_3: 9 of 17 (53); T_3>T_4
Joffe et al 1993b	UP	33 (11/22)	RA, DB, P	14	37.5	DMI, IMI	T_3: 10 of 17 (53); T_3=Li > P
Birkenhaeger et al 1997	UP	14 (12/2)	Open	28	37.5	TCA	2 (14)

Abbreviations:
AD=antidepressant, BD=bipolar disorder, DB=double-blind, Li=lithium, n.s.=not specified, RA=randomization, P=placebo-controlled, TCA=tricyclics, T_4=L-thyroxine, T_3=triiodothyronine, UP=unipolar depression, X=cross-over design.
Antidepressants: AMI=amitriptyline, DMI=desipramine, IMI=imipramine

weeks of treatment (Joffe et al 1993b). However, not all controlled double-blind studies showed significant results in favour of T_3; thus, the data are only partially supportive of the results given in the open studies. For example, in a 4-week, randomized, cross-over study of 16 unipolar depressed outpatients (seven women, nine men), there was no significant effect of T_3 compared to placebo (Gitlin et al 1987). As a result of these data, the efficacy of T_3 augmentation remains equivocal with criticisms noting the methodological deficiencies in the studies, e.g. lack of power in the randomized controlled trials due to small sample sizes (Stein and Avni 1988; Patten et al 1992). Furthermore, the efficacy of T_3 augmentation with today's widely used non-tricyclic antidepressants, e.g. SSRIs, has only been studied in one case series (Joffe 1992). Subsequently, a recent meta-analysis did not show consistent results in favour of T_3 augmentation (Aronson et al 1996). In this meta-analysis, for example, improvements in depression scores were moderately large. However, study quality was uneven, and among the four randomized double-blind studies, pooled effects were not significant. Aggregating eight prospective studies (unblinded

and double-blinded studies) with a total of 292 patients, patients treated with T_3 augmentation were twice as likely to respond as controls. As a result of their meta-analysis, Aronson et al (1996) concluded that additional placebo-controlled data are required for a "definite verdict". In the studies performed to date, antidepressant response to T_3 was not affected by gender, bipolar/unipolar diagnosis, type of antidepressant used, or the pre-augmentation thyroid status of the patients (Joffe et al 1993a; Joffe and Sokolov 1994).

• Maintenance studies
To our knowledge, T_3 has not been systematically studied in the continuation and maintenance treatment of affective disorders.

Studies with thyroxine (T_4)

• Acceleration studies
T_4 has not been studied systematically as an acceleration agent, probably because it acts as a prohormone for T_3. Also, its long half-life (approximately five to eight days) does not make T_4 a promising candidate for the acceleration paradigm.

• Augmentation studies
Compared to the large number of trials on T_3 supplementation, adjunctive treatment with T_4 has been studied less frequently in the treatment of depressive disorders. Joffe and Singer (1990) directly compared the augmenting effects of T_3 (37.5 mcg/d) versus T_4 (replacement dose, 150 mcg/d) in depressed patients. In this 3-week, randomized, double-blind study, nine of 17 patients (response rate: 53%) responded to T_3, which was significantly higher than the response rate to T_4 (four of 21 patients; 19%). However, it must be emphasized that due to the long half-life of T_4 (one week, leading to a steady state for approximately three to four weeks after the last increase), the therapeutic effects of T_4 may not have been evident in a 3-week trial, as suggested by the authors in a later review (Joffe and Sokolov 1994). In a recent 8-week, randomized, double-blind, crossover study, Spoov and Lahdelma (1998) compared lithium augmentation, an established strategy for refractory depressed patients, with T_4 augmentation (T_4 dose 200 mcg/d) in a group of unipolar depressed patients. The percentage reduction in the Montgomery-Asberg Depression Rating Scale (MADRS) was significantly greater in patients who started on T_4. However, the lithium dose was relatively small in this study, making the comparison somewhat unfair for lithium. Recent data from two open trials suggested that augmentation with supraphysiological doses of T_4 may cause substantial improvement in some patients with treatment-resistant and chronic depression. In an 8-week, open study of 17 patients (16 women, one man) with treatment-resistant major depressive disorders (bipolar and unipolar), significant improvement was achieved in approximately 50% of patients between weeks four and eight of treatment with T_4 (mean dose: 377 mcg/d) (Bauer et al 1998). Rudas et al (1999) reported that an 8-week augmentation trial with high-dose T_4 (mean dose: 235 mcg/d) showed antidepressant effects in six of seven patients with chronic depression and dysthymia. Placebo-controlled studies are warranted in the future to assess objectively the augmenting effects of supraphysiological T_4 doses in acute major depression.

• Maintenance studies
Open studies investigating the prophylactic effects of supraphysiological T_4 doses in addition to conventional mood stabilizers have suggested that T_4 may improve the course of patients with rapid cycling and non-rapid cycling bipolar disorder (Stancer and Persad 1982; Bauer and Whybrow 1990; Baumgartner et al 1994; Afflelou et al 1997; Bauer et al 2001) (Table 3).

In one study that used T_4 alone as a prophylactic medication, Stancer and Persad (1982) reported that rapid cycling ceased in five out of eight women with bipolar disorder, but did not in two men, following treatment with supraphysiological doses with up to 500 μg/d of T_4. In prospective open studies, our investigations demonstrated that adjunctive supraphysiological doses of T_4 may be beneficial in patients with mood disorders resistant to established medications for these disorders. Initially, the effects of adjunctive supraphysiological doses of T_4 in 11 patients (10 women, nine of whom were premenopausal, one male) with refractory rapid cycling bipolar illness were studied. Adjunctive treatment with T_4 reduced the manic and the depressive phases in both amplitude and frequency, and even led to remittance in some patients. Four patients also underwent single- or double-blind placebo substitution: after switching to placebo, three patients relapsed into depression or cycling (Bauer and Whybrow 1990). Later, in an 8-year maintenance study, adjunctive treatment of seriously ill and previously prophylaxis-resistant unipolar and bipolar patients with supraphysiological doses of T_4 also proved successful in preventing affective episodes in approximately 60% patients. There was a significant reduction in the number of affective recurrences and Morbidity Indexes during T_4 treatment compared with the same time period before T_4 administration. Although these results must be seen as preliminary, these studies indicate that in otherwise refractory patients with affective disorders, treatment with supraphysiological doses of T_4 is a viable augmentation strategy (Bauer et al 2001, Submitted).

Concerns regarding the high doses of T4 are related to bone metabolism and the cardiovascular system. Pre- and postmenopausal women with mood disorders who received supraphysiological T_4 treatment for 12 months or longer

Table 3

Results of thyroxine (T_4) supplementation in mood disorders: augmentation and maintenance studies

Author, Year	Subjects	Study Group Size (N F/M)	Design	Thyroid Status Pre T_4	T_4-Dose (µg/d)	Comedication	Duration of T_4 Treatment	Outcome No. of Responder
Augmentation Studies								
Joffe & Singer 1990	UP	38 (24/14)	RA, DB T_3 vs. T_4	Euthyroid	T_4: 150 T_3: 37.5	DMI, IMI	3 wks	T_4: 4/21 R T_3: 9/17 R
Bauer et al 1998	Treatment-resistant depression (unipolar/bipolar)	17 (16/1)	Open	Euthyroid	482 (300-600)	Various AD and MS	8 wks	8 R, 2 PR, 7 NR
Spoov & Lahdelma 1998[a]	21 UP, 1 BD	22 (16/6)	RA, DB, Li-X,	TSH elevated in 2 subjects	200	Various AD	4 wks	T_4 > lithium
Rudas et al 1999[a]	Chronic depression UP/dysthymia	9 (7/2)	Open	Euthyroid	235 (150-300)	Various AD, Lithium, CBZ	8 wks	Response rate 55%
Maintenance Studies								
Stancer & Persad 1982	RC-BD, refractory to prophylaxis	10 (8/2)	Open	Euthyroid	240-500	None, except NLP in 1 case	9 mo- 9 yrs	5 R (women), 3 PR, 2 NR
Bauer & Whybrow 1990[b]	RC-BD, refractory to prophylaxis	11 (10/1)	Open	7 hypothyroid	150-400	Various MS, 8 on lithium	123 d-150 wks	9 R, 1 PR, 1 NR
Bauer et al (Submitted)[c]	UP, BD, SAD, refractory to prophylaxis	20 (16/4)	Open	Euthyroid	377.5 (200-600)	Various MS and AD	53 mo (range 27-104)	Significant reduction of episodes and morbidity indexes
Afflelou et al 1997	RC-BD	6 (4/2)	Case series	Euthyroid	50-325	Various CNS drugs	5 wks-3 yrs	2 R, 2 PR, 2 NR

[a] Double-blind, cross-over with lithium augmentation; [b] Placebo substitution in 4 patients; [c] Preliminary results in Baumgartner et al. 1994.
Abbreviations: AD=antidepressant, BD=bipolar disorder, CBZ=carbamazepine, DMI=desipramine, Li-X=cross-over study with lithium, MS=mood stabilizer, NLP=neuroleptic, NR=non-response, PR=partial response, R=response, RC-BD=rapid cycling bipolar disorder, SAD=schizoaffective disorder, TCA=tricyclic antidepressant, UP=unipolar major depression, IMI=imipramine, RA=randomization, DB=double-blind

displayed no clinically significant loss of bone mineral density (Gyulai et al 1997; Gyulai et al In Press). With respect to the cardiovascular system, monitored with electrocardiograms and measurements of blood pressure, and body weight, no changes or adverse effects during long-term treatment with T_4 were detected (Baumgartner et al 1994; Whybrow 1994, Bauer et al Submitted). The long-term effects of treatment with supraphysiological doses of T_4 on other cardiovascular functions, e.g. ventricular function, cardiac output, systemic vascular resistance, remain to be studied objectively. However, there is no evidence from preliminary follow-up studies that the cardiovascular system is clinically impaired during supraphysiological T_4 treatment in patients with affective disorders (unpublished data).

Actions of thyroid hormones in the adult brain

Although there is substantial clinical literature supporting the role of thyroid hormone in mood disorder, relatively little is known about the effects of thyroid hormone on the adult mammalian brain and the molecular mechanisms that may underlie its mood-modulating properties. Despite an accepted body of knowledge on the essential role of thyroid hormones in the maturation and differentiation of the brain (Bernal and Nunez 1995), and in disregard of the clinical and therapeutic observations in association with affective illness, the action of thyroid hormones in CNS function in adults has not been widely acknowledged. This lack of interest seems to have originated in the 1950s and 1960s, when early physiological studies suggested that oxygen consumption in the mature human brain did not change with changing thyroid status, an effect that is considered a marker of thyroid hormone activity in the periphery (Sokoloff et al 1953; Sensenbach et al 1954; O'Brien and Harris 1968). Thus, in contrast to our understanding of the thyroid hormones' critically important role in the development of the CNS, until recently little has been known about the function and actions of thyroid hormones in the mature mammalian brain (Anderson et al 2000). However, improved methodology in basic science is providing better understanding of thyroid hormone action in mature neurons (Henley and Koehnle 1997). Among the most important findings are the identification of 1) specific homeostatic mechanisms by which thyroid hormone levels in the

brain are tightly regulated and largely independent of peripheral metabolic shifts, 2) significant amounts of T_4 and T_3 in the brain, 3) several forms of nuclear T_3 receptors, 4) the region-specific expression of deiodinase isoenzymes in brain and pituitary, and 5) the molecular analysis of thyroid-responsive genes in adult brain (Oppenheimer et al 1974; Schwartz and Oppenheimer 1978; Ruel et al 1985; Evans 1988). The T_3-receptor complex interacts with specific sequences (thyroid hormone-response elements) in regulatory regions of target genes modifying their expression (Brent 1994; Anderson et al 2000). Molecular studies have shown that the adult brain has various genetic loci that are responsive to thyroid hormones (e.g. RT3/neurogranin, growth hormone, TRH, corticotropin-releasing hormone, brain-derived neurotrophic factor [BDNF], nerve growth factor [NGF], neurotrophin 3, vasoactive intestinal peptide [VIP] and angiotensinogen) (Bernal et al 1992; Köhrle 2000; Anderson et al 2000; Baumgartner 2000).

Thyroid-monoamine system interaction in the brain and its implications for the mood-modulating effects of thyroid hormones

Changes of the brain thyroid hormone economy are associated with aberrant behaviour in patients with thyroid disease and with changes in the phenotypic expression in psychiatric disease. Examples include: the profound mental disturbances that are found in both hypo- and hyperthyroidism; depressive symptoms in subclinical hypothyroidism; the association of the rapid cycling variant of bipolar illness with hypothyroidism; and the therapeutic effect of thyroid hormones in both depression and bipolar illness.

It has been suggested that the biogenic amines, putatively disturbed in both affective and thyroid disorders, may mediate some of these associations (Whybrow and Prange 1981). These systems, specifically the norepinephrine and serotonin system, which have their origins in the brainstem and extend through the midbrain into the limbic system and cortex, modulate the activity of many of the brain regions related to emotion, mood and memory (Maes and Meltzer 1995).

• Thyroid-catecholamine system interaction

The catecholaminergic system was initially investigated because of the physiological association between sympathetic nervous system activity and thyroid hormones (Harrison 1964). Thyroid hormones appear to play an important role in regulating central noradrenergic (NA) function, and it has been suggested that thyroid dysfunction may be linked with abnormalities in central NA neurotransmission (Whybrow and Prange 1981). In the rat brain, the NA receptor systems are responsive to changes in HPT axis function; studies demonstrated that thyroidectomy results in region- and receptor-specific pre- and postsynaptic NA system changes (Tejani-Butt et al 2000). Thyroidectomy decreases ligand binding to β- and α_2-adrenergic receptors in the cortex and limbic regions of the rat brain. These changes can be reversed by administration of T_4, suggesting a neuromodulatory link between thyroid hormones and central NA systems (Tejani-Butt and Yang 1994). Further evidence for a thyroid-NA interaction stems from immunohistochemical mapping studies which indicate that T_3 is concentrated in both nuclei and projection sites of central NA systems (Rozanov and Dratman 1996). Recent evidence that T_3 is also delivered from the locus coeruleus to its NA targets via anterograde axonal transport suggests that T_3 may function as a cotransmitter with norepinephrine in the adrenergic nervous system (Gordon et al 1999).

• Thyroid-serotonin system interaction

Recent studies in animals and humans have shown that thyroid hormones also influence the activity of serotonin, as well as the functioning of its receptors (Tejani-Butt et al 1993; Kulikov et al 1999). Some evidence exists from neuroendocrine challenge studies in patients with thyroid dysfunction that the hypothyroid status is associated with a reduced 5-HT responsiveness, which is reversible with thyroid replacement therapy (Cleare et al 1995, 1996). Results from studies in animals provide evidence that the thyroid status has a considerable impact on serotonergic neurotransmission in the adult brain (reviewed in: Bauer et al Accepted). Experimentally-induced hypothyroid states result in an increase in 5-HT turnover in the brainstem (Henley and Koehnle 1997). Also, thyroid hormone application may increase cortical serotonergic neurotransmission via two independent mechanisms: 1) A recent in vivo microdialysis study by Gur et al (1999) indicated a loss of autoinhibitory 5-HT_{1A} receptor sensitivity mediated by T_3; in this study, the decrease in hippocampal and cortical serotonin release that usually follows the application of a 5-HT_{1A} agonist was significantly reduced by T_3 or combined T_3 and clomipramine administration in euthyroid rats; results indicate that thyroid hormone application may desensitize autoinhibitory 5-HT_{1A} receptors, and thus increase cortical and hippocampal serotonin release; 2) By increasing cortical 5-HT_2 receptor sensitivity, creating a potentially independent way of increasing 5-HT transmission (Heal and Smith 1988). A recent study in adult rats indicated synergistic effects of T_3 and 5-HT_{1A} receptors on the expression of hippocampal brain-derived neurotrophic factor (BDNF) (Vaidya et al 2001). In this study, thyroid hormone (T_3) administration prior to treatment with a 5-HT_{1A} agonist caused a downregulation of BDNF mRNA expression in the hippocampus.

Novel approaches to studying the thyroid system and brain metabolism *in vivo*

The metabolic effects of thyroid hormones in the adult mammalian brain have rarely been investigated *in vivo*. However, modern brain imaging techniques, e.g. positron emission tomography (PET) and spectroscopy, allow us to evaluate the thyroid system and brain function and have been initiated recently in human and animal studies. They may provide some clues for a better understanding of the thyroid-brain interaction.

A 31^{P}- magnetic resonance spectroscopy (MRS) study reported that hypothyroid patients exhibit decreased cerebral metabolism in the frontal lobes that returns to normal after T_4 replacement therapy (Smith and Ain 1995). Another indication that the adult brain is metabolically responsive to thyroid hormone stems from studies in adult rats using ^{13}C nuclear magnetic resonance (NMR) spectroscopy. These studies revealed that experimentally-induced hypothyroidism markedly reduces the cerebral metabolism of acetate and increases the concentrations of glutamate and GABA (Chapa et al 1995). A significant decline in ^{14}C-2-deoxyglucose uptake (as measured with autoradiography, an analogue method to the FDG-PET techniques used in animals) was demonstrated in hypothyroid adult rats throughout the brain, except for the brainstem and pons, indicating a general decline in metabolic/functional activity during thyroid hormone deficiency; the extent of these effects correlated with the duration of the thyroid dysfunction (Calza et al 1997).

In patients with major depression, Marangell et al (1997b) investigated relationships between serum levels of hormones of the HPT system and cerebral blood flow (CBF) and cerebral glucose metabolism using PET with [^{18}F]fluorodeoxyglucose (FDG). Serum TSH was inversely related to both global and regional CBF and cerebral glucose metabolism; left dorsolateral and mesial prefrontal cortices were the areas of maximal negative correlation between regional CBF and TSH. In a recent ongoing study, the effects of supraphysiological T_4 on regional cerebral glucose metabolism in women with bipolar depression were determined using FDG-PET. A preliminary analysis in six subjects indicated that the treatment with T_4 significantly improved mood, an effect that was accompanied by significant cerebral metabolic effects. The volume of interest (VOI) analyses displayed a significant increase in metabolism in the left middle frontal gyrus and a decrease in the left hippocampus by T_4 treatment; statistical parametric mapping (SPM99) analysis revealed that the T_4-induced reduction in hippocampal activity was part of a widespread deactivation of limbic and subcortical structures, including the amygdala. This deactivation was maximal in parahippocampal gyri and thalamus/brainstem. The findings suggest that T_4 may produce improvement in mood by actions on specific limbic/cortical and subcortical circuits that have been implicated in the pathophysiology of mood disorders (Bauer et al In Press).

Summary and conclusions

The therapeutic use of thyroid hormone supplementation in affective disorders has been studied in a series of clinical trials since the late 1960s. Indications, diagnostic groups, type of thyroid hormone and dosages studied in these trials varied widely. Initially, T_3 was the thyroid hormone on which clinical research focused because it was recognized that T_3 is the thyroid hormone with the highest biological activity. Later, research also paid attention to the use of T_4 because it had been discovered that the brain is dependent on the uptake of T_4 from the circulation, and that it is well tolerated even in higher, supraphysiological doses.

Acceleration strategies remain a major objective of research in depression. T_3 is the prime candidate among the thyroid hormones for such studies. In the past, the T_3 acceleration paradigm has yielded promising results that should be replicated in larger study groups controlling for thyroid status and placebo effects while evaluating the newer, more selective antidepressant agents. Studies to specifically assess the use of T_3 in combination with antidepressants in women may shed light on any gender-specific effect of T_3 on accelerating antidepressant response (Altshuler et al In Press). The therapeutic and prophylactic effects resulting from adjunctive use of supraphysiological T_4 doses in refractory mood disorders are promising but remain preliminary due to the open study design that has been applied in these severely ill patient populations. Double-blind, placebo-controlled trials to confirm these optimistic results are required. The acute treatment and prophylaxis of bipolar patients with T_4, particularly women, are among the most promising strategies. The optimal doses of T_4 are also a matter of debate; our own experience would suggest 200 to 400 mcg/d as the preferred dose range, depending on individual tolerability and response.

The interaction of thyroid hormone with brain noradrenergic and serotonergic systems may be relevant for the understanding of the mood-modulating effects of thyroid hormones in the clinical setting, and thus may enhance the understanding of the pathophysiology and treatment of mood disorders. However, the precise molecular actions underlying the efficacy of thyroid hormone treatment in patients with mood disorders, and in patients with primary hypothyroidism who have comorbid depression, remain to be elucidated. Functional brain ima-

ging techniques to further elucidate the relationship between thyroid status, brain and mood disorders may provide new insights into the pathophysiology and treatment of these disorders.

Acknowledgement

Supported by Deutsche Forschungsgemeinschaft (DFG) grant Ba 1504/3-1 (Dr. M. Bauer).

References

Afflelou S, Auriacombe M, Cazenave M, Chartres JP, Tignol J (1997) Administration of high dose levothyroxine in treatment of rapid cycling bipolar disorders. Review of the literature and initial therapeutic application apropos of 6 cases [Article in French]. Encephale 23: 209-217.

Altshuler L, Bauer M, Frye M, Gitlin M, Mintz J, Szuba M, Leight K, Whybrow PC (In Press) Does thyroid supplementation accelerate antidepressant response? A review and meta-analysis of the literature. Am J Psychiatry.

Anderson GW, Mariash CN, Oppenheimer JH (2000) Molecular actions of thyroid hormone. In: Braverman LE, Utiger RD (eds) Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text, 8th Edition. Lippincott Williams & Wilkins, Philadelphia, pp 174-195.

Aronson R, Offman HJ, Joffe RT, Naylor D (1996) Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. Arch Gen Psychiatry 53: 842-848.

Banki CM (1975) Triiodothyronine in the treatment of depression. Orv Hetil 116: 2543-2546.

Banki CM (1977) Cerebrospinal fluid amine metabolites after combined amitriptyline-triiodothyronine treatment of depressed women. Eur J Clin Pharmacol 11: 311-315.

Bauer MS, Whybrow PC (1988) Thyroid hormones and the central nervous system in affective illness: Interactions that may have clinical significance. Integr Psychiatry 6: 75-100.

Bauer MS, Whybrow PC (1990) Rapid cycling bipolar affective disorders. II. Treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study. Arch Gen Psychiatry 47: 435-440.

Bauer M, Whybrow PC (In Press) Thyroid hormone, brain and behavior. In: Pfaff D, Arnold A, Etgen A, Fahrbach S, Rubin R (eds) Hormones, Brain and Behavior. Academic Press, San Diego.

Bauer M, Hellweg R, Gräf KJ, Baumgartner A (1998) Treatment of refractory depression with high-dose thyroxine. Neuropsychopharmacology 18: 444-455.

Bauer M, London ED, Rasgon N, Berman S, Mandelkern M, Frye M, Mazziotta JJ, Altshuler L, Shinn AK, Gitlin M, Whybrow PC (In Press) Effects of supraphysiological levothyroxine (T4) on cerebral glucose metabolism in bipolar depression: findings from a positron emission tomographic study (Abstract). Bipolar Disord 3 (Suppl 1).

Bauer M, Priebe S, Berghöfer A, Bschor T, Kiesslinger K, Whybrow PC (2001) Subjective response to and tolerability of long-term supraphysiological doses of levothyroxine in refractory mood disorders. J Affect Disord 64: 35-42.

Bauer M, Berghöfer A, Bschor T, Baumgartner A, Hellweg R, Adli M, Baethge C, Müller-Oerlinghausen B (Submitted) Supraphysiological doses of thyroxine in the maintenance treatment of prophylaxis-resistant bipolar, unipolar and schizoaffective disorders.

Bauer M, Heinz A, Whybrow PC (Accepted) Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. Mol Psychiatry.

Baumgartner A (2000) Thyroxine and the treatment of affective disorders: an overview of the results of basic and clinical research. Int J Neuropsychopharmacol 3: 149-165.

Baumgartner A, Gräf KJ, Kürten I, Meinhold H (1988) The hypothalamic-pituitary-thyroid axis in psychiatric patients and healthy subjects: Parts 1-4. Psychiatry Res 24: 271-332.

Baumgartner A, Bauer M, Hellweg R (1994) Treatment of intractable non-rapid cycling bipolar affective disorder with high-dose thyroxine: an open clinical trial. Neuropsychopharmacology 10: 183-189.

Bernal J, Nunez J (1995) Thyroid hormones and brain development. Eur J Endocrinol 133: 390-398.

Bernal J, Rodriguez-Pena A, Iniguez MA, Ibarrola N, Munoz A (1992) Influence of thyroid hormone on brain gene expression. Acta Med Austriaca 19 (Suppl 1): 32-35.

Birkenhaeger TK, Vegt M, Nolen WA (1997) An open study of triiodothyronine augmentation of tricyclic antidepressants in inpatients with refractory depression. Pharmacopsychiatry 30: 23-26.

Brent GA (1994) The molecular basis of thyroid hormone action. N Engl J Med 29: 847-853.

Callahan AM, Frye MA, Marangell LB, George MS, Ketter TA, L'Herrou T, Post RM (1997) Comparative antidepressant effects of intravenous and intrathecal thyrotropin-releasing hormone: confounding effects of tolerance and implications for therapeutics. Biol Psychiatry 41: 264-272.

Calza L, Aloe L, Giardino L (1997) Thyroid hormone-induced plasticity in the adult rat brain. Brain Res Bull 44: 549-557.

Chapa F, Kunnecke B, Calvo R, Escobar del Rey F, Morreale de Escobar G, Cerdan S (1995) Adult-onset hypothyroidism and the cerebral metabolism of (1,2-13C2) acetate as detected by 13C nuclear magnetic resonance. Endocrinology 136: 296-305.

Cleare AJ, McGregor A, O'Keane V (1995) Neuroendocrine evidence for an association between hypothyroidism, reduced central 5-HT activity and depression. Clin Endocrinol (Oxf) 43: 713-719.

Cleare AJ, McGregor A, Chambers SM, Dawling S, O'Keane V (1996) Thyroxine replacement increases central 5-hydroxytryptamine activity and reduces depressive symptoms in hypothyroidism. Neuroendocrinology 64: 65-69.

Coppen A, Whybrow P, Noguera R, Maggs R, Prange AJ Jr (1972) The comparative antidepressant value of L-tryptophan and imipramine with and without attempted potentiation by liothyronine. Arch Gen Psychiatry 26: 234-241.

Crantz FR, Silva JE, Larsen PR (1982) Analysis of the sources and quantity of 3,5,3'-iodothyronine specifically bound to nuclear receptors in rat cerebral cortex and cerebellum. Endocrinology 110: 367-375.

Dratman MB, Crutchfield FL, Gordon JT, Jennings AS (1983) Iodothyronine homeostasis in rat brain during hypo- and hyperthyroidism. Am J Physiol 245: E185-193.

Earle BV (1970) Thyroid hormone and tricyclic antidepressants in resistant depressions. Am J Psychiatry 126: 1667-1669.

Evans RM (1988) The steroid and the thyroid hormone receptor superfamily. Science 240: 889-895.

Feighner JP, King LJ, Schuckit MA, Croughan J, Briscoe W (1972) Hormonal potentiation of imipramine and ECT in primary depression. Am J Psychiatry 128: 1230-1238.

Feldmesser-Reiss EE (1958) The application of triiodothyronine in the treatment of mental disorders. J Nerv Ment Dis 127: 540-546.

Flach FF, Celian CI, Rawson RW (1958) Treatment of psychiatric disorders with triiodothyronine. Am J Psychiatry 114: 841-842.

Frye MA, Gary KA, Marangell LB, George MS, Callahan AM, Little

JT, Huggins T, Cora-Locatelli G, Osuch EA, Winokur A, Post RM (1999) CSF thyrotropin-releasing hormone gender difference: implications for neurobiology and treatment of depression. J Neuropsychiatry Clin Neurosci 11: 349-353.

Gitlin MJ, Weiner H, Fairbanks L, Hershman JM, Friedfeld N (1987) Failure of T3 to potentiate tricyclic antidepressant response. J Affect Disord 13: 267-272.

Gjessing R (1938) Disturbances of somatic function in catatonia with a periodic course and their compensation. J Ment Sci 84: 608-621.

Goodwin F, Prange AJ Jr, Post RM, Muscettola G, Lipton MA (1982) Potentiation of antidepressant effects by L-triiodothyronine in tricyclic nonresponders. Am J Psychiatry 139: 34-38.

Gordon JT, Kaminski DM, Rozanov CB, Dratman MB (1999) Evidence that 3,3',5-triiodothyronine is concentrated in and delivered from the locus coeruleus to its noradrenergic targets via anterograde axonal transport. Neuroscience 93: 943-954.

Gur E, Lerer B, Newman ME (1999) Chronic clomipramine and triiodothyronine increase serotonin levels in rat frontal cortex in vivo: relationship to serotonin autoreceptor activity. J Pharmacol Exp Ther 288: 81-87.

Gyulai L, Whybrow PC, Jaggi J, Bauer MS, Younkin S, Rubin L, Attie M (1997) Bone mineral density and L-thyroxine treatment in rapidly cycling bipolar disorder. Biol Psychiatry 41: 503-506.

Gyulai L, Bauer M, Espana-Garcia F, Hierholzer J, Baumgartner A, Whybrow PC (In Press) Bone mineral density in pre- and postmenopausal women with affective disorder treated with high-dose thyroxine. J Affect Disord.

Haggerty JJ Jr, Stern RA, Mason GA, Beckwith J, Morey CE (1993) Subclinical hypothyroidism: A modifiable risk factor for depression? Am J Psychiatry 150: 508-510.

Harrison TS (1964) Adrenal, medullary, and thyroid relationships. Physiol Rev 44: 161-185.

Heal DJ, Smith SL (1988) The effects of acute and repeated administration of T3 to mice on 5-HT1 and 5-HT2 function in the brain and its influence on the actions of repeated electroconvulsive shock. Neuropharmacology 27: 1239-1248.

Henley WN, Koehnle TJ (1997) Thyroid hormones and the treatment of depression: An examination of basic hormonal actions in the mature mammalian brain. Synapse 27: 36-44.

Joffe RT (1992) Triiodothyronine potentiation of fluoxetine in depressed patients. Can J Psychiatry 37: 48-50.

Joffe RT, Singer W (1990) A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. Psychiatry Res 32: 241-251.

Joffe RT, Sokolov STH (1994) Thyroid hormones, the brain, and affective disorders. Crit Rev Neurobiol 8: 45-63.

Joffe RT, Levitt AJ, Bagby RM, MacDonald C, Singer W (1993a) Predictors of response to lithium and triiodothyronine augmentation of antidepressants in tricyclic non-responders. Br J Psychiatry 163: 574-578.

Joffe RT, Singer W, Levitt AJ, MacDonald C (1993b) A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. Arch Gen Psychiatry 50: 387-393.

Kastin AJ, Ehrensing RH, Schalch DS, Anderson MS (1972) Improvement in mental depression with decreased thyrotropin response after administration of thyrotropin-releasing hormone. Lancet ii: 740-742.

Köhrle J (2000) Thyroid hormone metabolism and action in the brain and pituitary. Acta Med Austriaca 27: 1-7.

Kulikov A, Moreau X, Jeanningros R (1999) Effects of experimental hypothyroidism on 5-HT1A, 5-HT2A receptors, 5-HT uptake sites and tryptophan hydroxylase activity in mature rat brain. Neuroendocrinology 69: 453-459.

Larsen PR, Davies TF, Hay ID (1998) The thyroid gland. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR (eds) Williams Textbook of Endocrinology, 9th Edition. Saunders, Philadelphia, pp 389-515.

Leonard JL (1988) Dibutyryl cAMP induction of type II 5'deiodinase activity in rat brain astrocytes in culture. Biochem Biophys Res Commun 151: 1164-1172.

Leonard JL, Koehrle J (2000) Intracellular pathways of iodothyronine metabolism. In: Braverman LE, Utiger RD (eds) Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text, 8th Edition. Lippincott Williams & Wilkins, Philadelphia, pp 136-171.

Loosen PT (1985) The TRH-induced TSH response in psychiatric patients: a possible neuroendocrine marker. Psychoneuroendocrinology 10: 237-260.

Maes M, Meltzer HY (1995) The serotonin hypotheses of major depression. In: Bloom FE, Kupfer DJ (eds) Psychopharmacology: The Fourth Generation of Progess. Raven Press, New York, pp 933-944.

Marangell LB, George MS, Callahan AM, Ketter TA, Pazzaglia PJ, L'Herrou TA, Leverich GS, Post RM (1997a) Effects of intrathecal thyrotropin-releasing hormone (protirelin) in refractory depressed patients. Arch Gen Psychiatry 54: 214-222.

Marangell LB, Ketter TA, George MS, Pazzaglia PJ, Callahan AM, Parekh P, Andreason PJ, Horwitz B, Herscovitch P, Post RM (1997b) Inverse relationship of peripheral thyrotropin-stimulating hormone levels to brain activity in mood disorders. Am J Psychiatry 154: 224-230.

O'Brien MD, Harris PH (1968) Cerebral-cortex perfusion-rates in myxoedema. Lancet 1: 1170-1172.

Ogura C, Okuma T, Uchida Y, Imai S, Yogi H, Sunami Y (1974) Combined thyroid (triiodothyronine)-tricyclic antidepressant treatment in depressive states. Folia Psychiatr Neurol Jpn 28: 179-186.

Okuno Y, Nakayasu N (1988) Thyroid function and therapeutic efficacy of thyroxine in depression. Jpn J Psychiatry Neurol 42: 763-770.

Oppenheimer JH, Schwartz HL, Surks MI (1974) Tissue differences in the concentration of triiodothyronine nuclear binding sites in the rat: liver, kidney, pituitary, heart, brain, spleen, and testis. Endocrinology 95: 897-903.

Patten SB, Lupin DA, Boucher SA, Lamarre CJ (1992) Pharmacologic management of refractory depression. Can Med Assoc J 146: 483-487.

Prange AJ Jr, Wilson IC, Rabon AM, Lipton MA (1969) Enhancement of imipramine antidepressant activity by thyroid hormone. Am J Psychiatry 126: 457-469.

Prange AJ Jr, Wilson IC, Knox A, McClane TK, Lipton MA (1970) Enhancement of imipramine by thyroid stimulating hormone: clinical and theoretical implications. Am J Psychiatry 127: 191-199.

Prange AJ Jr, Lara PP, Wilson IC, Alltop LB, Breese GR (1972) Effects of thyrotropin-releasing hormone in depression. Lancet ii: 999-1002.

Prange AJ Jr, Wilson IC, Breese GR, Lipton MA (1976) Hormonal alteration of imipramine response: a review. In: Sachar EJ (ed) Hormones, Behavior, and Psychopathology. Raven Press, New York, pp 41-67.

Rozanov CB, Dratman MB (1996) Immunohistochemical mapping of brain triiodothyronine reveals prominent localization in central noradrenergic systems. Neuroscience 74: 897-915.

Rudas S, Schmitz M, Pichler P, Baumgartner A (1999) Treatment of refractory chronic depression and dysthymia with high-dose thyroxine. Biol Psychiatry 45: 229-233.

Ruel J, Faure R, Dussault JH (1985) Regional distribution of nuclear T3 receptors in rat brain and evidence for preferential localization

in neurons. J Endocrinol Invest 8: 343-348.

Sattin A (1998) A heuristic model of mental depression derived from basic and applied research on thyrotropin-releasing hormone. Thyroid 8: 957-962.

Schwarcz G, Halaris A, Baxter L, Escobar J, Thompson M, Young M (1984) Normal thyroid function in desipramine nonresponders converted to responders by the addition of L-triiodothyronine. Am J Psychiatry 141: 1614-1616.

Schwartz HL, Oppenheimer JH (1978) Nuclear triiodothyronine receptor sites in brain: probable identity with hepatic receptors and regional distribution. Endocrinology 103: 267-273.

Sensenbach W, Madison L, Eisenberg S, Ochs L (1954) The cerebral circulation and metabolism in hyperthyroidism and myxedema. J Clin Invest 33: 1434-1440.

Smith CD, Ain KB (1995) Brain metabolism in hypothyroidism studied with 31P magnetic-resonance spectroscopy. Lancet 345: 619-620.

Sokoloff L, Wechsler RL, Mangold R, Balls K, Kety SS (1953) Cerebral blood flow and oxygen consumption in hyperthyroidism before and after treatment. J Clin Invest 32: 202-208.

Spoov J, Lahdelma L (1998) Should thyroid augmentation precede lithium augmentation - a pilot study. J Affect Disord 49: 235-239.

St Germain DL, Galton VA (1997) The deiodinase family of selenoproteins. Thyroid 7: 655-668.

Stancer HC, Persad E (1982) Treatment of intractable rapid-cycling manic-depressive disorder with levothyroxine. Arch Gen Psychiatry 39: 311-312.

Stein D, Avni J (1988) Thyroid hormones in the treatment of affective disorders. Acta Psychiatr Scand 77: 623-636.

Steiner M, Radwan M, Elizur A, Blum I, Atsmon A, Davidson S (1978) Failure of l-triiodothyronine (T_3) to potentiate tricyclic antidepressant response. Curr Ther Res 23: 655-659.

Targum SD, Greenberg RD, Harmon RL, Kessler K, Salerian AJ, Fram DH (1984) Thyroid hormone and the TRH stimulation test in refractory depression. J Clin Psychiatry 45: 345-346.

Tejani-Butt SM, Yang J (1994) A time course of altered thyroid states on the noradrenergic system in rat brain by quantitative autoradiography. Neuroendocrinology 59: 235-244.

Tejani-Butt SM, Yang J, Kaviani A (1993) Time course of altered thyroid states on 5-HT_{1A} receptors and 5-HT uptake sites in rat brain: an autoradiographic analysis. Neuroendocrinology 57: 1011-1018.

Tejani-Butt SM, Yang J, Pawlyk A, Hahn CG (2000) Receptors and molecular studies. Neuropsychopharmacology 23: S69.

Thase ME, Kupfer DJ, Frank E, Jarrett DB (1989) Treatment of imipramine-resistant recurrent depression: II. An open clinical trial of lithium augmentation. J Clin Psychiatry 50: 413-417.

Treadway CR, Prange AJ Jr, Doehne EF, Edens CJ, Whybrow PC (1967) Myxedema psychosis: Clinical and biochemical changes during recovery. J Psychiat Res 5: 289-296.

Tsutsui S, Yamazaki Y, Nanba T, Tsushima M (1979) Combined therapy of T_3 and antidepressants in depression. J Int Med Res 7: 138-146.

Vaidya VA, Castro ME, Pei Q, Sprakes ME, Grahame-Smith DG (2001) Influence of thyroid hormone on 5-HT_{1A} and 5-HT_{2A} receptor-mediated regulation of hippocampal BDNF mRNA expression. Neuropharmacology 40: 48-56.

Van Doorn J, Roelfsma F, van der Heide D (1985) Concentrations of thyroxine and 3,5,3'-triiodothyronine at 34 different sites in euthyroid rats as determined by an isotopic equilibrium technique. Endocrinology 117: 1201-1208.

Wheatley D (1972) Potentiation of amitriptyline by thyroid hormone. Arch Gen Psychiatry 26: 229-233.

Whybrow PC (1994) The therapeutic use of triiodothyronine and high-dose thyroxine in psychiatric disorder. Acta med Austriaca 21: 47-52.

Whybrow PC, Bauer M (2000a) Behavioral and psychiatric aspects of thyrotoxicosis. In: Braverman LE, Utiger RD (eds) Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text, 8th Edition. Lippincott Williams & Wilkins, Philadelphia, pp 673-678.

Whybrow PC, Bauer M (2000b) Behavioral and psychiatric aspects of hypothyroidism. In: Braverman LE, Utiger RD (eds) Werner & Ingbar's The Thyroid. A Fundamental and Clinical Text, 8th Edition. Lippincott Williams & Wilkins, Philadelphia, pp 837-842.

Whybrow PC, Prange AJ Jr (1981) A hypotheses of thyroid-catecholamine-receptor interaction. Arch Gen Psychiatry 38: 106-113.

Whybrow PC, Prange AJ Jr, Treadway CR (1969) Mental changes accompanying thyroid gland dysfunction. Arch Gen Psychiatry 20: 48-63.

Wilson IC, Prange AJ, McClane TK, Rabon AM, Lipton M (1970) Thyroid-hormone enhancement of imipramine in nonretarded depressions. N Engl J Med 282: 1063-1067.

Wilson IC, Prange AJ Jr, Lara PP (1974) L-Triiodothyronine alone and with imipramine in the treatment of depressed women. In: Prange AJ Jr (ed) The Thyroid Axis, Drugs, and Behavior. Raven Press, New York, pp 49-62.

World J Biol Psychiatry (2001) 2, 70 - 82

REVIEW/MINI-REVIEW ▸

Neurochemical Investigation of the Schizophrenic Brain by In Vivo Phosphorus Magnetic Resonance Spectroscopy

Hiroshi Fukuzako

Department of Neuropsychiatry, Faculty of Medicine, Kagoshima University, Kagoshima, Japan

Summary

Abnormal phospholipid metabolisms may play important roles in the pathophysiology of schizophrenia. Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) offers a new method for studying phosphorus-related metabolism in vivo. A decrease in the level of phosphomonoesters (PME) and an increase in the level of phosphodiesters (PDE) has been demonstrated in the prefrontal lobe of neuroleptic-naive schizophrenic patients. Most of the studies in medicated schizophrenic patients have shown decreased PME and/or increased PDE. The decreased PME in the frontal lobe appears to be associated with negative symptoms and poor working memory performance. ^{1}H-decoupled ^{31}P-MRS revealed a reduction in the phosphocholine element of PME and an elevation in the mobile phospholipids of PDE in the prefrontal region of medicated schizophrenic patients. PDE were elevated in the temporal lobes of neuroleptic-naive schizophrenic patients, and this increase was partially normalized by haloperidol administration. Data about the temporal lobes of medicated schizophrenic patients have not been consistent. Except for the reduction in the adenosine triphosphate (ATP) in the basal ganglia and the correlation between the increase in the frontal lobe phosphocreatine (PCr) and negative symptomatology, data related to changes in high-energy phosphates are contradictory. No consensus on the effect of neuroleptics on phosphorus metabolites has been achieved. Methodological problems inherent in ^{31}P-MRS may have contributed to the confusion in understanding available data. Future directions of MRS studies are suggested in the last section of the paper.

Key words: *schizophrenia, magnetic resonance spectroscopy, phosphorus metabolites.*

Correspondence:
Hiroshi Fukuzako, M.D., Ph.D.
Department of Neuropsychiatry
Faculty of Medicine
Kagoshima University
8-35-1 Sakuragaoka
Kagoshima 890-8520
Japan
Tel: +11 81 99 275 5346
Fax: +11 81 99 265 7089
E-mail: fukuzako@med4.kufm.kagoshima-u.ac.jp

Introduction

Functional and morphologic brain imaging studies have revealed subtle but significant abnormalities in the brains of schizophrenic patients. The most consistent structural abnormalities are ventricular enlargement and decreased cortical volume, especially in the superior temporal gyrus and the medial temporal lobe (Harrison 1999; McCarley et al 1999; Wright et al 2000). Functional imaging modalities have uncovered a variety of types of physiologic dysfunctions that involve diverse brain regions (Andreasen et al 1997; Egan and Weinberger 1997; Buchsbaum and Hazlett 1998; McClure et al 1998). These aberrances in function and structure are thought to be developmental in origin. Several lines of evidence suggest that frontal lobe dysfunction is associated with "negative" symptoms and the disorganization syndrome (Liddle et al 1992; Kaplan et al 1993; Shioiri et al 1994; Deicken et al 1995c), while temporal lobe dysfunction may be more closely related to "positive" symptoms (McCarley et al 1993; Fukuzako et al 1996; Klemm et al 1996; Nordahl et al 1996; Sabri et al 1997).

Disturbed phospholipid metabolism has been proposed as a neurodevelopmental element in the pathogenesis of schizophrenia (Horrobin 1998), and deficiencies of essential fatty acid components of red blood cell (RBC) membrane phospholipids have been reported in schizophrenic patients (Walker et al 1999; Fenton et al 2000). Changes in fatty acid composition affect membrane structure by changing its fluidity, and hence altering the functions of membrane-bound receptors, ion channels and enzymes. Membrane lipids are also important in cell signalling and are precursors for inositol-triphosphate and diacyl-glycerol synthesis. In vivo ^{31}phosphorus magnetic resonance spectroscopy (^{31}P-MRS) is able to quantitate membrane phospholipids and high-energy phosphate metabolism in the brain (Kegeles et al 1998; McClure et al 1998; Keshavan et al 2000; Vance et al 2000). Therefore, ^{31}P-MRS may be a technique to test such a hypothesis directly.

The general principles, strengths and weaknesses of MRS have been outlined in several review articles (Maier 1995; Kegeles et al 1998; McClure et al 1998; Vance et al 2000). This paper provides a thorough review of the literature on ^{31}P-MRS that is relevant to schizophrenia, with a brief introduction into spectroscopic techniques to assist the understanding of conflicting results in

this field. Suggestions for future studies are presented in the last section.

Methodological issues of ^{31}P-PMS

^{31}P has a nuclear magnetic moment and is present in 100% of naturally occurring phosphorus-containing compounds, so no labelling is required for ^{31}P-MRS imaging. The metabolites easily identified by clinical MR instruments include phosphomonoesters (PME), inorganic orthophosphate (Pi), phosphodiesters (PDE), phosphocreatine (PCr), and γ-, β-, and α-phosphates of 5'-adenosine triphosphates (ATP). Phospholipids are integral constituents of cell membranes and are involved in the preservation of structure, ion conduction, signal transduction and the maintenance of concentration gradients. The PME resonance obtained from in vivo ^{31}P-MRS is generated by freely mobile PME [mainly phosphocholine (PC) and phosphoethanolamine (PE)], less mobile PME moieties (phosphorylated proteins), and PME inserted into membrane phospholipids (McClure et al 1998). The PDE resonance arises from free mobile PDE [glycerophosphoethanolamine (GPE) and glycerophosphocholine (GPC)], mobile PDE moieties (small membrane phospholipid structures, such as micelles and vesicles) and bilayer membrane phospholipids (Murphy et al 1989; McNamara et al 1994; McClure et al 1998). Changes in levels of these metabolites provide information on metabolisms and components of membrane phospholipids. ATP is the fuel of virtually all energy-requiring reactions, including synthesis, membrane transport and muscle contraction. Any excess of energy is stored as PCr. PCr, the most metabolically labile of the brain high-energy phosphates, combines with adenosine diphosphate (ADP) to form ATP and creatine. ATP in turn is broken down to ADP and Pi and energy is released. The β-ATP peak is generally considered the most reliable indicator of tissue ATP levels because the γ- and α- resonances usually contain contributions from ADP (Bottomley 1989). Hypoxia, ischemia, anaerobic metabolism and impaired energy utilization all result in abnormal ATP, PCr and Pi concentrations.

Although ^{31}P-MRS has the potential to generate insights not available by other imaging techniques, methodological limitations inherent in this technique need to be addressed before interpreting the findings listed in Table 1. Differences in the spin-lattice (T_1) or spin-spin (T_2) relaxation time constant of phosphorus metabolites between schizophrenic patients and controls may yield positive results, without any real change in the concentration of the phosphorus metabolites. T_1 and T_2 prolongation have been reported in the frontal and temporal lobes and in the left basal ganglia of medicated patients with chronic schizophrenia (Williamson et al 1992). T_2 relaxation effects are negligible because changes in the T_2 of a metabolite usually do not reflect a change in spectral peak area (Stanley et al 1995). However, the PME and PDE spectra, which include short T_2 components, could be affected by the difference in T_2 values, when the MR acquisition method has a preacquisition delay time (Twieg et al 1989). On the other hand, the observed ^{31}P MR signal, which comprises long T_1 species, does not fully recover its equilibrium magnetization when a short repetition time is used between acquisitions. For example, an increase in the T_1 of PME could account for the decrease in the PME concentration observed in schizophrenic patients. Signal collection and spectral processing methods significantly affect the results. Surface coil methods, such as depth-resolved surface coil spectroscopy (DRESS), do not eliminate signals from the skull and cranial muscles. Chemical shift imaging (CSI) has the advantage of obtaining data from large areas of the brain in a single scan. However, it takes longer to acquire the image, and its spectra may be degraded by signal contamination (Frahm et al 1989). All spectroscopic methods have in common the problem that each voxel usually contains varying percentages of grey matter, white matter and cerebrospinal fluid (CSF), each of which may have different concentrations of metabolites. Phosphorus metabolites in the CSF contribute little if anything to the spectrum obtained by *in vivo* ^{31}P-MRS (Hugg et al 1992; Ernst et al 1993), while the concentrations of phosphorus metabolites are different in grey and white matter (Kilby et al 1990). Grey matter volume has been reported to be reduced in schizophrenic patients, especially in the superior temporal gyrus and the medial temporal lobe (McCarley et al 1999; Harrison 1999). Therefore, interpretation of MRS findings related to the temporal lobes should take into account this partial volume effect. Quantifying of the data in the frequency domain, such as phasing the spectral peaks and correcting baseline distortion, usually requires interaction by an operator, which can introduce a bias. Defining the spectral peaks itself also produces a bias, whether it is done manually or is automated, as does the choice of what number of fitted spectral peaks is to be used, e.g. singlet or triplet for PDE and β-ATP. In addition, cancellation of broad peaks by postprocessing (e.g. convolution difference method) significantly decreases the peak areas of PDE (Kilby et al 1991). All these methodological issues have been fully addressed in a recent review article by Stanley et al (2000).

MRS findings in schizophrenia

Findings from published studies and interesting abstracts are summarized in Table 1.

• Membrane phospholipids

Decreased levels of PME and increased levels of PDE have been observed in the prefrontal cortex of drug-naive schizophrenic patients relative to

Table 1:
^{31}P-MRS in schizophrenia

Author (yr)	Subject	MRS method	Location & Voxel size	Findings
Keshavan (1991)	A 31-year-old woman who suffered from schizophrenia one year after the MRS examination as a control	DRESS 15-20 cm^3	Prefrontal cortex (left + right)	PME ↓ (27.5%), PDE ↑ (25.6%)
O'Callaghan (1991)	18 medicated patients (31 yo, 11M/7F, 10 yrs illness duration), 10 controls (36 yo, 6M/4F)	Surface coil	Temporoparietal cortex (left)	pH ↑ (12.9%, M)
Pettegrew (1991)	11 drug-naive, first-episode patients (24 yo, 7M/4F), 10 controls (24 yo, 6M/4F)	DRESS 15-20 cm^3	Prefrontal cortex (left + right)	PME ↓ (23.6%), PDE ↑ (13.0%), β-ATP ↑ (21.6%), Pi ↓ (20.2%)
Williamson (1991)	10 medicated patients (39 yo, 9M/1F, 16 yrs), 7 controls (matched for age, sex, and handedness)	FROGS 15-20 cm^3	Prefrontal cortex (left)	PME ↓ (25.7%), PCr ↑ (10.1%), Pi ↑ (19.5%)
Calabrese (1992)	11 patients (2 neuroleptic-free, 9 medicated, 39 yo, 10M/1F), 9 controls (35 yo, 9M)	ISIS 87 cm^3	Temporal lobe	left β-ATP ↑ (11.1%), right PCr/β -ATP ↑ (14.9%), left PDE ↑ (8.7%); Inverse correlation between thinking disorder and PCr/ β-ATP
Fujimoto (1992a)	16 medicated patients (39 yo, 16M, 12 yrs), 20 controls (34 yo, 15M/5F)	CSI 36 cm^3	Temporal lobe Frontoparietal region	left PDE ↑ (5.4%), left ATP ↓ (7.8%) left PCr ↓ (9.2%)
Fujimoto (1992b)	17 medicated patients (39 yo, 17M), 20 controls (34 yo, 15M/5F)	CSI 36 cm^3	Basal ganglia	left PME ↑ (10.9%), right PDE ↓ (7.4%); right β-ATP ↓ (4.0%)
Keshavan (1993)	9 drug-naive, first-episode patients (8 schizophrenia, 1 schizophreniform disorder, 25 yo, 7M/2F, 1.7 yrs)	DRESS 15-20 cm^3	Prefrontal cortex (left + right)	Positive correlation between PDE and total corpus callosal area (especially anterior portion)
Deicken (1994)	20 patients (6 neuroleptic free, 14 medicated, 39 yo, 20M, 14 yrs), 16 controls (40 yo, 16M)	CSI 25 cm^3	Frontal and parietal lobes	PDE ↑ (frontal>parietal, left 11.8%, right 11.8%), PCr ↓ (frontal>parietal, left 2.9%, right 11.2%), right>left Pi (patients); Correlation between right frontal PDE (positive) and right frontal lPCr (negative), and hostility-suspiciousness and anxiety-depression subscale
Fukuzako (1994)	16 medicated patients with treatment-resistant positive symptoms (40 yo, 8M/8F, 17 yrs), 16 controls (40 yo, 8M/8F)	CSI 36 cm^3	Medial temporal lobe	PDE ↑ (left 12.6%, right 9.1%), left β-ATP ↓ (23.0%)
Shioiri (1994)	26 patients (6 neuroleptic free, 20 medicated, 32 yo, 16M/10F, 9 yrs), 26 controls (32 yo, 16M/10F)	DRESS	Prefrontal lobe (left + right)	No differences between the groups; Association of low PME with negative symptom score
Stanley (1994)	19 medicated patients (32 yo, 11 yrs), 18 controls (31 yo, 18M)	FROGS 15-20 cm^3	Prefrontal cortex (left)	PME ↓ (20.7%), PDE ↑ (9.5%, newly diagnosed patients)
Deicken (1995a)	18 patients (5 neuroleptic-free, 13 medicated, 39 yo, 18M, 14 yrs), 16 controls (40 yo, 16M)	CSI 25 cm^3	Basal ganglia	β-ATP ↓ (left 13.1%, right 8.2%)
Deicken (1995b)	18 patients (5 neuroleptic-free, 13 medicated, 39 yo, 18M, 14 yrs), 14 controls (39 yo, 14M)	CSI 25 cm^3	Temporal lobe	right PCr ↑ (23.8%), right β-ATP ↓ (21.4%); Negative correlation between thinking disturbance subscale of the BPRS and left PCr and degree of asymmetry for PCr
Deicken (1995c)	16 medicated patients (40 yo, 16M, 14 yrs), 13 controls (42 yo, 13M)	CSI 25 cm^3	Frontal lobe	PDE ↑ (12.2%), Association of lower left PME with fewer categories achieved, lower percent conceptual level, and greater total errors on WCST performance
Kato (1995)	27 patients (10 neuroleptic-free, 17 medicated, 30 yo, 12M/15F, 7 yrs), 26 controls (34 yo, 11M/15F)	CSI	Frontal lobe	PME ↓ (left 29.2%, right 26.9%), left β-ATP ↑ (19.8%), left PCr ↑ (Patients with high negative symptoms, 14.1%)
Keshavan (1995a)	15 drug-naive, first-episode patients (9 schizophrenia, 6 other psychotic disorder)	DRESS 15-20 cm^3	Prefrontal cortex (left + right)	Negative correlation between pretreatment PDE and improvement in BPRS positive symptoms
Keshavan (1995b)	19 neuroleptic free patients (14 schizophrenia, 4 psychotic depression, 1 unspecified psychosis, 29 yo, 9M/10F, 8 yrs), 19 controls (29 yo, 9M/10F)	DRESS 15-20 cm^3	Prefrontal cortex (left + right)	Correlation between PME and stage 4 sleep
Stanley (1995)	29 patients (11 drug-naive, 26 yo, 8M/3F, 2yrs; 8 newly diagnosed medicated, 23 yo, 8M, 4yrs; 10 long-term medicated, 43 yo, 9M/1F, 18 yrs), 21 controls (31 yo, 17M/4F)	FROGS 15-20 cm^3	Prefrontal cortex (left)	PME ↓ (20% in all three patient group), PDE ↑ (drug-naive patients), Pi ↓ (newly diagnosed patients)

Williamson (1995)	19 medicated patients (12yrs), 18 controls (matched for age, handedness, education, parental education)	FROGS 15-20 cm^3	Prefrontal cortex (left)	PME ↓, Negative correlation between SANS score and both β-ATP and PCr
Fukuzako (1996)	31 medicated patients (39 yo, 22M/9F, 16yrs), 31 controls (40 yo, 22M/9F)	CSI 72 cm^3	Temporal lobe	PDE ↑ (left 3.9%, right 5.1%), left β-ATP ↓ (9.3%), Correlation between BPRS positive symptoms and left PDE
Hinsberger (1997)	10 patients (5 neuroleptic-free, 5 medicated, 35 yo, 8M/2F, 12yrs), 10 controls (27 yo, 9M/1F)	FROGS 15-20 cm^3	Prefrontal cortex (left)	PME ↓ (21.0%), No correlation between PME and prefrontal grey matter volume
Shioiri (1997)	36 patients (9 neuroleptic free, 27 medicated, 30 yo, 22M/14F, 7yrs)	DRESS	Prefrontal lobe (left + right)	PME ↓ in patients with disorganized type, Correlation of decreased PME with psychomotor retardation, Association between increased PDE and emotional withdrawal and blunted affect
Volz (1997a)	13 medicated patients (30 yo, 11M/6F, 7 yrs), 14 controls (33 yo, 10M/4F)	ISIS 39 cm^3	Prefrontal cortex (left + right)	PDE ↓ (7.0%)
Volz (1997b)	60 patients (10 neuroleptic-free, 34 yo, 6M/4F, 6 yrs; 50 medicated, 38 yo, 31M/19F, 10 yrs), 36 controls (35 yo, 20M/16F)	ISIS 39 cm^3	Prefrontal cortex (left + right)	PCr ↑ (neuroleptic-treated 11.0%), PDE ↓ (neuroleptic-free 8.6%, neuroleptic-treated 6.8%); In neuroleptic-free patients, correlations of SANS total score with ATP (negative), PCr/ATP (positive), and Pi (positive) were observed.
Christensen (1998)	17 patients (8 neuroleptic-free, 11 medicated), 19 controls	CSI 60 cm^3	Prefrontal cortex (left + right)	No significant difference between the groups; Inverse correlation between PDE and positive symptoms after 4 weeks of haloperidol treatment
Volz (1998a)	26 medicated patients (42 yo, 18M/8F, 12 yrs), 23 controls (35 yo, 11M/12F)	ISIS 39 cm^3	Prefrontal cortex (left + right)	PME ↑ (11.0%); Negative correlation between PCr and PCr/ATP and WCST performance only in controls
Volz (1998b)	50 patients (47 medicated, 38 yo, 31M/19F, 10 yrs), 36 controls (35 yo, 20M/16F)	ISIS 39 cm^3	Prefrontal cortex (left + right)	PDE ↓(6.8%), PCr ↑ (11.0%)
Blüml (1999)	13 patients (2 neuroleptic-naive, 11 medicated, 34 yo), 15 controls (25 yo)	^{1}H-D PRESS 98 cm^3	Parietal lobe	GPC ↑ (25.8%), GPE ↑ (18.1%), PME ↑ (27.8%), PCr ↑ (9.2%)
Fukuzako (1999a)	17 neuroleptic-naive patients (23 yo, 10M/7F, 0.5 yrs), 17 controls (23 yo, 10M/7F)	CSI 72 cm^3	Temporal lobe	PME ↓ (bilateral 9.0%), PDE ↑ (bilateral 8.1%), left PCr ↑ (10.3%)
Fukuzako (1999b)	13 drug-naive, first-episode patients (23 yo, 7M/6F, 0.6 yrs), 13 controls (22 yo, 7M/6F)	CSI 72 cm^3	Temporal lobe	left PDE ↓ by 12 weeks of haloperidol (4.5%), Positive correlation between PDE decrease and BPRS positive symptom reduction
Potwarka (1999)	11 medicated patients (46 yo, 10M/1F, 21 yrs), 11 controls (45 yo, 10M/1F)	1H-D CSI 27 cm^3	Prefrontal region	PC ↓ (left 20.0%, right 15.2%), PDE ↑ (left 10.5%, right 8.1%), MP ↑ (left 14.6%, right 10.3%), Pi ↓ (left 42.8%, right 33.1%); Negative correlation between SANS and right prefrontal β-ATP
Riehemann (1999)	51 patients (31M/20F), 32 controls (19M/13F)	ISIS 39 cm^3	Frontal lobe	Pi ↑ and PCr ↓ in female controls compared to male controls, No such gender difference in schizophrenic patients
Stanley (1999)	15 drug-naive, first-episode patients (9 with FH, 21 yo, 8M/1F; 6 without FH, 20 yo, 4M/2F), 39 controls (without FH, 21 yo, 28M/11F)	DRESS 15-20 cm^3	Prefrontal cortex (left + right)	PME ↓ (patients with FH vs. controls); Negative correlation between PME, PDE, and β-ATP levels with time in patients without FH
Volz (1999)	8 patients (36 yo, 5M/3F, 6 yrs)	ISIS 39 cm^3	Frontal lobe	left PDE ↓ (15.3%), right PDE ↑ (4.9%) by 3 weeks of neuroleptic treatment
Puri (2000)	A 31-year-old neuroleptic-free man	CSI		PME ↓, PDE ↓ after 6 months eicosapentaenoic acid treatment
Volz (2000)	11 patients (7drug-naive, 4 neuroleptic-free, 33 yo, 8M/3F, 7 yrs), 11 controls (34 yo, 8M/3F)	CSI 19cm^3	Frontal lobe	right PDE ↓, left PCr ↓, right ATP ↓

Abbreviations: ATP, Adenosine triphosphates; BPRS, Brief Psychiatric Rating Scale; CSI, Chemical Shift Imaging; DRESS, Depth-Resolved Surface Coil Spectroscopy; F, Female; FH, Family History; FROGS, Fast Rotating Gradient Spectroscopy; GPC, Glycerophosphocholine; GPE, Glycerophosphoetanolamine; 1H-D, 1H-Decoupled; ISIS, Image-Selected In Vivo Spectroscopy; M, Male; PC, Phosphocholine; PCr, Phosphocreatine; PDE, Phosphodiesters; Pi, Inorganic Orthophosphate; PME, Phosphomonoesters; PRESS, Point-Resolved Spectroscopy; SANS, Scale for the Assessment of Negative Symptoms; WCST, Wisconsin Card Sorting Test; yo, years old
Demographic variables and MRS technique were not fully described in several studies.

healthy controls (Pettegrew et al 1991; Stanley et al 1995). Medicated patients have also showed decreased PME (Williamson et al 1991; Kato et al 1995; Hinsberger et al 1997) and increased PDE (Deicken et al 1994) in their frontal lobes. Some reports have found an association between the decrease in frontal lobe PME and negative symptoms, poor performance on the Wisconsin Card Sorting Test (WCST), and reduced slow wave sleep (Shioiri et al 1994; Keshavan et al 1995b; Deicken et al 1995c). The magnitude of the phospholipid abnormalities (PME decrease and PDE increase) in the frontal lobes may be greater in patients with the disorganized subtype than in those with other subtypes (Shioiri et al 1997). On the other hand, Volz et al (2000) found a reduction in PDE levels in the frontal lobe of neuroleptic-free schizophrenic patients. They also demonstrated a decrease in PDE (Volz et al 1997a, 1997b, 1998a, 1998b) and an increase in PME (1998a) in the frontal lobes of medicated schizophrenic patients. In order to elucidate the relationship between morphologic change in brain structures and phosphorus metabolite levels, Hinsberger et al (1997) compared phosphorus metabolites and the volume of the prefrontal cortex in patients and healthy subjects. While PME concentrations were lower in the patient group, the prefrontal grey matter volume was not significantly different in the two groups, and the level of PME did not correlate with the left prefrontal grey matter volume in the schizophrenic patients. These findings suggest that phosphorus metabolite abnormalities may antedate the morphologic changes observed in schizophrenia. The volume of the anterior portion of the corpus callosum correlated with the concentration of prefrontal PDE (Keshavan et al 1993). This finding was interpreted as suggesting that failure to 'prune' callosal axons may be related to impaired prefrontal cortical proliferation.

Few studies have investigated phosphorus metabolites in the temporal lobes. ^{31}P-MRS specifically investigating the temporal lobes has yielded contradictory results in medicated schizophrenic patients (Kegeles et al 1998; McClure et al 1998). An increase in PDE among schizophrenic patients was noted by three groups of investigators (Calabrese et al 1992; Fujimoto et al 1992a; Fukuzako et al 1994, 1996), while two other groups found no difference between schizophrenic patients and controls (O'Callaghan et al 1991; Deicken et al 1995b). Reduced PME levels in the temporal lobes have not been reported. Neuroleptic-naive patients showed higher levels of PDE and lower levels of PME in the temporal lobes than healthy subjects (Fukuzako et al 1999a). In long-term medicated schizophrenic patients, a positive correlation was observed between the PDE level in the left temporal lobe and the positive symptom score on the Brief Psychiatric Rating Scale (BPRS) (Fukuzako et al 1996). These results suggest that membrane phospholipid metabolism is disturbed in both temporal lobes of drug-naive schizophrenic patients, and that the disturbance in the left temporal lobe is associated with neuroleptic-resistant positive symptoms in chronic schizophrenic patients.

MRS methods employed in the above mentioned studies could not discriminate which PME and PDE components contribute to the changes in resonance observed in schizophrenic patients. Several recent studies have used ^{1}H-decoupled ^{31}P-MRS to try to resolve this problem (Blüml et al 1999; Potwarka et al 1999). A preliminary study found that PC is decreased and mobile phospholipids (MP) of PDE are increased in the frontal lobes of schizophrenic patients with long-term medication (Potwarka et al 1999). Blüml et al (1999) have demonstrated elevations of PME, GPE and GPC concentrations in the parietal lobes of medicated schizophrenic patients compared with healthy controls. PME was decreased in the frontal lobe in drug-naive schizophrenic patients, suggesting a disturbance in the production of membrane phospholipids. No ^{1}H-decoupled ^{31}P-MRS study of temporal lobes in schizophrenic patients has been reported. A preliminary study of *in vitro* ^{31}P-MRS in the temporal lobes of post-mortem brains showed a nonsignificant decrease in the amount of phosphoethanolamine (PE) and increases in GPE and GPC in schizophrenic subjects; these changes were smaller than, but otherwise similar to, *in vivo* findings (Williamson et al 1996). Stanley et al (1997, 1999) used another technique, with application of a longer preacquisition delay time, to extract components that contribute to the breakdown and production of membrane phospholipids.

• Membrane phospholipids and phospholipase A_2

In vivo detection of abnormalities in membrane phospholipids in schizophrenic brains by ^{31}P-MRS further emphasizes the importance of lipid neurochemistry in understanding the pathophysiology of schizophrenia. There is abundant evidence that lipids and fatty acids play important roles in brain neurotransmission. Changes in rat brain fatty acid concentrations induced by dietary fatty acid deficiency alter dopaminergic and serotonergic neurotransmission (Delion et al 1994; de-la-Presa-Owens and Innis 1999) and induce an increase in 5-HT_2 and a decrease in D_2 receptor density in the frontal cortex (Delion et al 1996). Fatty acids have been reported to modify agonist binding affinity for several neurotransmitters, including dopaminergic, GABAergic, cholinergic and NMDA receptors (Miller et al 1992; Witt and Nielsen 1994; Chalon et al 1998; Kjome et al 1998). A number of studies have suggested that membrane phospholipids are altered in patients with schizophrenia. Phosphatidylethanolamine was found to be decreased in the frontal lobe (Horrobin et al 1991) and caudate region (Yao et

al 2000) of post-mortem brains of schizophrenic patients. The rate of turnover of platelet arachidonic acid (AA) and phosphatidylinositol has been reported to be accelerated in schizophrenia (Demisch et al 1987; Vial and Piomelli 1995; Yao et al 1992). In addition, most of the studies that have measured the tissue concentrations of essential fatty acids found that schizophrenia is associated with a deficiency in AA and docosahexaenoic acid (DHA) in the cell membrane (Walker et al 1999; Fenton et al 2000). Decreased concentrations of AA and DHA in RBC phospholipids have been found in patients presenting primarily with negative symptoms (Glen et al 1994), and the severity of the positive symptoms was inversely related to dietary eicosapentaenoic acid (EPA) (Mellor et al 1995). In addition, administration of EPA resulted in a reduction in the Positive and Negative Syndrome Scale (PANSS) score of treatment-resistant patients by 24% (Peet and Mellor 1998). Puri et al (2000) reported a patient with schizophrenia who was treated only with EPA and who was completely remitted of his symptoms for more than two years. His repeated MRI scans, performed before and six months after EPA treatment, showed normalization of the cerebral atrophy. Serial ^{31}P-MRS revealed a decrease in PME and PDE, suggesting a reduced neuronal membrane phospholipid turnover caused by the EPA supplementation.

Many enzymes are candidates for producing the phospholipid abnormalities that characterize schizophrenia, and phospholipid catabolic enzyme phospholipase A_2 (PLA_2) is one of the front-runners. PLA_2 is a key enzyme in the metabolism of phospholipids that also affects receptor function and signal transduction (Farooqui et al 1992; Horrobin and Bennett 1999). Biochemical studies found higher serum, platelet and brain PLA_2 activity in schizophrenic patients than in healthy controls (Gattaz et al 1987, 1995; Noponen et al 1993; Ross et al 1997, 1999), although contradictory results have also been published (Albers et al 1993; Katila et al 1997; Doris et al 1998). In post-mortem studies of the brains of schizophrenic patients, calcium-independent PLA_2 activity has been shown to be higher in the temporal cortex than it is in the brains of matched controls (Ross et al 1999). This finding seems to be consistent with the increased PDE found in temporal lobes of schizophrenic patients (Fukuzako et al 1999a). However, our preliminary investigation of both the phosphorus metabolites observable by ^{31}P-MRS and serum PLA_2 activity in 21 neuroleptic-naive schizophrenic patients failed to demonstrate any significant correlation between these two parameters (unpublished data). This result could imply that the rise in the PDE level in schizophrenic patients is not a direct effect of higher serum PLA_2 activity. However, the failure to identify an association may reflect technical factors involved in measuring PDE resonance by MRS.

• High-energy phosphates

Pettegrew et al (1991) demonstrated that the levels of β-ATP are higher and Pi levels are lower in the prefrontal cortex of drug-naive patients than in controls. In contrast, the levels of ATP and PCr were decreased in frontal lobes of neuroleptic-free patients (Volz et al 2000). No significant differences in any high-energy phosphate metabolite were found between drug-naive patients and healthy control subjects in another study (Stanley et al 1995). Several groups of investigators have reported changes in the Pi, PCr and ATP levels in the frontal lobes of medicated schizophrenic patients; however, the direction of their change was not consistent across studies (increase vs. decrease; Pi 1:2, PCr 2:1, ATP 1:0) (Williamson et al 1991, 1995; Fujimoto et al 1992a; Kato et al 1995; Stanley et al 1995; Volz et al 1997b, 1998b; Potwarka et al 1999). The one relatively consistent finding is a higher PCr in medicated patients than in controls. The PCr decrease reported by Fujimoto et al (1992a) was observed in the left *medial* frontal lobe. On the other hand, studies presenting an increase in PCr obtained signals from the *dorsal* prefrontal lobe (Williamson et al 1991, 1995; Volz et al 1997b, 1998b). Patients who presented with predominantly negative symptoms (n=14) showed an increase in frontal PCr, while data from the whole patient group (n=27) were not different from those in controls (Kato et al 1995). The dorsal part of the frontal lobe has been reported to be related to negative symptoms (Liddle et al 1992; Kaplan et al 1993). Volz et al (1997b) reported that the % PCr is increased in neuroleptic-treated patients whereas no differences were detected in neuroleptic-free patients. In addition, the degree of negative symptoms correlated inversely with the ATP level and positively with the PCr/ATP ratio. These authors suggested that the energy demand in the frontal lobes is reduced by either neuroleptics or a trait in schizophrenic patients with predominantly negative symptomatology. These results are consistent with the report of a decreased activation pattern in the frontal lobes of schizophrenic patients with high negative symptoms (Catafau et al 1994). In contrast, one study demonstrated a negative correlation between the PCr level and negative symptoms (Williamson et al 1995). The % PCr and PCr/ATP ratio were reported to be inversely correlated with WCST performance in healthy subjects but not in schizophrenic patients (Volz et al 1998a). These correlations may represent an association between reduced performance in a specific frontal lobe task and decreased energy demand at rest. The authors speculated that the lack of correlation in schizophrenic patients might be caused by a ceiling effect during mental activity or may be a direct effect of neuroleptic medication.

Fukuzako et al (1999a) demonstrated that the level of PCr is increased in the left temporal lobe of neuroleptic-naive schizophrenic patients. PCr

is known to be transformed rapidly into ATP when ATP is consumed by neuronal activity (Sappey-Marinier et al 1992). An increased percentage of PCr may represent reduced ATP utilization in the left temporal lobe of neuroleptic-naive schizophrenic patients. This asymmetric abnormality in energy metabolism agrees with the left-sided functional impairments observed in the temporal lobes of schizophrenic patients by single photon emission computed tomography (SPECT) (Catafau et al 1994; Klemm et al 1996; Russell et al 1997). However, these findings appear to contradict the increased glucose utilization in the left temporal lobe identified by positron emission tomography (PET) (DeLisi et al 1989; Gur et al 1995). A negative correlation was noted between the thought disturbance subscale of the BPRS and the PCr/β-ATP ratio bilaterally in the temporal lobes (Calabrese et al 1992). Using a more advanced MRS technique, the same group of investigators demonstrated a higher right relative to left temporal PCr/ATP ratio, PCr/Pi ratio and % PCr, as well as significantly lower right relative to left temporal lobe ATP (Deicken et al 1995b). No asymmetries in temporal lobe phosphorus metabolites were observed in the control group. In addition, both the left temporal PCr level and the degree of asymmetry in the temporal lobe PCr level showed a high negative correlation with the thought disturbance subscale of the BPRS. Their results suggest a link between impaired high-energy phosphate metabolism and thought disturbance in schizophrenic patients. Our studies, however, did not show any significant associations between high-energy phosphate metabolites and specific symptoms in either neuroleptic-naive or chronically medicated patients (Fukuzako et al 1996, 1999a).

The PCr concentration was increased in the parietal lobe of medicated schizophrenic patients, implying decreased energy demand in this region (Blüml et al 1999). Two reports have found lower ATP concentrations in the basal ganglia, suggesting an imbalance between ATP production and ATP utilization by oxidative phosphorylation (Fujimoto et al 1992b; Deicken et al 1995a).

Except for the reduction in the ATP level in the basal ganglia and the correlation between the increase in the PCr level in the frontal lobe and negative symptomatology, data related to high-energy phosphates in schizophrenia are contradictory.

• Neuroleptics and phosphorus metabolites

Neuroleptics have been reported to affect regional cerebral blood flow and glucose metabolism, although the direction of reported changes in these parameters has not been consistent across studies (Nilsson et al 1977; Gur et al 1985; Berman et al 1996; Miller et al 1997; Bartlett et al 1998; Buchsbaum and Hazlett 1998). Few MRS studies have examined the effects of neuroleptics on phosphorus metabolites. Stanley et al (1994) observed an increase in the % PDE in left prefrontal cortex in newly diagnosed patients but not in chronic patients. It is not certain whether this difference between groups is due to chronicity of illness or neuroleptic treatment. Keshavan et al (1995a) reported that the levels of PDE were increased at pretreatment imaging and no significant change in PDE was observed after four weeks of haloperidol treatment. Volz et al (1999) performed serial ^{31}P-MRS of the frontal lobe in schizophrenic patients first after a one-week neuroleptic-free period and second after three weeks of neuroleptic treatment. The % PDE increased significantly in the left frontal lobe and tended to decrease on the right with medication. Therefore, it is not yet possible to determine what neuroleptic-induced changes in phosphorus metabolites occur in the frontal lobe.

Fukuzako et al (1999b) examined changes in the levels of phosphorus metabolites in the temporal lobes following a 12-week administration of haloperidol. Prior to treatment, the patients had higher levels of PDE in both temporal lobes than healthy subjects. Haloperidol administration significantly reduced the excess PDE in the left temporal lobe, although the PDE level remained somewhat higher bilaterally than in controls. Treatment was associated with a decline in the total BPRS symptom score, and the decline in the positive symptom score correlated highly with the reduction of the PDE in the left temporal lobe. The PDE reduction in the right temporal lobe showed a weak correlation with the decline in the positive symptom score. The total amount of haloperidol did not correlate significantly with changes in any metabolite levels. The authors suggested that haloperidol may partially normalize the disturbed metabolism or correct abnormalities in membrane phospholipid components in the left temporal lobe of untreated schizophrenic patients, and that these changes are responsible for symptom alleviation. These *in vivo* results seem to be consistent with biochemical findings which demonstrate that supernormal PLA_2 activity is reduced by neuroleptic administration (Gattaz et al 1987, 1995), even though it remains higher than in healthy subjects (Ross et al 1997). Neuroleptics may alter brain phospholipid metabolism and composition by regulating PLA_2 activity in a manner similar to that seen in platelets and RBCs. In fact, the PLA_2 activity in rat brain plasma membranes declined after either a single dose or four-week administration of chlorpromazine, trifluoperazine, haloperidol and sulpiride (Trzeciak et al 1995). Moreover, a two-week course of haloperidol in rats reduced calcium-independent PLA_2 by 21% in the striatum (Ross et al 1999). Additionally, haloperidol has been shown to reduce the synthesis of a number of phospholipids in

rat brain (Singh and Shankar 1996). It is unknown whether typical and atypical neuroleptics have any different effects on the ^{31}P-MR spectrum in humans. Administration of haloperidol and clozapine for three weeks increased the level of γ-, β-, and α-ATP in the brains of rats (Skinner et al 1995). Clozapine was shown to be associated with a rise in the RBC membrane concentrations of several polyunsaturated fatty acids (Horrobin et al 1997). Effects of neuroleptics on membrane phospholipid metabolism and composition remain areas of active investigation.

It is a matter of debate whether prediction of treatment response is possible using ^{31}P-MRS. Keshavan et al (1995a) reported that poor response to neuroleptic treatment was associated with the higher pretreatment % PDE in the prefrontal cortex of psychotic patients. Christensen et al (1998) investigated whether regional brain concentration of phosphorus metabolites predicted the level of residual symptoms after four weeks of neuroleptic treatment. The prefrontal PDE concentration in schizophrenic patients was not different from the concentration in controls. However, the positive and the negative symptom score each correlated negatively with the prefrontal PDE concentration. These results suggest that the PDE concentration is associated with a trait that determines the responsiveness to drug treatment and is consistent with the findings of Keshavan et al (1995a). On the other hand, no pretreatment level of any metabolite in the temporal lobe predicted treatment response (Fukuzako et al 1999b).

Future directions of ^{31}P-MRS research

As described above, results of ^{31}P-MRS studies are often inconsistent. Age and gender are potential confounding factors. The PCr level (expressed as PCr/ATP or % PCr) in the frontal lobes has been reported to correlate positively with age (Longo et al 1993; Smith et al 1995). On the other hand, one study has shown that PME levels in the dorsal prefrontal cortex decrease and PDE levels increase with age, without age-related changes in the levels of Pi, PCr and ATP (Pettegrew et al 1995). Riehemann et al (1999) have demonstrated that healthy women have higher Pi and lower PCr levels in their frontal lobes than men, but gender differences were not observed in schizophrenic patients. However, age and gender were comparable between schizophrenic patients and comparison subjects in most published studies (Table 1). The number of subjects that have been recruited for MRS studies so far is relatively low (9-60 schizophrenic patients). As schizophrenia is characterized by heterogeneity in symptomatology, treatment response, clinical course and other features, inconsistencies between published data may reflect differences in patient characteristics. More than 100 subjects are needed to clarify the degree of contribution of these factors to MRS results. Because the effects of neuroleptics and other drugs on the MRS spectra have yet to be determined, investigation with a prospective design in neuroleptic-naive patients is essential.

There is no doubt that genetic factors contribute to the aetiology of schizophrenia. Data from brain imaging studies such as MRS may help identify intermediate phenotypes linking genetic factors and clinical phenotypes. An association between a genetic marker and cerebral ventricular enlargement and parietal cortex atrophy has already been reported (Shihabudin et al 1997). The existence of an association between allele 3 of neurotrophin-3 and reduced hippocampal volume has also been suggested (Kunugi et al 1999). Wassink et al (1999) failed to demonstrate an association between the presence of allele 1 of brain-derived neurotrophic factor and schizophrenia. Subjects who had at least one copy of allele 1, however, had larger parietal lobes than those who did not when controlling for overall cortical volume and age at the time of MRI. Subjects with the 9-repeat/10-repeat genotype showed a significant reduction in dopamine transporter protein availability in the putamen compared with 10-repeat homozygous individuals (Heinz et al 2000). These findings suggest that allelic variability influences brain morphology and function in humans. On the other hand, D_2 receptor binding potential, as measured by ^{123}I-IBZM SPECT, was not related to TaqI polymorphism at the D_2 receptor gene (Laurelle et al 1998). To date, no study has attempted to correlate phosphorus MRS data with a specific gene or genetic marker. Reported associations between polymorphisms of cytosolic PLA_2 (excess of long poly-A repeats, variation in the BAN-1 polymorphism site in the first intron) and schizophrenia are contradictory (Hudson et al 1996; Price et al 1997; Doris et al 1998; Peet et al 1998; Wei et al 1998). The combined examination of phosphorus MRS, PLA_2 activity and gene polymorphism of PLA_2 may determine whether MRS phosphorus metabolite abnormalities are caused by gene-related aberrant PLA_2 activity. However, the genetic coding of calcium-independent PLA_2 has not yet been determined (Horrobin and Bennett 1999), and this is the type of PLA_2 that is believed to be most intimately involved in the pathophysiology of schizophrenia (Ross et al 1997). Similar investigations of other enzymes, such as phospholipase C, phospholipase D, fatty acid coenzyme A ligases and acyl-coenzyme A: lyso-phospholipid acyltransferase, are also important in the clarification of enzyme-MRS parameter relationships.

Reports examining relationships between MRS and genetic factors in schizophrenia are rare. Stanley et al (1999) presented preliminary results that the levels of PME were decreased in the prefrontal lobes of neuroleptic-naive schizophrenic patients, and that the reduction in PME

was more pronouced in patients with a family history of mental illness. In addition, longitudinal investigation revealed that the % PME decreased progressively more in patients without a family history of mental illness compared with patients with such a family history. Keshavan et al (1991) presented a patient who showed decreased PME levels and increased PDE levels by ^{31}P-MRS prior to the onset of schizophrenia. This finding suggests that a person with genetic predisposition to schizophrenia has membrane phospholipid pathology that antedates the first outbreak. Hopefully, clinical studies will help to identify children at high risk of developing schizophrenia, and will guide clinicians towards early intervention. ^{1}H-MRS may also play a role in detecting such pathology (Callicott et al 1998). Longitudinal investigation of high-risk children using ^{31}P-MRS and ^{1}H-MRS may help to discriminate between the children who will and those who will not develop schizophrenia. In addition, ^{31}P-MRS studies in monozygotic twins discordant for schizophrenia may offer valuable information on the pathophysiology of schizophrenia.

Cognitive dysfunction, as measured by electroencephalography and evoked potentials, has been reported in schizophrenic patients (McCarley et al 1993; Takeuchi et al 1994; Hughes 1996; Adler et al 1999). A number of neurochemical abnormalities, involving neurotransmitters, neurotrophic factors and cytokines, have also been observed in schizophrenic patients (Byne et al 1999; Muller et al 1999). No correlative studies between these parameters and ^{31}P-MRS in schizophrenic patients have been published, as far as I know.

Methodological problems that limit the interpretation of earlier findings need to be overcome. First, reliability is improved by fully automated processing of data. Second, most previous studies employed mole percentages of total phosphorus metabolites. Absolute metabolite quantitation is preferable, although it is time-consuming and is easily affected by the partial volume effect, as compared with metabolite percentage. Third, sophisticated software that collects signals from grey matter, white matter and CSF separately may be better able to determine how subtle morphologic abnormalities in schizophrenic patients might interact with phosphorus MRS findings *in vivo*. However, ^{31}P-MRS is only about 5% as sensitive as ^{1}H-MRS, primarily because of the lower gyromagnetic ratio of ^{31}P, which hampers correction for the partial volume effect. MRS with higher magnetic field strengths of 3.0-7.0 tesla will improve both the signal-to-noise ratio and spectral resolution. The next generation of ^{31}P-MRS, which addresses these problems, will soon be available (Blüml et al 1999; Jensen et al 1999; Potwarka et al 1999). Combined investigations using improved ^{31}P-MRS and molecular genetics will offer new opportunities to identify the causes of disturbances in membrane phospholipid and high-energy phosphate metabolisms, and should expand our knowledge of the pathophysiology of schizophrenia.

Acknowledgments

This study was partially supported by Grants-in-Aid from the Ministry of Education, Science, Sports and Culture (03770738, 05770735, 06770764 and 10672129) and the National Center of Psychiatry and Neurology of the Ministry of Health and Welfare (3A-5) of Japan (Dr. H. Fukuzako).

References

Adler LE, Freedman R, Ross RG, Olincy A, Waldo MC (1999) Elementary phenotypes in the neurobiological and genetic study of schizophrenia. Biol Psychiatry 46: 8-18.

Albers M, Meurer H, Märki F, Klotz J (1993) Phospholipase A_2 activity in serum of neuroleptic-naive psychiatric inpatients. Pharmacopsychiatry 26: 94-98.

Andreasen NC, O'Leary DS, Flaum M, Nopoulos P, Watkins GL, Ponto LLB, Hichwa RD (1997) Hypofrontality in schizophrenia: Distributed dysfunctional circuits in neuroleptic-naïve patients. Lancet 349: 1730-1734.

Bartlett EJ, Brodie JD, Simkowitz P, Schlösser R, Dewey SL, Lindenmayer J-P, Rusinek H, Wolkin A, Cancro R, Schiffer W (1998) Effect of a haloperidol challenge on regional brain metabolism in neuroleptic-responsive and nonresponsive schizophrenic patients. Am J Psychiatry 155: 337-343.

Berman I, Merson A, Sison C, Allan E, Schaefer C, Loberboym M, Losonczy MF (1996) Regional cerebral blood flow changes associated with risperidone treatment in elderly schizophrenia patients: A pilot study. Psychopharmacology Bull 32: 95-100.

Blüml S, Tan J, Harris K, Adatia N, Karme A, Sproull T, Ross BD (1999) Quantitative proton-decoupled ^{31}P MRS of the schizophrenic brain in vivo. J Comp Assist Tomogr 23: 272-275.

Bottomley PA (1989) Human in vivo NMR spectroscopy in diagnostic medicine: Clinical tool or research probe ? Radiology 170: 1-15.

Buchsbaum MS, Hazlett EA (1998) Positron emission tomography studies of abnormal glucose metabolism in schizophrenia. Schizophr Bull 24: 343-364.

Byne W, Kemether E, Jones L, Haroutunian V, Davis KL (1999) The neurochemistry of schizophrenia. In: Charney DS, Nestler EJ, Bunney BS (eds) Neurobiology of Mental Illness. Oxford University Press, Oxford, pp 236-245.

Calabrese G, Deicken RF, Fein G, Merrin EL, Schoenfeld F, Weiner MW (1992) ^{31}Phosphorus magnetic resonance spectroscopy of the temporal lobes in schizophrenia. Biol Psychiatry 32: 26-32.

Callicott JH, Egan MF, Bertolino A, Mattay VS, Langheim FJP, Frank JA, Weinberger DR (1998) Hippocampal N-acetyl aspartate in unaffected siblings of patients with schizophrenia: A possible intermediate neurobiological phenotype. Biol Psychiatry 44: 941-950.

Catafau AM, Parellada E, Lomeña FJ, Bernardo M, Pavía J, Ros D, Setoain J, Gonzalez-Monclús E (1994) Prefrontal and temporal blood flow in schizophrenia: Resting and activation technetium-99m-HMPAO SPECT patterns in young neuroleptic-naive patients with acute disease. J Nucl Med 35: 935-941.

Chalon S, Delion-Vancassel S, Belzung C, Guilloteau D, Leguisquet

AM, Besnard JC, Durand G (1998) Dietary fish oil affects monoaminergic neurotransmission and behavior in rats. J Nutr 128: 2512-2519.

Christensen JD, Holcomb J, Nair TR, Garver DL (1998) Schizophrenic prefrontal [PDE] correlates with residual symptoms following neuroleptic treatment (abstract). Proc 6th Ann Scientific Meeting SMR, p 503.

de-la-Presa-Owens S, Innis SM (1999) Docosahexaenoic and arachidonic acid prevent a decrease in dopaminergic and serotonergic neurotransmitters in frontal cortex caused by a linoleic and alpha-linolenic acid deficient diet in formula-fed piglets. J Nutr 129: 2088-2093.

Deicken RF, Calabrese G, Merrin EL, Meyerhoff DJ, Dillon WP, Weiner MW, Fein G (1994) ^{31}Phosphorus magnetic resonance spectroscopy of the frontal and parietal lobes in chronic schizophrenia. Biol Psychiatry 36: 503-510.

Deicken RF, Calabrese G, Merrin EL, Fein G, Weiner MW (1995a) Basal ganglia phosphorous metabolism in chronic schizophrenia. Am J Psychiatry 152: 126-129.

Deicken RF, Calabrese G, Merrin EL, Vinogradov S, Fein G, Weiner MW (1995b) Asymmetry of temporal lobe phosphorus metabolism in schizophrenia: A ^{31}Phosphorus magnetic resonance spectroscopic imaging study. Biol Psychiatry 38: 279-286.

Deicken RF, Merrin EL, Floyd TC, Weiner MW (1995c) Correlation between left frontal phospholipids and Wisconsin Card Sorting Test performance in schizophrenia. Schizophr Res 14: 177-181.

Delion S, Chalon S, Herault J, Guilloteau D, Besnard JC, Durand G (1994) Chronic dietary alpha-linolenic acid deficiency alters dopaminergic and serotonergic neurotransmission in rats. J Nutr 124: 2466-2475.

Delion S, Chalon S, Guilloteau D, Besnard JC, Durand G (1996) Alpha-linolenic acid deficiency alters age-related changes of dopaminergic and serotonergic neurotransmission in rats. J Neurochem 66: 1582-1591.

DeLisi LE, Buchsbaum MS, Holcomb HH, Laugston KC, King AC, Kessler R, Pickar D, Carpenter WT, Morihisa JM, Margolin R, Weinberger DR (1989) Increased temporal lobe glucose use in chronic schizophrenic patients. Biol Psychiatry 25: 835-851.

Demisch L, Gerbaldo H, Gebhart P, Georgi K, Bochnik HJ (1987) Incorporation of ^{14}C-arachidonic acid into platelet phospholipids of untreated patients with schizophreniform or schizophrenic disorders. Psychiatry Res 22: 275-282.

Doris AB, Wahle K, MacDonald A, Morris S, Coffey I, Muir W, Blackwood D (1998) Red cell membrane fatty acids, cytosolic phospholipase-A_2 and schizophrenia. Schizophr Res 31: 185-196.

Egan MF, Weinberger DR (1997) Neurobiology of schizophrenia. Curr Opin Neurobiol 7: 701-707.

Ernst T, Kreis R, Ross BD (1993) Absolute quantitation of water and metabolites in the human brain. Part I: Compartments and water. J Magn Reson 102: 1-8.

Farooqui AA, Hirashima Y, Horrocks LA (1992) Brain phospholipases and their role in signal transduction. In: Bazan NG, Murphy MG, Tofano G (eds) Neurobiology of Essential Fatty Acids. Plenum Press, New York, pp 11-26.

Fenton WS, Hibbeln J, Knable M (2000) Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. Biol Psychiatry 47: 8-21.

Frahm J, Michaelis T, Merboldt K-D, Hänicke W, Gyngell ML, Chien D, Bruhn H (1989) Localized NMR spectroscopy *in vivo*: Progress and Problems. NMR Biomed 2: 188-195.

Fujimoto T, Nakano T, Takano T, Fukuzako H, Hokazono Y, Asakura T, Tsuji T (1992a) Study of chronic schizophrenia using ^{31}P chemical shift imaging (abstract). Proc Soc Magn Reson Med, p 1935.

Fujimoto T, Nakano T, Takano T, Hokazono Y, Asakura T, Tsuji T (1992b) Study of chronic schizophrenics using ^{31}P magnetic resonance chemical shift imaging. Acta Psychiatr Scand 86: 455-462.

Fukuzako H, Takeuchi K, Ueyama K, Fukuzako T, Hokazono Y, Hirakawa K, Yamada K, Hashiguchi T, Takigawa M, Fujimoto T (1994) ^{31}P magnetic resonance spectroscopy of the medial temporal lobe of schizophrenic patients with neuroleptic-resistant marked positive symptoms. Eur Arch Psychiatry Clin Neurosci 244: 236-240.

Fukuzako H, Fukuzako T, Takeuchi K, Ohbo Y, Ueyama K, Takigawa M, Fujimoto T (1996) Phosphorus magnetic resonance spectroscopy in schizophrenia: Correlation between membrane phospholipid metabolism in the temporal lobe and positive symptoms. Prog Neuropsychopharmacol Biol Psychiat 20: 629-640.

Fukuzako H, Fukuzako T, Hashiguchi T, Kodama S, Takigawa M, Fujimoto T (1999a) Changes in levels of phosphorus metabolites in temporal lobes of drug-naive schizophrenic patients. Am J Psychiatry 156: 1205-1208.

Fukuzako H, Fukuzako T, Kodama S, Hashiguchi T, Takigawa M, Fujimoto T (1999b) Haloperidol improves membrane phospholipid abnormalities in temporal lobes of schizophrenic patients. Neuropsychopharmacology 21: 542-549.

Gattaz WF, Kollisch M, Thurn T, Virtanen JA, Kinnunen PKJ (1987) Increased plasma phospholipase-A_2 activity in schizophrenic patients: Reduction after neuroleptic therapy. Biol Psychiatry 22: 421-426.

Gattaz WF, Schmitt A, Maras A (1995) Increased platelet phospholipase A_2 activity in schizophrenia. Schizophr Res 16: 1-6.

Glen AIM, Glen EMT, Horrobin DF, Vaddadi KS, Spellman M, Morse-Fisher N, Ellis K, Skinner FS (1994) A red cell membrane abnormality in a subgroup of schizophrenic patients: Evidence for two diseases. Schizophr Res 12: 53-61.

Gur RE, Gur RC, Skolnik BE, Caroff S, Obrist WO, Resnick S, Reirich S (1985) Brain function in psychiatric disorders: III. Regional cerebral blood flow in unmedicated schizophrenics. Arch Gen Psychiatry 42: 329-334.

Gur RE, Mozley PD, Resnick SM, Mozley LH, Shtasel DL, Gallacher F, Arnold SE, Karp JS, Alavi A, Reivich M, Gur RC (1995) Resting cerebral glucose metabolism in first-episode and previously treated patients with schizophrenia relates to clinical features. Arch Gen Psychiatry 52: 657-667.

Harrison PJ (1999) The neuropathology of schizophrenia: A critical review of the data and their interpretation. Brain 122: 593-624.

Heinz A, Goldman D, Jones DW, Palmour R, Hommer D, Gorey JG, Lee KS, Linnoila M, Weinberger DR (2000) Genotype influences *in vivo* dopamine transporter availability in human striatum. Neuropsychopharmacology 22: 133-139.

Hinsberger AD, Williamson PC, Carr TJ, Stanley JA, Drost DJ, Densmore M, MacFabe GC, Montemurro DG (1997) Magnetic resonance imaging volumetric and phosphorus 31 magnetic resonance spectroscopy measurements in schizophrenia. J Psychiatry Neurosci 22: 111-117.

Horrobin DF (1998) The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. Schizophr Res 30: 193-208.

Horrobin DF, Bennett CN (1999) New gene targets related to schizophrenia and other psychiatric disorders: Enzymes, binding proteins and transport proteins involved in phospholipid and fatty acid metabolism. Prostaglandins Leukot Essent Fatty Acids 60: 141-167.

Horrobin DF, Manku MS, Hillman H, Iain A, Glen M (1991) Fatty acid levels in the brains of schizophrenics and normal controls. Biol Psychiatry 30: 795-805.

Horrobin DF, Glen AIM, Cantrill RC (1997) Clozapine: Elevation of membrane unsaturated lipid levels as a new mechanism of action (abstract). Schizophr Res 24: 214.

Hudson CJ, Kennedy JL, Gotowiec A, Lin A, King N, Gojtan K, Macciardi F, Skorecki K, Meltzer Hy, Warsh JJ, Horrobin DF (1996) Genetic variant near cytosolic phospholipase A_2 associated with schizophrenia. Schizophr Res 21: 111-116.

Hugg JW, Matson GB, Twieg DB, Maudsley AA, Sappey-Marinier D, Weiner MW (1992) Phosphorous-31 MR spectroscopic imaging (MRSI) of normal and pathological brains. Magn Reson Imaging 10: 227-243.

Hughes JR (1996) A review of the usefulness of the standard EEG in psychiatry. Clin Electroencephalogr 27: 35-39.

Jensen JE, Drost DJ, Williamson PC, Menon RS (1999) Comparing *in-vivo* brain ^{31}P spectroscopy: 1.5 T ^{1}H-decoupled vs 4.0 T ^{1}H-coupled in normal human volunteers (abstract). Proc 7th Ann Scientific Meeting SMR, p 1419.

Kaplan RD, Szechtman H, Franco S, Szechtman B, Nahmias C, Garnett ES, List S, Cleghorn JM (1993) Three clinical syndromes of schizophrenia in untreated subjects: Relation to brain glucose activity measured by positron emission tomography. Schizophr Res 11: 47-54.

Katila H, Appelberg B, Rimon R (1997) No differences in phospholipase A_2 activity between acute psychiatric patients and controls. Schizophr Res 26: 103-105.

Kato T, Shioiri T, Murashita J, Hamakawa H, Inubushi T, Takahashi S (1995) Lateralized abnormality of high-energy phosphate and bilateral reduction of phosphomonoester measured by phosphorus-31 magnetic resonance spectroscopy of the frontal lobes in schizophrenia. Psychiatry Res Neuroimag 61: 151-160.

Kegeles LS, Humaran TJ, Mann JJ (1998) In vivo neurochemistry of the brain in schizophrenia as revealed by magnetic resonance spectroscopy. Biol Psychiatry 44: 382-398.

Keshavan MS, Pettegrew JW, Panchalingam K, Kaplan D, Bozik E (1991) Phosphorus 31 magnetic resonance spectroscopy detects altered brain metabolism before onset of schizophrenia. Arch Gen Psychiatry 48: 1112-1113.

Keshavan MS, Sanders RD, Pettegrew JW, Dombrowsky SM, Panchalingam KS (1993) Frontal lobe metabolism and cerebral morphology in schizophrenia: ^{31}P MRS and MRI studies. Schizophr Res 10: 241-246.

Keshavan MS, Pettegrew JW, Panchalingam K (1995a) MRS in the study of psychoses: psychopharmacological studies. In: Nasrallah HA, Pettegrew JW (eds) NMR Spectroscopy in Psychiatric Brain Disorders. American Psychiatric Press, Washington DC, pp 131-146.

Keshavan MS, Pettegrew JW, Reynolds CF, Panchalingam KS, Montrose D, Miewald J, Kupfer DL (1995b) Biological correlates of slow wave sleep deficits in functional psychoses: ^{31}P-magnetic resonance spectroscopy. Psychiatry Res 57: 91-100.

Keshavan MS, Stanley JA, Pettegrew JW (2000) Magnetic resonance spectroscopy in schizophrenia: Methodological issues and findings-Part II. Biol Psychiatry 48: 369-380.

Kilby PM, Allis JL, Radda GK (1990) Spin-spin relaxation of the phosphodiester resonance in the ^{31}P NMR spectrum of human brain: the determination of the concentrations of phosphodiester components. FEBS Lett 272: 163-165.

Kilby PM, Bolas NM, Radda GK (1991) ^{31}P-NMR study of brain phospholipid structures in vivo. Biochim Biophys Acta 1085: 257-264.

Kjome JR, Swenson KA, Johnson MN, Bordayo EZ, Anderson LE, Klevan LC, Fraticelli AI, Aldrich SL, Fawcett JR, Venters HD Jr, Ala TA, Frey WH (1998) Inhibition of antagonist and agonist binding to the human muscarinic receptor by arachidonic acid. J Mol Neurosci 10: 209-217.

Klemm E, Danos P, Grünwald F, Kasper S, Möller H-J, Biersack H-J (1996) Temporal lobe dysfunction and correlation of regional cerebral blood flow abnormalities with psychopathology in schizophrenia and major depression: A study with single photon emission computed tomography. Psychiatry Res Neuroimag 68: 1-10.

Kunugi H, Hattori M, Nanko S, Fujii K, Kato T (1999) Dinucleotide repeat polymorphism in the neurotrophin-3 gene and hippocampal volume in psychoses. Schizophr Res 37: 271-273.

Laruelle M, Gelernter J, Innis RB (1998) D_2 receptors binding potential is not affected by Taq1 polymorphism at the D_2 receptor gene. Mol Psychiatry 3: 261-265.

Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T, Frackowiak RSJ (1992) Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry 160: 179-186.

Longo R, Ricci C, Dalla Palma L, Vidimari R, Giorgini A, den Hollander JA, Segebarth CM (1993) Quantitative ^{31}P MRS of the normal adult human brain: Assessment of interindividual differences and aging effects. NMR Biomed 6: 53-57.

Maier M (1995) In vivo magnetic resonance spectroscopy: applications in psychiatry. Br J Psychiatry 167: 299-306.

McCarley RW, Shenton ME, O'Donnell BF, Nestor PG (1993) Uniting Kraepelin and Bleuler: The Psychology of schizophrenia and the biology of temporal lobe abnormalities. Harv Rev Psychiatry 1: 36-56.

McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA, Shenton ME (1999) MRI anatomy of schizophrenia. Biol Psychiatry 45: 1099-1119.

McClure RJ, Keshavan MS, Pettegrew JW (1998) Chemical and physiologic brain imaging in schizophrenia. Psychiat Clin North America 21: 93-122.

McNamara R, Arias-Mendoza F, Brown TR (1994) Investigation of broad resonances in ^{31}P NMR spectra of the human brain in vivo. NMR Biomed 7: 237-242.

Mellor JE, Laugharne JDE, Peet M (1995) Schizophrenic symptoms and dietary intake of n-3 fatty acids. Schizophr Res 18: 85-86.

Miller B, Sarantis M, Traynelis SF, Attwell D (1992) Potentiation of NMDA receptor currents by arachidonic acid. Nature 355: 722-725.

Miller DD, Rezai K, Alliger R, Andreasen NC (1997) The effect of antipsychotic medication on relative cerebral blood perfusion in schizophrenia: Assessment with technetium-99m hexamethylpropyleneamine oxime single photon emission computed tomography. Biol Psychiatry 41: 550-559.

Muller N, Riedel M, Ackenheil M, Schwarz MJ (1999) The role of immune function in schizophrenia: An overview. Eur Arch Psychiatry Clin Neurosci 249: 62S-68S.

Murphy EJ, Rajagopalan B, Brindle KM, Radda GK (1989) Phospholipid bilayer contribution to ^{31}P NMR spectrum in vivo. Magn Reson Med 12: 282-289.

Nilsson A, Risberg J, Johnason M, Gustafson L (1977) Regional changes of cerebral blood flow during haloperidol therapy in patients with paranoid symptoms. Acta Neurol Scand Suppl 64: 478-479.

Noponen M, Sanfilipo M, Samanick K, Ryer H, Ko G, Angrist B, Wolkin A, Duncan E, Rotrosen J (1993) Elevated PLA_2 activity in schizophrenics and other psychiatric patients. Biol Psychiatry 34: 641-649.

Nordahl TE, Kusubov N, Carter C, Salamat S, Cummings AM, O'Shora-Celaya L, Eberling J, Robertson L, Huesman RH, Jagust W, Budinger TF (1996) Temporal lobe metabolic differences in medication-free outpatients with schizophrenia via the PET-600. Neuropsychopharmacology 15: 541-554.

O'Callaghan E, Redmond O, Ennis R, Stack J, Kinsella A, Ennis JT, Larkin C, Waddington JL (1991) Initial investigation of the left temporoparietal region in schizophrenia by ^{31}P magnetic resonance spectroscopy. Biol Psychiatry 29: 1149-1152.

Peet M, Mellor J (1998) Double-blind placebo controlled trial of n-3 polyunsaturated fatty acids as an adjunct to neuroleptics. Presented at the 9th Schizophrenia Winter Workshop. Davos, Switzerland.

Peet M, Ramchand CN, Lee J, Telang SD, Vankar GK, Shah S, Wei J (1998) Association of the Ban I dimorphic site at the human cytosolic phospholipase A2 gene with schizophrenia. Psychiatr Genet 8: 191-192.

Pettegrew JW, Keshavan MS, Minshew NJ, McClure RJ (1995) ^{31}P-MRS of metabolic alterations in schizophrenia and neurodevelopment. In: Nasrallah HA, Pettegrew JW (eds) NMR Spectroscopy in Psychiatric Brain Disorders. American Psychiatric Press, Washington DC, pp 45-77.

Pettegrew JW, Keshavan MS, Panchalingam K, Strychor S, Kaplan DB, Tretta MG, Allen M (1991) Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first-episode, drug-naive schizophrenics: A pilot study of the dorsal prefrontal cortex by in vivo phosphorus 31 nuclear magnetic resonance spectroscopy. Arch Gen Psychiatry 48: 563-568.

Potwarka J, Drost DJ, Williamson PC, Carr T, Canaran G, Rylett WJ, Neufeld RWJ (1999) A ^{1}H-decoupled ^{31}P chemical shift imaging study of medicated schizophrenic patients and healthy controls. Biol Psychiatry 45: 687-693.

Price SA, Fox H, St Clair D, Shaw DJ (1997) Lack of association between schizophrenia and polymorphism close to the cytosolic phospholipase A2 gene. Psychiatr Genet 7: 111-114.

Puri BK, Richardson AJ, Horrobin DF, Easton T, Saeed N, Oatridge A, Hajnal JV, Bydder GM (2000) Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalization of blood fatty acids, reduced neuronal membrane phospholipid turnover and structural brain changes. Int J Clin Pract 54: 57-63.

Riehemann S, Volz H-P, Wenda B, Hübner G, Rößger G, Rzanny R, Sauer H (1999) Frontal lobe *in vivo* ^{31}P-MRS reveals gender differences in healthy controls, not in schizophrenics. NMR Biomed 12: 483-489.

Ross BM, Hudson C, Erlich J, Warsh JJ, Kish SJ (1997) Increased phospholipid breakdown in schizophrenia: Evidence for the involvement of a calcium-independent phospholipase A_2. Arch Gen Psychiatry 54: 487-494.

Ross BM, Turenne S, Moszczynska A, Warsh JJ, Kish SJ (1999) Differential alteration of phospholipase A_2 activities in brain of patients with schizophrenia. Brain Res 821: 407-413.

Russell JM, Early TS, Patterson JC, Martin JL, Villanneva-Meyer J, McGee MD (1997) Temporal lobe perfusion asymmetries in schizophrenia. J Nucl Med 38: 607-612.

Sabri O, Erkwoh R, Schreckenberger M, Owega A, Sass H, Buell U (1997) Correlation of positive symptoms exclusively to hyperperfusion or hypoperfusion of cerebral cortex in never-treated schizophrenics. Lancet 349: 1735-1739.

Sappey-Marinier D, Calabrese G, Fein G, Hugg JW, Biggins C, Weiner MW (1992) Effect of photic stimulation on human visual cortex lactate and phosphates using ^{1}H and ^{31}P magnetic resonance spectroscopy. J Cereb Blood Flow Metab 12: 584-592.

Shihabuddin L, Silverman JM, Buchsbaum MS, Siever LJ, Luu C, Germans MK, Metzger M, Mohs RC, Smith CJ, Spiegel-Cohen J, Davis KL (1997) Ventricular enlargement associated with linkage marker for schizophrenia-related disorders in one pedigree. Mol Psychiatry 1: 215-222.

Shioiri T, Kato T, Inubushi T, Murashita J, Takahashi S (1994) Correlations of phosphomonoesters measured by phosphorus-31 magnetic resonance spectroscopy in the frontal lobes and negative symptoms in schizophrenia. Psychiatry Res Neuroimag 55: 223-235.

Shioiri T, Someya T, Murashita J, Kato T, Hamakawa H, Fujii K, Inubushi T (1997) Multiple regression analysis of relationship between frontal lobe phosphorus metabolism and clinical symptoms in patients with schizophrenia. Psychiatry Res Neuroimag 76: 113-122.

Singh SP, Shankar R (1996) Effect of haloperidol on phospholipid biosynthesis in rat brain. Ind J Exp Biol 34: 111-114.

Skinner TE, O'Donnell JM, Robitaille PM, Nasrallah HA (1995) ^{31}P MRS study of clozapine vs haloperidol effects on brain metabolism (abstract). Biol Psychiatry 37: 648.

Smith CD, Pettigrew LC, Avison MJ, Kirsch JE, Tinkhtman AJ, Schmitt FA, Wermeling DP, Wekstein DR, Markesberry WR (1995) Frontal lobe phosphorus metabolism and neuropsychological function in aging and in Alzheimer's disease. Ann Neurol 38: 194-201.

Stanley JA, Williamson PC, Drost DJ, Carr TJ, Rylett RJ, Morrison-Stewart S, Thompson RT (1994) Membrane phospholipid metabolism and schizophrenia: An *in vivo* ^{31}P-MR spectroscopy study. Schizophr Res 13: 209-215.

Stanley JA, Williamson PC, Drost DJ, Carr TJ, Rylett RJ, Malla A, Thompson RT (1995) An *in vivo* study of the prefrontal cortex of schizophrenic patients at different stages of illness via phosphorus magnetic resonance spectroscopy. Arch Gen Psychiatry 52: 399-406.

Stanley JA, Panchalingam K, Miller G, McClure RJ, Pettegrew JW (1997) A new method to quantify the broad component under the phosphodiester resonance and its application to study first-episode never medicated schizophrenics (abstract). Proc 5th Ann Scientific Meeting SMR, p 1408.

Stanley JA, Keshavan MS, Panchalingam K, McClure RJ, Pettegrew JW (1999) The effect of family history on the membrane phospholipid metabolism in schizophrenia: A longitudinal *in vivo* ^{31}P MRS study (abstract). Biol Psychiatry 45: 57S.

Stanley JA, Pettegrew JW, Keshavan MS (2000) Magnetic resonance spectroscopy in schizophrenia: Methodological issues and findings-Part I. Biol Psychiatry 48: 357-368.

Takeuchi K, Takigawa M, Fukuzako H, Hokazono Y, Hirakawa K, Fukuzako T, Ueyama K, Fujimoto T, Matsumoto K (1994) Correlation of third ventricular enlargement and EEG slow wave activity in schizophrenic patients. Psychiatry Res Neuroimag 55: 1-11.

Trzeciak H, Kalacinski W, Malecki A, Kokot D (1995) Effect of neuroleptics on phospholipase A_2 activity in the brain of rats. Eur Arch Psychiatry Clin Neurosci 245: 179-182.

Twieg DB, Meyerhoff DJ, Hubesch B, Roth K, Sappey-Marinier D, Boska MD, Gober JR, Schaefer S, Weiner MW (1989) Phosphorus-31 magnetic resonance spectroscopy in humans by spectroscopic imaging: Localized spectroscopy and metabolite imaging. Magn Reson Med 12: 291-305.

Vance ALA, Velakoulis D, Maruff P, Wood SJ, Desmond P, Pantelis C (2000) Magnetic resonance spectroscopy and schizophrenia: What have we learnt ?. Aust NZ J Psychiatry 34: 14-25.

Vial D, Piomelli D (1995) Dopamine D_2 receptors potentiate arachidonate release via activation of cytosolic, arachidonic-specific phospholipase A2. J Neurochem 64: 2765-2772.

Volz H-P, Rzanny R, May H, Hegewald H, Preußler B, Hajek M, Kaiser WA, Sauer H (1997a) ^{31}P magnetic resonance spectroscopy in the dorsolateral prefrontal cortex of schizophrenics with a volume selective technique: Preliminary findings. Biol Psychiatry 41: 644-648.

Volz H-P, Rzanny R, Rößger G, Hübner G, Kreischmann-Andermahr I, Kaiser WA, Sauer H (1997b) Decreased energy demanding processes in the frontal lobes of schizophrenics due to neuroleptics?: A ^{31}P-magneto-resonance spectroscopic study. Psychiatry Res Neuroimag 76: 123-129.

Volz H-P, Hübner G, Rzanny R, Rößger G, Preußler B, Eichhorn M, Kreischmann-Andermahr I, Kaiser WA, Sauer H (1998a) High-energy phosphates in the frontal lobe correlate with Wisconsin Card Sort Test performance in controls, not in schizophrenics: A ^{31}phosphorus magnetic resonance spectroscopic and neuropsychological investigation. Schizophr Res 31: 37-47.

Volz H-P, Rzanny R, Rößger G, Hübner G, Kreischmann-Andermahr I, Kaiser WA, Sauer H (1998b) ^{31}Phosphorus magnetic resonance spectroscopy of the dorsolateral prefrontal region in schizo-

phrenics: A study including 50 patients and 36 controls. Biol Psychiatry 44: 399-404.

Volz H-P, Rößger G, Riehemann S, Hübner G, Maurer I, Wenda B, Rzanny R, Kaiser WA, Sauer H (1999) Increase of phosphodiesters during neuroleptic treatment of schizophrenics: A longitudinal ^{31}P-magnetic resonance spectroscopic study. Biol Psychiatry 45: 1221-1225.

Volz H-P, Riehemann S, Maurer I, Smesny S, Sommer M, Rzanny R, Holstein W, Czekalla J, Sauer H (2000) Reduced phosphodiesters and high-energy phosphates in the frontal lobe of schizophrenic patients: A ^{31}P chemical shift spectroscopic-imaging study. Biol Psychiatry 47: 954-961.

Walker NP, Fox HC, Whalley LJ (1999) Lipids and schizophrenia. Br J Psychiatry 174: 101-104.

Wassink TH, Nelson JJ, Crowe RR, Andreasen NC (1999) Heritability of BDNF alleles and their effect on brain morphology in schizophrenia. Am J Med Genet 88: 724-728.

Wei J, Lee K-H, Hemmings GP (1998) Is the $cPLA_2$ gene associated with schizophrenia ? Mol Psychiatry 3: 480-481.

Williamson PC, Braner M, Leonard S, Thompson T, Drost D (1996) ^{31}P magnetic resonance spectroscopy studies in schizophrenia. Prostaglandins Leukot Essent Fatty Acids 55: 115-118.

Williamson PC, Drost DJ, Stanley JA, Carr TJ (1995) ^{31}P-MRS in the study of schizophrenia. In: Nasrallah HA, Pettegrew JW (eds) NMR Spectroscopy in Psychiatric Brain Disorders. American Psychiatric Press, Washington DC, pp 107-129.

Williamson P, Drost D, Stanley J, Carr T, Morrison S, Merskey H (1991) Localized phosphorus 31 magnetic resonance spectroscopy in chronic schizophrenic patients and normal controls. Arch Gen Psychiatry 48: 578.

Williamson P, Pelz D, Merskey H, Morrison S, Karlik S, Drost D, Carr T, Conlon P (1992) Frontal, temporal, and striatal proton relaxation times in schizophrenic patients and normal comparison subjects. Am J Psychiatry 149: 549-551.

Witt M-R, Nielsen M (1994) Characterization of the influence of unsaturated free fatty acids on brain GABA/benzodiazepine receptor binding in vitro. J Neurochem 62: 1432-1439.

Wright IC, Rabe-Hesketh S, Woodruff PWR, David AS, Murray RM, Bullmore ET (2000) Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157: 16-25.

Yao JK, Yasaei P, van Kammen DP (1992) Increased turnover of platelet phosphatidylinositol in schizophrenia. Prostaglandins Leukot Essent Fatty Acids 46: 39-46.

Yao JK, Leonard S, Reddy RD (2000) Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. Schizophr Res 42: 7-17.

World J Biol Psychiatry (2001) 2, 83 - 88

REVIEW/MINI-REVIEW ▸

Structural Neuroimaging Studies in Late-Life Depression: A Review

Isaac Schweitzer[1], Virginia Tuckwell[1], David Ames[1], John O'Brien[2]

[1] Department of Psychiatry, University of Melbourne, Australia

[2] Department of Psychiatry, Newcastle-upon-Tyne, UK

Summary

Which patients presenting with depression in late life will progress to a dementia syndrome has been an important research question in recent times. In this paper we review selectively structural neuroimaging investigations of late-life depression (LLD) that have been performed over the past two decades. These studies indicate that there are neuroimaging changes commonly observed in LLD patients when compared to normal controls. Findings include ventricular enlargement and sulcal widening, and reduction in volume size of frontal lobes, hippocampus and caudate nucleus. White matter lesions are more common in depressed subjects and tend to be more severe. Some studies report these changes to be more pronounced in patients who present with late-onset depression (LOD) but this has been contradicted by other studies. Preliminary work suggests that these changes may be associated with a poor prognosis but there is a dearth of systematic, well-controlled longitudinal studies.

Key words: *late-life depression, dementia, neuroimaging.*

Correspondence:
Prof. Isaac Schweitzer
Professorial Unit
The Melbourne Clinic
130 Church Street
Richmond Vic 3121
Australia
Tel: +613 9420 9350
Fax: +613 9428 5990
E-mail: i.schweitzer@medicine.unimelb.edu.au

Introduction

A relationship between the depressions of late life and dementia has long been clinically recognised. That elderly depressed patients may present with cognitive impairment (CI) which resolves with remission of depressive symptoms has been referred to as "pseudodementia". Recently, however, research observations suggest that not all depressed patients who present with memory impairment will recover fully and that some will in fact progress to develop a dementia syndrome. It has been suggested that in cases such as this, the depressive state is an early warning sign and the prodrome of a degenerative disorder.

In the past, the depression of late life had been largely studied as a single entity. The majority of individuals who present with depression in late life have in fact a recurrent depressive disorder, experiencing their first depressive episode during early or middle adulthood. The depressions that begin for the first time in late middle age or later, although less common than early-onset depression (EOD), have been the subject of considerable research interest over the past decade. Clinical and biological differences between depressive disorders that emerge for the first time in middle age or late life, (EOD) and late-onset depression (LOD), have been reported. LOD patients are more likely to have associated cognitive impairment (Steingart and Herrmann 1991; van Ojen et al 1995), possibly more likely to develop dementia (Alexopoulos et al 1993; Steffens et al 1997), are less likely to have bipolar disorder, more likely to have medical co-morbidity and have a poorer prognosis than EOD patients. It has been argued that LOD may be a prodromal syndrome for the development of dementia (Weiner et al 1994; Buntinx et al 1996; Steffens, et al 1997; Sunderland et al 1997; van Reekum et al 1999).

Structural neuroimaging has been a tool that has been applied extensively in the investigation of the neurodegenerative disorders, and more recently in late-life depression. In this paper we review selectively structural neuroimaging investigations of late-life depression (LLD) that have been performed over the past two decades, focussing on differences and similarities between late-life depression and dementia, and LOD and EOD.

Structural neuroimaging studies

• Whole brain volumes
Most studies show no significant differences between LLD and normal control subjects when whole brain volumes are determined (Sheline et al 1999; Kumar et al 1998; Krishnan et al 1993). Sheline's group, who selected women with recurrent depression with no medical co-morbidity and matched for age (23-86 years), educational level and height (a predictor of general brain volume) with normal controls, found no differences in overall brain size between the women with a history of recurrent depression and controls. Kumar et al (1999) studied age of onset of depression and volumetric neuroanatomic measures in a group of depressed elderly, and treated age of onset as a continuous as well as a dichotomised variable.

They found no significant relationship between total brain volume and age of onset or between the EOD and LOD groups after controlling for age. Pantel and colleagues (1997a), on the other hand, found a significantly smaller whole brain volume in patients with late-onset depression compared to age-matched normal controls.

• Cerebral cortex and ventricles
Cerebral atrophy and ventricular enlargement is almost a universal finding in dementia, while similar but substantially less severe changes are reported in major depression. A meta-analysis of 29 studies assessing ventricular enlargement and/or cortical sulcal prominence (23 with computed tomography (CT) and six by magnetic resonance imaging (MRI)) yielded a statistically significant effect size between depressed subjects and normal controls (Elkis et al 1995).

There are few structural imaging studies comparing LODs to EODs, however, differences between the two groups have been reported. Alexopoulos et al (1992) studied elderly depressed subjects with CT. Late-onset subjects (older than 60 years) had larger ventricules than those with an earlier age of illness onset. Alexopoulos' group judged CT parameters of LODs to be comparable to those of patients with Alzheimer's Disease (AD). EODs had significantly smaller ventricles and less sulcal widening than demented patients. Rabins et al (1991) found cortical sulcal atrophy to correlate with age at onset of depression in a study of 21 depressed patients aged 60 years and older.

• Frontal lobes
Coffey et al (1993) and Kumar et al (1998) found reductions in the volumes of the frontal lobes of depressed elderly patients. The latter study found similar changes in patients with minor depression and those with major depression. On the other hand, Pantel et al (1997a) reported no difference in frontal lobe volume in patients with LOD when compared to normal controls.

• Temporal lobe structures
Atrophy affecting temporal structures, in particular the hippocampus, has been consistently reported in AD. Several groups have found atrophy of temporal lobe structures in patients with AD with CT and MRI (Jack et al 1992; Desmond et al 1994; Laakso et al 1995; Heun et al 1997). The reliability of radiological diagnosis of clinical AD based on temporal lobe measures has been substantiated by neuropathological studies (Davis et al 1995). This group compared premortem neuroimaging findings and neuropathology evidence at autopsy of temporal lobe atrophy. A significant correlation between general CI and the volume of the amygdala-hippocampus complex and temporal lobe bilaterally found by Pantel et al (1997b) was supported by Kesslak et al (1991), Scheltens et al (1992) and Murphy et al (1993), but not by Seab et al (1988), Pearlson et al (1992) and Wahlund et al (1993). All these studies were case-control studies.

A smaller number of studies have examined temporal lobe structures in depression. Our group found that visualization of the temporal lobe structures was able to discriminate accurately between AD and depression. Forty-three patients with AD were compared with 32 patients with depression using visual rating of hippocampal atrophy; 89% of patients were correctly grouped overall (O'Brien et al 1994). In this study no significant differences were found between depressed patients and normal controls. Subjects in this study had been carefully defined, that is, depressed patients with no significant CI and AD subjects who were non-depressed (O'Brien et al 1994). Furthermore, O'Brien et al (1997) were able to distinguish dementia of the Alzheimer's type from vascular and other causes of dementia by visualisation of temporal lobe structures.

Sheline et al (1999) used quantitative MRI methods to compare a group of older, recurrently depressed women with age-matched normal controls. The depressed group had bilateral smaller hippocampal volumes which correlated with lifetime duration of depression. This was not supported by a study in 40 elderly, unipolar male and female depressives and 46 controls, all aged over 65 years, where significant differences in hippocampal-amygdala volumes were not found between the two groups (Ashtari et al 1999). A recent study found that the left hippocampus was significantly smaller (19%) in 16 remitted major depressives compared to case-matched, non-depressed control subjects with a mean age of 43 and 45 years, respectively (Bremner et al 2000).

Our group (O'Brien et al 1994) also identified a small subgroup of depressed subjects with anterior hippocampal atrophy on MRI. These patients were significantly older than those without atrophy and showed a trend for a later age at onset of the first episode of depression.

Furthermore, we followed over two years a small subsample of elderly depressives and normal controls who showed evidence of hippocampal atrophy (Swann et al 1997). Of seven depressed subjects, two developed dementia and two died.

The first study to investigate systematically differences in temporal lobe structures in early- and late-onset depression was by Greenwald and colleagues (Greenwald et al 1997), who found that later onset depressives had significantly more left medial temporal and left caudate atrophy than early-onset counterparts of similar age. Medial temporal atrophy correlated with CI in the depressed group, and depressives with medial temporal lobe atrophy (n=7) had a later age at onset of depression than those without atrophy (Greenwald et al 1997). Ashtari et al (1999) from the same group of researchers later reported on a larger cohort using quantifiable volumetric methods; there were no significant differences between LOD and EOD. The authors suggest that volume calculations may miss subtle indications of brain pathomorphology. Hippocampal volumes were correlated with age, cognitive rating on the Mini-Mental State Examination (MMSE) and depression ratings in the depressed group.

Vakili et al (2000) studied hippocampal volume in 38 patients with unipolar depression and 20 controls matched for age, sex and education. No significant differences in hippocampal volume were found, although there was a correlation between left hippocampal volume and depression rating scores in the male patients. It must be noted that subjects in this group were under 60 years; the authors suggest that the effects of severity and gender may influence hippocampal volume.

• Basal ganglia

Krishnan et al (1992) reported reductions in basal ganglia structures. Depressed patients had decreased caudate nucleus volumes compared with normal controls (mean age 48 years). This has not been widely investigated. Elderly hospitalised depressed patients were found to have greater cortical, subcortical and more basal ganglia white matter lesions than their control group (Rabins et al 1991).

• White matter lesions

MRI has been used to investigate deep white matter lesions (DWMLs) in late-life depression and several studies have shown them to be more common in depressed subjects than age- and sex-matched normal control subjects (NCs) (Coffey et al 1990; Rabins et al 1991; O'Brien et al 1996a). In addition, a number of research groups, including our own, have reported that an increased severity of DWMLs, particularly those of a subcortical nature, is present in LOD compared to EOD (O'Brien et al 1996b; Figiel et al 1991; Salloway et al 1996). Our research group (O'Brien et al 1996b) found that 50% (8/16) of LODs (age over 65 years) had severe DWMLs compared to 20% (6/30) of EODs and 9.5% (2/21) of NCs. DWMLs were more common in the left basal ganglia, lending support to the role of left basal ganglia/frontal dysfunction in depression (O'Brien et al 1996b). Figiel's group reported lesions in the basal ganglia in six of 10 LOD (age of onset after 60 years) subjects, compared to one of nine of the EOD group (Figiel et al 1991). Salloway et al (1996) found greater severity of subcortical hyperintensities and more cognitive impairment in patients with LOD than EOD. Lesser et al (1996) found that LOD subjects had larger areas of white matter lesions than psychiatric controls. Severe white matter changes were found in 17% of LOD subjects compared with 6% in the matched non-depressed group. The presence of large amounts of white matter lesions was associated with significantly poorer executive function on neuropsychological testing.

Hickie et al (1995) found a strong association between white matter lesions and later age of onset of affective disorder (over 50 years). More severe white matter changes was associated with a reduction in psychomotor speed. In a follow-up study (Hickie et al 1997) they reported that 10 of 37 (29%) developed a probable dementia syndrome of the vascular type. The syndrome was predicted by age of onset of depression and white matter lesions. Our group (O'Brien et al 1998) similarly found that severe DWMLs were predictive of poor outcome in a sample of 60 depressive elderly outpatients.

An association between MRI hyperintensities and poorer course of depressive illness was reported by Baldwin et al (2000). Later development of dementia or earlier death were shown to be related to later age of onset of depression, deep periventricular hyperintensities, and confluent DWMH. This was a three-year follow-up study of 38 patients using retrospective case analysis.

Miller et al (1994) and Greenwald et al (1996) found no differences in high intensity signals between LODs and EODs after controlling for cerebrovascular risk factors, nor did Kumar and colleagues in a group of 51 elderly depressives, where age of onset was analysed as a continuous as well as a dichotomous variable (Kumar et al 1999). Van Swieten et al (1991) found that hypertensive patients with confluent lesions of the white matter had poorer performance on the MMSE, the Stroop colour-word test, Trailmaking test, and the visual subtest of the Weschler Memory Scale.

The finding of increased white matter lesions in depression, particularly late-onset depression, has led some to propose the concept of "vascular depression" (Alexopoulos et al 1997; Krishnan et

al 1997). Though such lesions, particularly when large and confluent, may reflect vascular changes (Fazekas et al 1993), some caution is necessary as similar appearances on MRI can be caused by diverse pathological mechanisms (Chimowitz et al 1992; Fazekas et al 1993; Scheltens et al 1995). Thomas et al (2001) performed a postmortem study on 20 patients who had a history of depression and compared them to 20 controls; the depressed subjects had significantly greater degrees of atheromatous disease affecting the aortic and cerebral vessels but there was no increase in microvascular disease. Although the depressed patients had not been scanned and therefore correlation with antemortem findings had not been possible, nonetheless these findings give some credence to the concept of a vascular depression in late life.

Discussion

We have reviewed the structural neuroimaging literature of late-life depression. In summary, there is evidence that elderly depression is associated with cerebral cortical atrophy and ventricular enlargement and that this is greater in LOD than EOD. It is likely that atrophy of the frontal lobe occurs in LLD as does a shrinking of the caudate nucleus. The evidence regarding temporal lobe structures, in particular the hippocampus, is conflicting, nonetheless the current indication is that hippocampal atrophy does occur in depressed subjects when compared to normal controls; whether this is more likely in LOD's than EOD's awaits further research. The prognostic significance of these atrophic changes in depressed subjects who have no or minimal CI and who do not have AD is uncertain as these patients have not been systematically studied with long-term follow-up. There is only one small longitudinal study of depressed subjects with hippocampal atrophy which indicates a poor prognosis in this group.

The evidence regarding DWMLs is more consistent in depression. Though DWMLs are common in normal controls, they are more extensive in depressed patients. DWMLs are more severe in depressions that have a later age of first episode onset and these lesions are associated with some evidence of CI. There are three longitudinal studies and each has reported a poor prognosis for patients with severe DWML's with an increased likelihood for the development of dementia. The link of a "vascular depression" that progresses to a "vascular dementia" is further supported by recent neuropathological findings.

Conclusions from the findings of structural neuroimaging investigations have been limited by methodological differences between studies: selection and diagnostic criteria have not been standardized; there are selection biases and a lack of controls in some of the studies; the cut-off point separating EOD and LOD is always arbitrary and varies from study to study. Not all studies have clearly accounted for medical comorbidity, such as vascular risk factors. From a technical perspective, scanner parameters and acquisition parameters have varied, as have the methods for defining regions of interest. As can be seen from the above, most studies have been cross-sectional, with only a small number being prospective and long-term. Nonetheless, despite these difficulties, there is now a large body of evidence indicating that at least some forms of elderly depression are associated with signicant changes in structural neuroimaging that are suggestive of neurodegenerative changes, and it is likely that some patients will go on to develop a dementia. While DWMLs appear to be associated with the development of a vascular dementia, the presence of cortical atrophy would be expected to be a non-specific indicator for dementia. If hippocampal atrophy is present one would predict the development of AD as being the most likely, though with the absence of long-term follow-up studies this remains conjectural.

These studies have made it abundantly clear that depression in the elderly cannot be conceptualized as being of a single disease type. There are certainly those types that begin for the first time in middle to later life, and these are to be distinguished from young age of onset depression. Further divisions must also be considered, however, such as those with medical comorbidity and those without, and those who have major depression versus those with minor depression. The role of psychosocial stressors, such as bereavement, are of particular importance in some depressions of late life and not others. Such divisions of a clinical population are by necessity arbitrary and artificial but, just as in other phases of life, they have heuristic value in a similar way as endogenous versus reactive depression. The current data suggest that elderly depressed subjects who have CI and are LOD are at increased risk of developing dementia. Evidence of possible neurodegenerative changes on MRI may add to the clinical picture but for the present many of the techniques described above are only available to the researcher and not the clinician. Also, on a clinical level, the interpretation of individual scans must continue to be made cautiously because of the overlapping nature of group data. Interpretation of the neuroimaging findings must take into account the age of the individual as many of these changes are to some degree age-related. This is particularly the case for the so-called "old-old", that is, over the age of 85.

It should certainly not be concluded that all LODs or all depressed patients who have CI or neurodegenerative changes on MRI will inevitably go on to develop dementia, but merely that some may.

Pathophysiological mechanisms underlying the development of a depressive syndrome as a prelude to a chronic degenerative condition are not known. It may be speculated that this mechanism may reside in the observation that depletion of most neurotransmitters occurs in dementia and as such would include serotonin, dopamine and noradrenaline; the role of these neurotransmitters in depression is established. Cell loss and structural change in structures of the limbic system in dementia are also likely mechanisms.

Our understanding of cross-sectional biological changes in elderly depression is now vast. However, our scientific knowledge base remains scant concerning carefully controlled studies that combine biological indices and psychosocial variables and that are performed over the long term.

References

Alexopoulos GS, Young RC, Shindledecker RD (1992) Brain computed tomography findings in geriatric depression and primary degenerative dementia. Biol Psychiatry 31: 591-599.

Alexopoulos GS, Young RC, Meyers BS (1993) Geriatric depression: age of onset and dementia. Biol Psychiatry 34: 141-145.

Alexopoulos GSS, Meyers B, Young RC, Campbell S, Silbersweig D, Charlson, M (1997) 'Vascular depression' hypothesis. Arch Gen Psychiat 54: 915-922.

Ashtari M, Greenwald BS, Kramer-Ginsberg E, Hu J, Wu H, Patel M, Aupperle P, Pollack S (1999) Hippocampal/amygdala volumes in geriatric depression. Psychol Med 29: 629-638.

Baldwin RC, Walker S, Simpson SW, Jackson A, Burns A (2000) The prognostic significance of abnormalities seen on magnetic resonance imaging in late life depression: clinical outcome, mortality and progression to dementia at three years. Int J Ger Psych 15: 1097-1104.

Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS (2000) Hippocampal volume reduction in major depression. Am J Psychiat 157: 115-117.

Buntinx F, Kester A, Bergers J, Knottnerus JA (1996) Is depression in elderly people followed by dementia? A retrospective cohort study based in general practice. Age Ageing 25: 231-233.

Chimowitz MI, Estes ML, Furlan AJ (1992) Further observations on the pathology of subcortical lesions identified on magnetic resonance imaging. Arch Neurol 49: 747-752.

Coffey CE, Figiel GS, Djang WT, Weiner RD (1990) Subcortical hyperintensity on MRI: a comparison of normal and depressed elderly subjects. Am J Psychiat 147: 187-189.

Coffey CE, Wilkinson WE, Weiner RD, Parashos IA, Djang WT, Webb MC, Figiel GS, Spritzer CE (1993) Quantitative cerebral anatomy in depression: a controlled magnetic resonance imaging study. Arch Gen Psychiat 50: 7-16.

Davis PC, Gearing M, Gray L, Mirra SS, Morris JC, Edland SD, Lin T, Heyman A (1995) The CERAD experience, part VIII: Neuroimaging-neuropathology correlates of temporal lobe changes in Alzheimer's disease. Neurology 45: 178-179.

Desmond P, Tress B, Ames D, O'Brien J, Clement J, Clement P, Schweitzer I, Tuckwell V, Robinson G (1994) Volumetric and visual assessment of the mesial temporal structures in Alzheimer's disease. Aust NZJ Med 24: 547-553.

Elkis H, Friedman L, Wise A, Meltzer HY (1995) Meta-analyses of studies of ventricular enlargement and cortical sulcal prominence in mood disorders. Comparisons with controls or patients with schizophrenia. Arch Gen Psychiat 52: 735-746.

Fazekas F, Kleimert R, Offenbacher H (1993) Pathologic correlates of incidental MRI white matter hyperintensities. Neurology 43: 1683-1689.

Figiel GS, Krishnan KR, Doraiswamy PM, Rao VP, Nemeroff CB, Boyko OB (1991) Subcortical hyperintensities on brain magnetic resonance imaging: a comparison between late age onset and early onset elderly depressed subjects. Neurobiol Aging 12: 245-247.

Greenwald BS, Kramer-Ginsberg E, Krishnan KRR, Ashtari M, Aupperle PM, Patel M (1996) MRI signal hyperintensities in geriatric depression. Am J Psychiat 153: 1212-1215.

Greenwald BS, Kramer-Ginsberg E, Bogerts B, Ashtari M, Aupperle PM, Wu H, Allen L, Zeman D, Patel M (1997) Qualitative magnetic resonance imaging findings in geriatric depression. Possible link between later-onset depression and Alzheimer's disease? Psychol Med 27: 421-431.

Heun R, Mazanek M, Atzor K-R, Tintera J, Gawehn J, Burkart M, Gansicke M, Falkai P, Stoeter P (1997) Amyygdala-hippocampal atrophy and memory performance in dementia of Alzheimer type. Dement Geriatr Cogn Disord 8: 329-336.

Hickie I, Scott E, Mitchell P, Wilhelm K, Austin M.-P, Bennett B (1995) Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. Biol Psychiatry 37: 151-160.

Hickie I, Scott E, Wilhelm K, Brodaty H (1997) Subcortical hyperintensities on magnetic resonance imaging in patients with severe depression - A longitudinal evaluation. Biol Psychiatry 42: 367-374.

Jack C, Petersen R, O'Brien P, Tangalos E (1992) MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology 42: 183-188.

Kesslak JP, Nalcioglu O, Cotman CW (1991) Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. Neurology 41: 51-54.

Krishnan KRR, McDonald WM, Escalona PR, Doraiswamy PM, Na C, Husan MM, Figiel GS, Koyko OB, Ellinwood EH, Nemeroff CB (1992) Magnetic Resonance Imaging of the caudate nuclei in depression. Arch Gen Psychiat 49: 553-557.

Krishnan KRR, McDonald WM, Doraiswamy PM, Tupler LA, Hussain M, Boyko OB, Figiel GS, Ellinwood Jr EH (1993) Neuroanatomical substrates of depression in the elderly. Eur Arch Psychiatry Neurosci 243: 41-46.

Krishnan KR, Hays JC, Blazer DG (1997) MRI-defined vascular depression. Am J Psychiat 154: 497-501.

Kumar A, Jin Z, Bilker W, Udupa J, Gottleib G (1998) Late-onset minor and major depression: early evidence for common neuroanatomical substrates detected by using MRI. Proc Natl Acad Sci U S A 95: 7654-7658.

Kumar A, Bilker W, Jin Z, Udupa J, Gottlieb G (1999) Age of onset of depression and quantitative neuroanatomic measures: absence of specific correlates. Psychiatry Res Neuroimaging 91: 101-110.

Laakso MP, Soininen H, Partanen K, Helkala E-L, Hartikainen P, Vainio P, Hallikainen M, Hanninen T, Reikkinen PJ (1995) Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory function. J Neural Transm 9: 73-86.

Lesser IM, Boone KB, Mehringer M, Wohl MA, Miller BL, Berman NG (1996) Cognition and white matter hyperintensities in older depressed patients. Am J Psychiat 153: 1280-1287.

Miller DS, Kumar A, Yousem DM, Gottlieb GL (1994) MRI high-

intensity signals in late-life depression and Alzheimer's disease. Am J Geriatr Psychiat 2: 332-337.

Murphy DGM, DeCarli CD, Daly E, Gillette JA, McIntosh AR, Haxby JV, Teichberg D, Schapiro MB, Rapoport SI, Horwitz B (1993) Volumetric magnetic resonance imaging in men with dementia of the Alzheimer type: correlations with disease severity. Biol Psychiatry 34: 612-621.

O'Brien JT, Desmond P, Ames D, Schweitzer I, Tuckwell V, Tress B (1994) The differentiation of depression from dementia by temporal lobe magnetic resonance imaging. Psychol Med 24: 633-640.

O'Brien J, Ames D, Schweitzer I (1996a) White matter changes in depression and Alzheimer's disease: a review of magnetic resonance imaging studies. Int J Geriatr Psychiat 11: 681-694.

O'Brien JT, Desmond P, Ames D, Schweitzer I, Harrigan S, Tress B (1996b) A magnetic resonance imaging study of white matter lesions in depression and Alzheimer's disease. Brit J Psychiat 168: 477-485.

O'Brien J, Ames D, Desmond P, Schweitzer I, Tress B (1997) Magnetic Resonance Imaging correlates in memory impairment in the healthy elderly: associated with medial temporal lobe atrophy but not white matter lesions. Int J Geriatr Psychiat 12: 369-374.

O'Brien J, Ames D, Chiu E, Schweitzer I, Desmond P, Tress B (1998) Severe deep white matter lesions and outcome in elderly patients with major depressive disorder: follow up study. BMJ 317: 982-984.

Pantel J, Schröder J, Essig M, Popp D, Dech H, Knopp MV, Schad LR, Eysenbach K, Backenstrab M, Friedlinger MK (1997a) Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. J Affective Dis 42: 69-83.

Pantel J, Schröder J, Schad LR, Friedlinger MK, Schmitt R, Geissler M, Blüml S, Essig M, Sauer H (1997b) Quantitative imaging and neuropsychological functions in dementia of the Alzheimer type. Psychol Med 27: 221-229.

Pearlson GD, Harris GJ, Powers RE, Barta PE, Camargo EE, Chase GA, Noga T, Tune LE (1992) Quantitative changes in mesial temporal volume, regional cerebral blood flow, and cognition in Alzheimer's disease. Arch Gen Psychiat 49: 402-408.

Rabins PV, Pearlson GD, Aylward E, Kumar A.J, Dowell K (1991) Cortical magnetic resonance imaging changes in elderly inpatients with major depression. Am J Psychiat 148: 617-620.

Salloway S, Malloy P, Kohn R, Gillard E, Duffy J, Rogg J, Tung G, Richardson E, Thomas C, Westlake R (1996) MRI and neuropsychological differences in early - and late life - onset geriatric depression. Neurology 46: 1567-1574.

Scheltens P, Leys DL, Barkhof F, Huglo D, Weinstein HC, Vermesch P, Kuper M, Steinling M, Wolters EC, Valk J (1992) Atrophy of medial temporal lobes on MRI in 'probable' Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiat 5: 967-972.

Scheltens P, Barkhof F, Leys D (1995) Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. Neurology 45: 883-888.

Seab JP, Jagust WJ, Wong STS, Roos MS, Reed BR, Budinger TF (1988) Quantitative NMR measurements of hippocampal atrophy in Alzheimer's disease. Magn Reson Med 8: 200-208.

Sheline YI, Sanghavi M, Mintun MA, Gado MH (1999) Depression duration but not age predicts hippocampal volume loss in medically healthy women. J Neurosci 19: 5034-5043.

Steffens DC, Plassman BL, Helms MJ, Welsh-Bohmer KA, Saunders AM, Breitner JCS (1997) A twin study of late-onset depression and Apolipoprotein E e4 as risk factors for Alzheimer's disease. Biol Psychiat 41: 851-856.

Steingart A, Herrmann N (1991) Major depressive disorder in the elderly: the relationship between age of onset and cognitive impairment. Int J Geriatr Psychiat 6: 593-598.

Sunderland T, Lasser RA, Levin R, Dukoff RA (1997) Depression in the elderly: biologic considerations. Int Clin Psychopharmacol 12: S15-S18.

Swann A, O'Brien J, Ames D, Schweitzer I, Desmond P, Tress B (1997) Does hippocampal atrophy on MRI predict cognitive decline? A prospective follow-up study. Int J Geriatr Psychiat 12: 1182-1188.

Thomas AJ, Ferrier IN, Kalaria RN, Perry RH, Brown A, O'Brien JT (2001) A neuropathological study of vascular factors in late-life depression. J Neurol Neurosurg Psychiat 70: 83-87.

Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM, Yurgelun-Todd DA (2000) Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. Biol Psychiatry 47(12): 1087-1090.

van Ojen R, Hooijer C, Bezemer D, Jonker C, Lindeboom J, Van Tilburg W (1995) Late life depressive disorder in the community. I The relationship between MMSE score and depression in subjects with and without psychiatric history. Brit J Psychiat 166: 311-315.

van Reekum R, Simard M, Clarke D, Binns MA, Conn D (1999) Late-life depression as a possible predictor of dementia. Am J Geriatr Psychiat 7: 151-159.

van Swieten C, Geyskes GG, Derix MMA, Peeck BM, Ramos LMP, van Latum JC, van Gijn J (1991) Hypertension in the elderly is associated with white matter lesions and cognitive decline. Ann Neurol 30: 825 - 830.

Wahlund L-O, Andeersson-Lundman G, Basun H, Almkvist, O, Bjorksten KS, Saaf J, Wetterberg L (1993) Cognitive functions and brain structures: a quantitative study of CSF volumes on Alzheimer patients and healthy control subjects. Magn Reson Imaging 11: 169-174.

Weiner MF, Edland SD, Luszcrynska H (1994) Prevalence and incidence of major depression in Alzheimer's disease. Am J Psychiat 151: 1006-1009.

World J Biol Psychiatry (2001) 2, 89 - 94

Alterations of Host Defence System after Sleep Deprivation are followed by Impaired Mood and Psychosocial Functioning

Philip Heiser[1,3], Britta Dickhaus[1], Claus Opper[1], Ulrich Hemmeter[2], Helmut Remschmidt[3], Wolfgang Wesemann[1], Jürgen-Christian Krieg[2], Wolfgang Schreiber[2]

[1] Department of Neurochemistry, Philipps University, Marburg, Germany

[2] Department of Psychiatry and Psychotherapy, Philipps University, Marburg, Germany

[3] Department of Child and Adolescent Psychiatry and Psychotherapy, Philipps University, Marburg, Germany

Summary

In healthy humans, sleep deprivation (SD) has consistently been demonstrated to impair different parameters of the host defence system and of psychosocial functioning. However, the individual timing of these alterations and their possible association have remained unknown so far. We therefore investigated functional measures of the individual host defence system as well as of subjective well-being and psychosocial performance in 10 healthy male adults before and after SD, as well as after recovery sleep. In detail, we examined the number of leukocytes, granulocytes, monocytes, lymphocytes, B cells, T cells, T helper and cytotoxic T cells, natural killer (NK) cells as well as the interleukin-1ß (IL-1ß) release from platelets after serotonin (5-HT) stimulation. Mood and psychosocial performance (excitement, energy, ability to work and timidity) were measured by visual analogue scales. Taken together, SD induced a deterioration of both mood and ability to work, which was most prominent in the evening after SD, while the maximal alterations of the host defence system could be found twelve hours earlier, i.e., already in the morning following SD. Our findings therefore suggest an SD-induced alteration of these psychoimmune response patterns in healthy humans preceding deterioration of mood and psychosocial functioning.

Key words: *sleep deprivation, host defence system, mood, psychosocial functioning.*

Correspondence:
Philip Heiser, M.D.
Department of Child and Adolescent Psychiatry and Psychotherapy
Philipps University
Hans-Sachs-Str. 6
35037 Marburg
Germany
Tel: +49 6421 286 3079
Fax: +49 6421 286 3028
E-mail: heiser@mailer.uni-marburg.de

Introduction

Sleep deprivation (SD), sleep disruption and rotating shift work have become a fundamental part of the modern high-tech based economy in order to allow industry to run 24 hours a day and thereby to amortize high financial investments in this area. On the other hand, SD has consistently been demonstrated to impair individual mood and psychosocial functioning, especially in those people who are professionally exposed to such working conditions, for example rotating shift workers (Chang et al 1993), airline pilots (Price and Holley 1990), firefighters (Paley and Tepas 1994) or hospital physicians (Engel et al 1987; Lingenfelser et al 1994; Orten and Gruzelier 1989), but also in controls (Meney et al 1998).

In detail, these alterations of subjective well-being and psychosocial functioning include lower positive and higher negative mood scores or depression-like changes in mood 24 hours or longer after SD, as well as fatigue and greater sleepiness ratings (Engel et al 1987; Orten and Gruzelier 1989; Paley and Tepas 1994), reduced cognitive function (Lingenfelser et al 1994), severe performance decrements (Price and Holley 1990), and psychological disturbances and family dysfunctions (Chang et al 1993). The above-mentioned impairments could be further corroborated by respective neuropsychological testing including vigilance tests, reaction time tasks and code tests (Opstad et al 1978).

Host defence mechanisms are of decisive impact for the regulation of sleep (Benca and Quintas 1997; Pollmächer et al 1995). As regards interleukin-1ß (IL-1ß), the key cytokine of neuroimmune sleep control, the endogenous release of IL-1ß peaks at the beginning of non-rapid eye movement (NREM) sleep. In parallel, an increase of NREM sleep has been repeatedly reported after the application of IL-1ß. Finally, animal trials have revealed a correlation of the somnogenic potency of IL-1ß with the injected IL-1ß dosage (Opp et al 1992). Since SD represents an exogenous variant of sleep dysregulation, one would

expect respective alterations of the immune system. In fact, an increase in plasma IL-1ß is seen after SD (Krueger and Majde 1995), which is followed by a decrease of IL-1ß during and after recovery sleep (Dinges et al 1995; Moldofsky et al 1989).

With respect to further parameters of the host defence system, Dinges et al (1994) found a leukocytosis and a decrease in the number of T helper cells after SD, in contrast to the other lymphocyte subpopulations which remained unaltered. Both partial SD (PSD) and total SD (TSD) led to a reduction of cell number and of activity of NK cells. After a night of recovery sleep, NK activity returned to baseline levels (Irwin et al 1996; Moldofsky et al 1989). After stress and SD, neutrophils and monocytes were found to be increased in contrast to a decrease of eosinophils and all lymphocyte subgroups (Boyum et al 1996).

Based on these results, which clearly show that mood and immune function are affected by sleep deprivation, we were interested to evaluate the timing of alterations of mood, psychosocial functioning and variations within the host defence system in healthy, sleep-deprived human volunteers.

Subjects and methods

• Experimental design

Ten paid male volunteers (age: 27.4 ± 2.8 years) were enrolled in this study. Their medical history was carefully screened, and a thorough physical and psychiatric examination, including a complete blood count, electrolytes, c-reactive-protein, serum protein electrophoresis, liver enzymes, amylase, lipase, creatinine, urea, serotonin, norepinephrine and cortisol, was performed to exclude any present illness (including sleep disorders) or current stressful life events. None of the participants had been exposed to rotating shift work or other disturbances of internal circadian rhythms such as intercontinental flights within the last year.

The investigation took place on three consecutive days and included a night of total sleep deprivation (TSD) between day one and day two, and a recovery night between day two and day three. During the daytime, all participants followed their usual daily work schedule. Whereas the nights before and after TSD were spent at home, to ensure undisturbed nocturnal sleep, TSD was carried out in our laboratory rooms in groups of three or four participants. To prevent unwanted sleep, including short naps, continuous personal supervision was provided. Blood samples were drawn on each day at 7 a.m., 1 p.m. and 7 p.m., after a rest period of at least 30 minutes in which the participants remained in a half-supine position. All participants were non-smokers (Schreiber et al 1997).

The experimental protocol was approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Before entering the study, and after the nature of all procedures had been fully explained to them, all participants gave their written informed consent.

• Measurement of subjective well-being and psychosocial functioning

All probands were asked to fill out questionnaires to assess individual well-being (Adjective Mood Scale AMS and its parallel version AMS', each with 28 items (von Zerrsen 1986)) and psychosocial functioning (Visual Analogue Scale VIS-A for the retrospective assessment of excitement, energy, ability to work and timidity (Ott et al 1981)). The AMS and AMS' were filled out three times (7 a.m., 1 p.m., 7 p.m.) on each of the three consecutive days to measure the present degree of well-being (***high*** AMS scores indicate a ***low*** degree of individual well-being), while the VIS-A was recorded once a day in the evening (7 p.m.) to assess psychosocial functioning for this particular day (Heiser et al 2000b).

• Differentiation of leukocytes

100 µl of blood and 10 µl of the specific antibody solution (FACS Ak, IQ Products, Netherlands) were incubated for 30 minutes at room temperature in darkness. The differentiation of white blood cells was performed as follows:

- Monocytes from leukocytes by co-incubation of anti-CD 45 antibodies (leukocytes) and anti-CD 14 antibodies (monocytes).
- T helper cells from T cells by co-incubation of anti-CD 3 antibodies (T cells) and anti-CD 4 antibodies (T helper cells).
- Cytotoxic T cells from T cells by co-incubation of anti-CD 3 antibodies and anti-CD 8 antibodies (cytotoxic T cells).
- B cells from lymphocytes by co-incubation of anti-CD 3 Fits antibodies (lymphocytes) and anti-CD 19 Pe antibodies (B cells); the number of T cells was determined indirectly.
- NK cells from T cells by co-incubation of anti-CD 3 antibodies and anti-CD 16 antibodies (NK cell macrophages) as well as anti-CD 56 antibodies (NK cells).

The solutions were then incubated with 2 ml lysis reagent for 10 minutes. After this step, the solutions were centrifuged for five minutes at 4° C with 300 gMAX. The supernatant was discarded and the pellet was resuspended with 2 ml PBS (2 % FCS) and again centrifuged in the above-mentioned way. The pellet was mixed with 500 µl sheet fluid. The results were obtained with FACS (Becton Dickinson FACS Scan, New Jersey).

Granulocytes were counted in a cell counter. For further methodological information, see Heiser et al (2000a).

• IL-1ß release from platelets after 5-HT activation

EDTA blood was sampled and centrifuged with 1280 rotations/min for 15 minutes at 15°C (Omnifuge 2.0 RS, Fa. Heraeus) to obtain platelet rich plasma (PRP). PRP was sampled and layered onto two Percoll density gradients (Fa. Pharmacia) with a density of 1.040 g/ml and 1.080 g/ml, respectively. This solution was centrifuged with 3500 gmax for 15 minutes at 4°C. The platelets are located between the density layers (Jung et al 1985). In this way, we obtained platelet-free plasma (PFP). The platelets were washed twice with Gainter wash buffer with 1000 gmax for 15 minutes at 15°C. After this step the platelets were resuspended in Tyrode buffer and an aliquot was used for counting (Sysmex Microcellcounter F-800, Fa. Digitana).

Platelets were then stimulated with 50 µM serotonin + 2 mM calcium + 1 mM magnesium and incubated for 10 minutes at 37°C. After incubation the suspension was immediately centrifuged with 7000 gmax for two minutes (Minifuge 2, Fa. Heraeus). The supernatant was used according to the instructions of the Quantikine High Sensitivity Human Il-1ß Immunoassay (Fa. R&D Systems). The results were compared to a standard curve and related to the platelet number of 10^9/ml (Heiser et al 1997).

• Data analysis

For statistical evaluation, a parametric analysis of variance (ANOVA) with repeated measurements (two levels: day and hour) was used. In case of significant effects, a comparison by planned contrast analysis was performed to verify significant differences between day one, day two and day three. The statistics were performed using STATISTICA software (StatSoftInc., Tulsa OK 74104, USA).

Results

• Subjective well-being and psychosocial functioning

ANOVA with repeated measurements revealed significant differences concerning the overall time course pattern (p = 0.0015) and interaction between day and hour (time of day) of the Adjective Mood Scale (*AMS + AMS'* / 2) scores (p = 0.014). Comparison of the 7 p.m. values by planned contrast analysis yielded significant differences between days one, two and three (p = 0.008) due to an increase of the *AMS + AMS'* / 2 score after SD (Figure 1).

An examination of the Visual Analogue Scales (VIS-A) for the assessment of psychosocial functioning revealed a significant interaction concerning the VIS-A ability to work (p = 0.009), which was found to be lowest after SD (Figure 1). No significant interactions were seen for VIS-A energy, VIS-A excitement and VIS-A timidity.

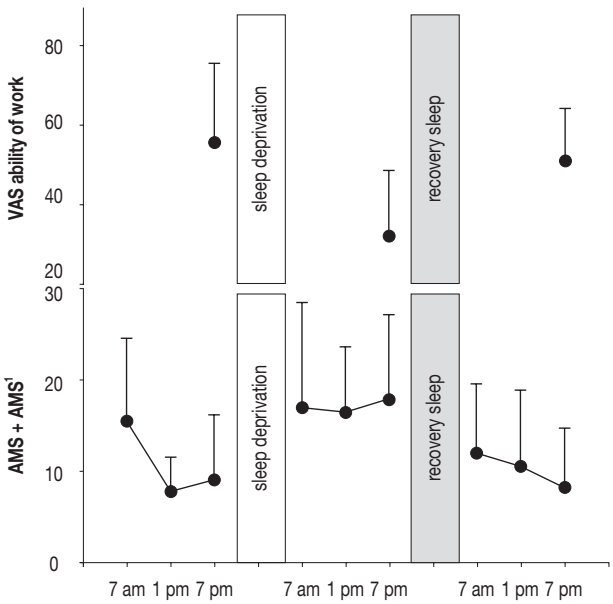

Figure 1
Mean values (± SD) of psychosocial functioning and subjective well-being before and after sleep deprivation, and after recovery sleep (Note, that ***high*** AMS scores indicate a ***low*** degree of individual well-being)

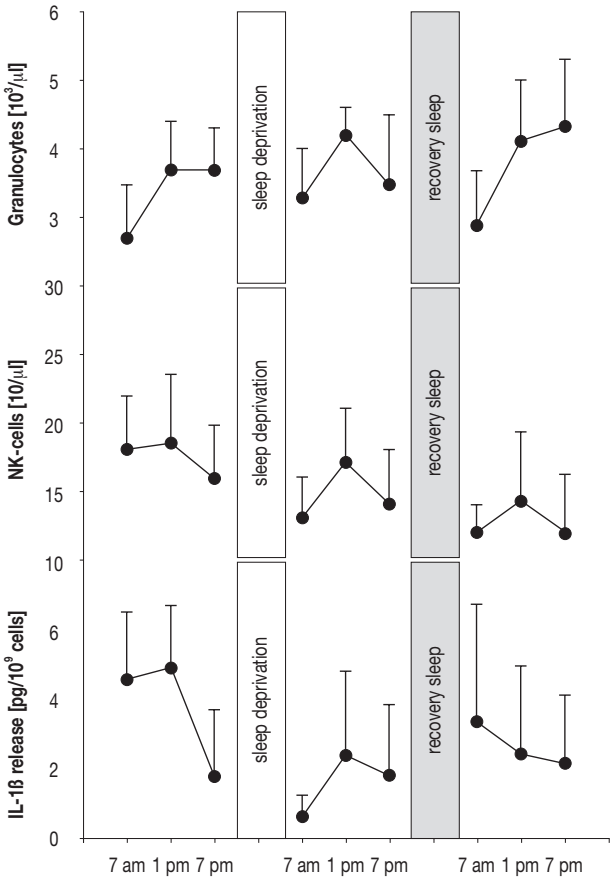

Figure 2
Mean values (± SD) of granulocyte and NK cell counts as well as IL-1ß release from platelets before and after sleep deprivation, and after recovery sleep

• Leukocytes
Comparison of the 7 a.m. values by contrast analysis yielded significant differences for granulocytes ($p = 0.044$) and NK cells ($p = 0.001$) (Figure 2). NK cells decreased and granulocytes increased after SD and after recovery sleep. Significant differences between single points in time across the day were found for granulocytes ($p = 0.022$), monocytes ($p = 0.031$), T cells ($p = 0.005$), T helper cells ($p = 0.004$), cytotoxic T cells ($p = 0.005$) and NK cells ($p = 0.017$). Contrast analysis yielded significant differences between days one, two and three for monocytes ($p = 0.017$) and NK cells ($p = 0.0001$). No significant interaction at all could be found for leukocytes, lymphocytes and B cells.

• IL-1ß release from platelets
With respect to the IL-1ß release from platelets after 5-HT stimulation, our data analysis revealed a significant difference concerning the overall time course pattern ($p = 0.004$) (Figure 2). The significant interaction between the day and hour (time of day) of IL-1ß release was reflected by the steep decline from high morning to low evening levels before SD, as well as by an inverted course of values on the day after SD. Further comparison of the 7 a.m. values by contrast analysis yielded no statistically significant differences between days one, two and three.

Discussion

Taken together, our study revealed two main findings:

1. Sleep deprivation (SD) - induced alterations of the host defence system in healthy subjects were characterized by a significant increase of granulocytes, a significant decrease of NK cells and IL-1ß release from platelets, all of which were evident as early as the morning after SD.
2. On the other hand, an evening-prone deterioration of subjective well-being was observed in these probands after SD, which was paralleled by a decrease of subjective psychosocial functioning in regard to their ability to work.

In more detail, the 7 a.m. number of granulocytes was increased after SD, which persisted beyond recovery sleep. These findings parallel the results of Dinges et al (1994), who found an increase of granulocytes even 64 hours after SD.

The observed reduction of NK cells is likewise in line with the respective results of Dinges et al (1994). In our experiment, however, the NK cell number remained significantly reduced after recovery sleep, whereas in other studies NK cell activity returned to baseline levels after a night of recovery sleep (Irwin et al 1996; Moldofsky et al 1989; Palmblad et al 1979).

Monocytes, T cells, T helper cells and cytotoxic T cells yielded significant differences between single points in time during the day in this study, suggesting a significant circadian variation. No significant variation at all could be detected for leukocytes, lymphocytes and B cells after SD and/or recovery sleep. These observations contrast in part the respective findings of Dinges et al (1994), who reported a reduction in CD4 cells (T helper cells) as well as in CD16 and CD57 lymphocytes, while other lymphocyte subpopulations remained unchanged after one night of SD.

After a combination of stress and SD, an increase in neutrophils and monocytes as well as a reduction of eosinophils and of all lymphocyte subgroups was seen by Boyum et al (1996). Compared with lasting wakefulness, consecutive nocturnal sleep reduced the numbers of monocytes, NK cells and counts of all lymphocyte subsets. However, in the afternoon and evening of the day following recovery sleep, counts of NK cells and lymphocytes were higher than after nocturnal wakefulness (Born et al 1997).

In line with previous findings, the results of our study provide some evidence that the SD-induced alterations of the host defence system, especially of the NK cells, lead to enhanced nocturnal plasma IL-1-like and IL-2-like activities (Moldofsky et al 1989), since central administration of IL-1ß is associated with suppressed NK cell activity (Hodgson et al 1999). This increase of somnogenic IL-1ß after SD (Krueger and Majde 1995) is followed by a decrease of IL-1ß during and after recovery sleep (Dinges et al 1995; Moldofsky et al 1989).

The deterioration of mood after sleep deprivation – as observed in this study – is a well-known finding in healthy subjects. A variety of studies could consistently show that SD impairs mood, cognitive performance and psychosocial functioning (Chang et al 1993; Paley and Tepas 1994; Price and Holley 1990). In contrast to these effects of SD on mood in healthy subjects, SD in patients with major depression displays an antidepressant, mood-elevating efficacy in about 60% of patients (Wiegand et al 1993; Wu and Bunney 1990).

As compared to healthy subjects, alterations of different immunological parameters have been repeatedly demonstrated in major depression as well as in dysthymia (Dantzer et al 1999; Maes et al 1995; Licino and Wong 1999; Ravindran et al 1996a; Seidel et al 1996), which were characterized by an elevation of the number of circulating leukocytes and granulocytes, and a reduction of NK cells and NK cell activity (Maes et al 1995; Schleifer et al 1996).

The immunological response patterns to SD in healthy subjects in this and other investigations reflect these immunological profiles in depressed patients under basal conditions, thus providing additional hints for a possible relationship

between alterations of the host defence system and mood changes.

The suggestion of a relationship between changes of mood and immune function, which were both affected by SD in this study, is further supported by the finding that in major depression a negative correlation between the severity of depression and the activity of NK cells has been detected (Irwin et al 1990). Also, the observation that NK cell activity increased in parallel with a reduction of depressive symptoms under antidepressant treatment (Irwin et al 1992), and that NK cell levels were correlated with an emotion-focused coping style (Ravindran et al 1996b), support this assumption. Finally, it could be demonstrated that sleep disturbances - which are closely linked to a worsening of mood (Lingenfelser et al 1994; Orten and Gruzelier 1989) – display a negative correlation with NK cell activity in depression (Cover and Irwin 1994).

Based on these findings and the results of this study, we conclude that SD in healthy subjects alters mood and immune function to a state comparable with that found in patients with major depression under baseline conditions. The above-mentioned, close relationship between the severity of depression and the alteration of immune pattern in patients with depression is in clear favour of such an assumption. Furthermore, our finding of SD effects on host defence mechanisms preceding the respective mood-worsening effects might provide a clue towards a causal link between alterations of immune function in the morning and alterations of mood in the evening; these could be attributed, for example, to changes within circadian neuroendocrinological rhythms (Baumgartner et al 1993; von Treuer et al 1996).

Due to the restrictions of our study design, we could not perform a causal analysis of this supposed relationship. Nonetheless, the timing of SD effects on immune function and mood, which show that the alteration of different immune patterns precedes respective mood changes, supports the assumption of such a link.

References

Baumgartner A, Dietzel M, Saletu B, Wolf R, Campos-Barros A, Graf KJ, Kurten I, Mannsmann U (1993) Influence of partial sleep deprivation on the secretion of thyrotropin, thyroid hormones, growth hormone, prolactin, luteinizing hormone, follicle stimulating hormone, and estradiol in healthy young women. Psychiatry Res 48: 153-178.

Benca RM, Quintas J (1997) Sleep and host defenses: a review. Sleep 20: 1027-1037.

Born J, Lange T, Hansen K, Molle M, Fehm HL (1997) Effects of sleep and circadian rhythm on human circulating immune cells. J Immunol 158: 4456-4464.

Boyum A, Wiik P, Gustavsson E, Veiby OP, Reseland J, Haugen H, Opstad PK (1996) The effect of strenuous exercise, calorie deficiency and sleep deprivation on white blood cells, plasma immunoglobulins and cytokines. Scand J Immunol 43: 228-235.

Chang CJ, Wang SY, Liu HW (1993) The effect of shift work on sleep quality, sleep quantity, psychosocial disturbance, and family function of workers in Taiwan. Kao Hsiung I Hsueh Ko Hsueh Tsa Chih 9: 410-417.

Cover H, Irwin M (1994) Immunity and depression: insomnia, retardation and reduction of natural killer cell activity. J Behav Med 17: 217-223.

Dantzer R, Wollman E, Vitkovic L, Yirmiya R (1999) Cytokines and depression: fortuitous or causative association? Mol Psychiatry 4: 328-332.

Dinges DF, Douglas SD, Zaugg L, Cambell DE, McMann JM, Whitehouse WG, Orne EC, Kapoor SC, Icaza E, Orne MT (1994) Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 6 hours of sleep deprivation. J Clin Invest 93: 1930-1939.

Dinges DF, Douglas SD, Hamarman S, Zaugg L, Kapoor S (1995) Sleep deprivation and human immune function. Adv Neuroimmunol 5: 1397-1410.

Engel W, Seime R, Powell V, D'alessandri R (1987) Clinical performance of interns after being on call. South Med J 80: 761-763.

Heiser P, Dickhaus B, Opper C, Schreiber W, Clement HW, Hasse C, Hennig J, Krieg JC, Wesemann W (1997) Platelet serotonin and interleukin-1ß after sleep deprivation and recovery sleep in humans. J Neural Transm 104: 1049-1058.

Heiser P, Dickhaus B, Schreiber W, Clement HW, Hasse C, Remschmidt H, Krieg JC, Wesemann W, Opper C (2000a) White blood cells and cortisol after sleep deprivation and recovery sleep in humans. Eur Arch Psychiatry Clin Neurosci 250: 16-23.

Heiser P, Dickhaus B, Opper C, Remschmidt H, Wesemann W, Krieg JC, Schreiber W (2000b) The deterioration of mood and psychosocial functioning after sleep deprivation is preceded by an increase of serotoninergic transmission. Somnology 3: 1-4.

Hodgson DM, Yirmiya R, Chiappelli F, Taylor AN (1999) Intercerebral interleukin-1beta impairs responses to tumor invasion: involvement of adrenal catecholamines. Brain Res 816: 200-208.

Irwin M, Patterson T, Smith TL, Caldwell C, Brown SA, Gilin JC, Grant I (1990) Reduction of immune function in life stress and depression. Biol Psychiat 270: 22-30.

Irwin M, Lacher U, Caldwell C (1992) Depression and reduced natural killer cytotoxity: a longitudinal study of depressed patients and control subjects. Psychol Med 22: 1045-1050.

Irwin M, McClintick J, Costlow C, Fortner M, White J, Gilin JC (1996) Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. FASEB 10: 643-653.

Jung S, Tanoue K, Yamazaki H (1985) The electrophoretic mobility heterogeneity of human platelet subpopulations of different buoyant densities. Thromb Haemost 53: 188-194.

Krueger JM, Majde J (1995) Cytokines and sleep. Int Arch Allerg Immunol 106: 97-100.

Licinio J, Wong ML (1999) The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry 4: 317-327.

Lingenfelser T, Kaschel R, Weber A, Zaiser-Kaschel H, Jakober B, Kuper J (1994) Young hospital doctors after night duty: their task-specific cognitive status and emotional condition. Med Educ 28: 566-572.

Maes M, Smith R, Scharpé S (1995) The monocyte-T-lymphocyte hypothesis of major depression. Psychoneuroendocrinology 20: 111-116.

Meney I, Waterhouse J, Atkinson G, Reilly T, Davenne D (1998) The effect of one night's sleep deprivation on temperature, mood, and physical performance in subjects with different amounts of habitual physical activity. Chronobiol Int 15: 349-363.

Moldofsky H, Lue F, Davidson J, Gorczynski R (1989) Effects of sleep deprivation on human immune functions. FASEB 3: 1972-1977.

Opp MR, Kapas L, Toth LA (1992) Cytokine involvement in the regulation of sleep. Proc Soc Exp Biol Med 201: 16-27.

Opstad PK, Ekanger R, Nummestad M, Raabe N (1978) Performance, mood, and clinical symptoms in men exposed to prolonged, severe physical work and sleep deprivation. Aviat Space Environ Med 49: 1065-1073.

Orten DI, Gruzelier JH (1989) Adverse changes in mood and cognitive performance of house officers after night duty. BMJ 298: 21-23.

Ott H, Oswald I, Fichte K, Sastre M (1981) VIS-A und VIS-M. In: Collegium Internationale Psychiatrie Scalarum (eds) Internationale Skalen für Psychiatrie. Weinheim.

Paley MJ, Tepas DI (1994) Fatigue and the shiftworker: firefighters working on a rotating shift schedule. Hum Factors 36: 269-284.

Palmblad J, Petrini B, Wassermann J, Akerstedt T (1979) Lymphocyte and granulocyte reactions during sleep deprivation. Psychsom Med 41: 273-278.

Pollmächer T, Mullington J, Korth C, Hinze-Selch D (1995) Influence of host defense activation on sleep in humans. Adv Neuroimmunol 5: 155-169.

Price WJ, Holley DC (1990) Shiftwork and safety in aviation. Occup Med 5: 343-377.

Ravindran AV, Griffiths J, Merali Z, Anisman H (1996a) Primary dysthymia: a study of several psychological, endocrine and immune correlates. J Affect Disord 40: 73-84.

Ravindran AV, Griffiths J, Merali Z, Anisman H (1996b) Variations of lymphocyte subsets associated with stress in depressive populations. Psychoneuroendocrinology 21: 659-671.

Schleifer SJ, Keller SE, Bartlett JA, Eckholdt HM, Delaney BR (1996) Immunity in young adults with major depressive disorder. Am J Psychiatry 153: 477-482.

Schreiber W, Opper C, Dickhaus B, Heiser P, Wesemann W, Krieg JC (1997) Alterations of blood platelet MAO-B activity and LSD-binding in humans after sleep deprivation and recovery sleep. J Psychiatric Res 31: 323-331.

Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H (1996) Increased CD56+ natural killer cells and related cytokines in major depression. Clin Immunol Immunopathol 78: 83-85.

von Treuer K, Norman TR, Armstrong SM (1996) Overnight human plasma melatonin, cortisol, prolactin, TSH, under conditions of normal sleep, sleep deprivation, and sleep recovery. J Pineal Res 20: 7-14.

Wiegand M, Riemann D, Schreiber W, Lauer C, Berger M (1993) Morning and afternoon naps in depressed patients after total sleep deprivaton: sleep structure and impact on mood. Biol Psychiat 33: 467-476.

Wu JC, Bunney WE (1990) The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. Am J Psychiat 147: 14-21.

von Zerssen D (1986) Clinical Self-Rating Scales (CSRS) of the Munich Psychiatric Information System (PSYCHIS München). In: Sartorius NT, Ban A (eds) Assessment of depression. Springer, Berlin, pp 270-303.

World J Biol Psychiatry (2001) 2, 95 - 98

Inositol Monophosphatase Activity in Brain and Lymphocyte-Derived Cell Lines of Bipolar Patients

Galit Shaltiel [1,3,4], Alon Shamir [1,3,4], Lubov Nemanov [5], Yuri Yaroslavsky [1,2,4], Boris Nemets [1,2,4], Richard P. Ebstein [4,5], Robert H Belmaker [1,2,4], Galila Agam [1,3,4]

[1] Stanley Research Center, Beersheva, Israel

[2] Ministry of Health, Mental Health Center, Beersheva, Israel

[3] Department of Clinical Biochemistry, Ben-Gurion University of the Negev, Beersheva, Israel

[4] Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheva, Israel

[5] S. Herzog Hospital, Jerusalem, Israel

Summary

Background: *Inositol monophosphatase (IMPase) activity was reported to be low in lymphocyte-derived cell lines of bipolar patients.*

Methods: *IMPase activity was measured spectrophotometrically as inorganic phosphate liberated from inositol-1-phosphate.*

Results: *The previously reported reduction was replicated in a new, small group of bipolar patients. The reduction is not present in cell lines of unipolar or schizophrenic patients. IMPase activity in postmortem frontal and occipital cortical samples of unipolar, bipolar and schizophrenic patients was not different from controls.*

Conclusions: *A reduction in lymphocyte-derived IMPase activity without a parallel reduction in cortical IMPase activity could be due to the fact that most leukocyte IMPase activity is the product of the IMPA-2 gene.*

Key words: *inositol monophosphatase (IMPase), enzyme activity, lymphcyte-derived cell lines, postmortem brain, bipolar disorder.*

Correspondence:
Galila Agam, Ph.D.
Psychiatry Research Unit
Ministry of Health
Mental Health Center
PO Box 4600
Beersheva 84170
Israel
Tel: +972 7 6401 737 /738
Fax: +972 7 6401 621/737
E-mail: galila@bgumail.bgu.ac.il

Acknowledgment
Supported by a NARSAD Independent Investigator award to Dr. Galila Agam.

Introduction

The aetiology of bipolar disorder (BPD), as well as the molecular mechanism of action of mood-stabilizing drugs, are as yet unknown. Lithium (Li) has therapeutic and prophylactic effects on both the manic and the depressive phases of BPD. Several biochemical actions have been attributed to Li (Jope 1999) but none has been incontrovertibly associated with its effect on behaviour or mood. In recent years investigation has focused on the phosphoinositide (PI) cycle as a possible molecular substrate of Li's mode of action (Jope et al 1996; Manji et al 1995). Particular focus has been placed on the enzyme inositol monophosphatase (IMPase), which is a key enzyme in this second messenger cycle. Hallcher and Sherman (1980) first showed that IMPase is uncompetitively inhibited by therapeutically relevant concentrations of Li, and Berridge et al (1989) then proposed that the physiological consequence of the inhibition of IMPase by Li is a depletion of free inositol and consequent attenuation of neurotransmitter-driven phosphoinositide second messenger signal generation.

Mammalian IMPase exists as a homodimer with a subunit molecular weight of 30 kDa. The enzyme has three motifs (A, B and C), which contain most of the key amino acids involved in substrate and metal binding (Atack et al 1995).

Because Li inhibits IMPase, the enzyme was studied for possible overactivity as an aetiology of manic-depressive illness (Berridge et al 1989). Counter-intuitively, a 50% decreased IMPase activity in lymphocyte-derived cell lines of 79 bipolar patients vs. 29 controls was found (Shamir et al 1998). When the bipolar patients were grouped according to clinical response to Li therapy, the Li responders exhibited significantly lower IMPase activity compared to those patients with poor Li response (Shamir et al 1998). Previous Li treatment of the patients seemed an unlikely explanation, since the cells were grown in drug-free standard culture conditions for numerous generations before assay. We speculated that low IMPase activity could be ameliorated by Li treatment because of Li's ability to

increase IMPase mRNA transcription (Nemanov et al 1999a).

In the present study we evaluated the specificity of low IMPase in lymphocyte-derived cell lines by using a sample derived from unipolar depressive and schizophrenic patients compared to a simultaneous run of new control cell lines and re-assay of the previously studied control cell lines. We also re-assayed the previously studied bipolar patients and a new, small group of bipolar patients. Previous studies of frontal and occipital cortex and cerebellum postmortem brain specimens showed no differences between bipolar and schizophrenic patients and controls (Shimon et al 1997; Shimon et al 1998), but our lymphocyte-derived cell lines finding suggested that a re-evaluation in a larger and well-standardized series would be justified.

Methods and materials

• Lymphocyte-derived cell lines

Epstein-Barr-Virus (EBV)-transformed lymphoblastoid cell lines were established and grown as previously described (Bennett et al 1991; Ebstein et al 1990). Cell lines were established from four diagnostic groups of subjects. Thirty-nine control subjects with no history of psychiatric illness were recruited from the Beer-Sheva and Jerusalem areas. Non-hospitalized bipolar patients (7 male, 5 female; average age = 49.8 ± 13 (SD) years; range 29-73) were recruited from the Li Clinic of the Beer-Sheva Mental Health Center. Unipolar patients (14 male, 37 female; average age = 50.6 ± 11 (SD) years; range 21-68) were from the Beer-Sheva Mental Health Center Outpatient Depression Clinic (B.N), and schizophrenic patients (16 male, 12 female; average age = 42.4 ± 13 (SD) years; range 20-67) were hospitalized patients from the Beer-Sheva Mental Health Center (Y.Y). All patients were diagnosed according to DSM IV criteria.

• Postmortem brain specimens

Fifteen frontal and 15 occipital cortex specimens from each of the four groups (bipolar, unipolar and schizophrenic patients, and controlled subjects) were obtained from the Stanley Foundation Brain Collection (Torrey et al 1999).

The study of both collections (brain and lymphocyte-derived cell lines) was approved by our hospital ethics committee (IRB).

• IMPase activity

IMPase activity in the postmortem brain specimens and in the lymphocyte-derived cell lines was measured as previously described (Nemanov et al 1999b). Inorganic phosphate liberated from inositol-1-phosphate was quantified spectrophotometrically in an ELISA reader (iEMS, Labsystems) using the malachite green colour reagent (Nemanov et al 1999b). In order to distinguish IMPase activity from non-specific phosphatases, the reaction was carried out in the presence and absence of 30mM LiCl. LiCl is a specific inhibitor of this enzyme, and at these concentrations totally inhibits IMPase activity. The enzyme activity was calculated as the difference between the value in the absence of minus the activity in the presence of lithium.

Results

We found no correlation between IMPase activity in cell lines from the previous series and the same cell lines re-assayed in the present study (controls: r=0.024, n=16; bipolars: r=0.09, n=47). Comparison between IMPase activity in cell lines from bipolar patients responding to Li-treatment vs. those of Li non-responders, including previously assayed and new cell lines, revealed a result opposite to that previously reported (Shamir et al 1998): a significantly higher IMPase activity [121±13.3 (SE) nmoles/minXmg protein, n=47] in Li responders vs. Li non-responders [58.7±12 (SE) nmoles/minXmg protein, n=11] was now obtained (ANOVA, F=5.001, df=1,56, p<0.03). However, comparison of the mean IMPase activity in the re-assayed controls, new controls, re-assayed bipolars and new bipolars cell lines (Table 1) using a two-way ANOVA showed a significant difference between the control and bipolar lymphocyte-derived cell lines (F=7.04, df=1,97, p<0.01), no significant difference between the previous and the present assays, and no interaction.

Table 1
IMPase activity in re-assayed and new lymphocyte-derived cell lines

	IMPase activity, nmoles/minXmg protein	
	Control	**Bipolar**
Re-assayed subjects	161±33.4 n=16	115.5±12.3* n=47
New subjects	147.4±26.9 n=26	64.6±16.5* n=12

Results are means ± SEM

* Two-way ANOVA, bipolar patients differ significantly from control subjects (p<0.01)

There was no difference in IMPase activity of lymphocyte-derived cell lines between the unipolar patient [155.5 ± 20.5 (SE) nmoles/minXmg protein, n=51], schizophrenic patient [164.9 ± 29.5 (SE) nmoles/minXmg protein, n=28] and control [152.6 ± 20.6 (SE) nmoles/minXmg protein, n=42] groups (ANOVA, NS). Table 2 shows the absence of differences in postmortem frontal and occipital cortical IMPase activity between the four diagnostic groups.

Table 2
IMPase activity in postmortem brain specimens

Subjects	IMPase activity, nmoles/minXmg protein	
	Frontal cortex	Occipital cortex
Bipolar patients	1.52±0.11	1.54±0.11
	n=15	n=15
Control subjects	1.61±0.10	1.59±0.14
	n=14	n=15
Schizophrenic patients	1.61±0.14	1.37±0.10
	n=13	n=15
Unipolar patients	1.36±0.12	1.50±0.12
	n=15	n=15

Results are means ± SEM
ANOVA for both frontal and occipital cortex = Not Significant

Discussion

The present study does not explain the discrepancy in our previous findings of reduced IMPase activity in lymphocyte-derived cell lines from bipolar patients (Shamir et al 1998) vs. the lack of difference in postmortem brain tissue (Shimon et al 1997). Using the Stanley Brain Collection (Torrey et al 1999), which is a newer and a better-controlled brain bank, we again found no difference in the enzyme's activity among the groups, and in a small group of lymphocyte-derived cell lines from bipolar patients we confirmed a reduced IMPase activity. The latter reduction was shown to be specific to cells derived from bipolar patients compared with schizophrenic or unipolar patients.

Lymphocyte-derived cell line IMPase activity is reduced in bipolar disorder but not in schizophrenia or unipolar depression. However, the poor re-assay correlation suggests that the finding is not a consistent trait marker that defines an individual, in the way that serum cholesterol is a risk marker for cardiovascular disease. Rather, the low IMPase activity in lymphocyte-derived cell lines seems to replicate only as a group effect. This might be similar to haemoglobin levels in glucose-6-phosphate dehydrogenase (G6PD) deficiency, which are low in a group of G6PD-deficient patients but not low in the same individual at different points sampled over time (Lotspeich-Steininger et al 1992). If this analogy is correct, perhaps the IMPase gene (IMPA) in bipolar disorder responds with turn-off to various delicate environmental differences in handling of cultured lymphocyte-derived cell lines, whereas the IMPA gene in controls is less likely to respond this way. Speculatively, this could be due to a mutation in the promotor region.

A possible clue to the discrepancy of findings between brain and lymphocyte-derived cell lines may be given by the recent cloning of two human IMPA genes: the IMPA-1 gene was mapped to chromosome 8q21.13-21.3 (Sjoholt et al 1997); IMPA-2 was located on chromosome 18p11.2 (Yoshikawa et al 1997). Sjoholt et al (1999) reported that IMPA-1 and IMPA-2 are similarly expressed in brain, while in peripheral leukocytes IMPA-2 expression is higher than that of IMPA-1.

It is possible that, despite the numerous divisions in cell culture, lymphocyte-derived cell line IMPase is still affected by patients' drug treatment at the time of sampling, as reported for O6-alkylguanine-DNA alkyltransferase activity in lymphocyte-derived cell lines from Hodgkin's disease patients (Sagher et al 1989). Since most drugs for bipolar disorder affect second messengers, altered IMPase could be an artifact of such treatment. However, if lymphocyte-derived cell lines IMPA-2 levels reflect IMPA-2 levels in some specific brain area where IMPA-2 is the critical IMPase, then our findings could be aetiologically important for bipolar disorder.

Acknowledgment
Supported by a NARSAD Independent Investigator Award to G.A. Postmortem brains were donated by the Stanley Foundation Brain Consortium courtesy of Drs. Liewellyn B. Bigelow, Juraj Cervenak, Mary M. Herman, Thomas M. Hyde, Joel E. Kleinman, Jose D. Paltan, Robert M. Post, E. Fuller Torrey, Maree J. Webster and Robert H. Yolken.

References

Atack JR, Broughton HB, Pollack SJ (1995) Structure and mechanism of inositol monophosphatase. FEBS Lett 361: 1-7.

Bennett ER, Yedgar S, Lerer B, Ebstein RP (1991) Phospholipase A2 activity in Epstein-Barr virus-transformed lymphoblast cells from schizophrenic patients. Biol Psychiatry 29: 1058-1062.

Berridge MJ, Downes CP, Hanley MR (1989) Neural and developmental actions of lithium: a unifying hypothesis. Cell 59: 411-419.

Ebstein RP, Bennett ER, Hadjez J, Silver H, Yedgar S, Lerer B (1990) Cyclic AMP second messenger signal generation in EBV-transformed lymphoblastoid cells from schizophrenic patients. J Psychiatr Res 24: 121-127.

Hallcher LM, Sherman WR (1980) The effects of lithium ion and other agents on the activity of myo-inositol-1-phosphatase from bovine brain. J Biol Chem 255: 10896-10901.

Jope RS (1999) A bimodal model of the mechanism of action of lithium. Mol Psychiary 4: 21-25.

Jope RS, Song L, Li PP, Young LT, Kish SJ, Pacheco MA, Warsh JJ (1996) The phosphoinositide signal transduction system is impaired in bipolar affective disorder brain. J Neurochem 66: 2402-2409.

Lotspeich-Steininger CA, Steine-Martin EA, Kopeke JA (1992) Clinical Hematology. In: Hansen DM (ed) Hereditary Anemias of Increased Destruction. J. B. Lippincott Company, Philadelphia, pp 250-254.

Manji HK, Potter WZ, Lenox RH (1995) Signal transduction

pathways. Molecular targets for lithium's action. Arch Gen Psychiatry 52: 531-543.

Nemanov L, Ebstein R, Belmaker R, Osher Y, Agam G (1999a) Effect of bibolar disorder on lymphocyte inositol monophosphatase mRNA levels. Int J Neuropsycopharmacol 2: 25-29.

Nemanov L, Ebstein RP, Shamir A, Etack JR, Belmaker RH, Agam G (1999b) Effect of affective disorders and lithium treatment on inositol monophosphatase transcription and translation. In: Birch NJ, Gallicchio V, Becker RW (eds) Lithium: 50 Years of Psychopharmacology; new perspectives in biochemical research. Weinder Publishing Group, Cheshire, Connecticut, pp 116-135.

Sagher D, Karrison T, Schwartz JL, Larson RA, Strauss B (1989) Heterogeneity of O6-alkylguanine-DNA alkyltransferase activity in peripheral blood lymphocytes: relationship between this activity in lymphocytes and in lymphoblastoid lines from normal controls and from patients with Hodgkin's disease or non-Hodgkin's lymphoma. Cancer Res 49: 5339-5344.

Shamir A, Ebstein RP, Nemanov L, Zohar A, Belmaker RH, Agam G (1998) Inositol monophosphatase in immortalized lymphoblastoid cell lines indicates susceptibility to bipolar disorder and response to lithium therapy. Mol Psychiatry 3: 481-482.

Shimon H, Agam G, Belmaker RH, Hyde TM, Kleinman JE (1997) Reduced frontal cortex inositol levels in postmortem brain of suicide victims and patients with bipolar disorder. Am J Psychiatry 154: 1148-1150.

Shimon H, Sobolev Y, Davidson M, Haroutunian V, Belmaker RH, Agam G (1998) Inositol levels are decreased in postmortem brain of schizophrenic patients. Biol Psychiatry 44: 428-432.

Sjoholt G, Molven A, Lovlie R, Wilcox A, Sikela JM, Steen VM (1997) Genomic structure and chromosomal localization of a human myo-inositol monophosphatase gene (IMPA). Genomics 45: 113-122.

Sjoholt G, Ak G, Lovlie R, Jo BAM, Steen VM (1999) Characterization and polymorphism screening of inositol monophosphatase genes in manic-depressive patients. 50th Anniversary of Lithium in Clinical Medicine. KY, Lexington.

Torrey EF, Webster M, Knable M, Johnston N, Tolken RH (1999) The Stanley Foundation brain collection and Neuropathology Consortium. Schizoph Res 39 :101-106.

Yoshikawa T, Turner G, Esterling LE, Sanders AR, Detera-Wadleigh SD (1997) A novel human myo-inositol monophosphatase gene, IMP.18p, maps to a susceptibility region for bipolar disorder. Mol Psychiatry 2: 393-397.

World J Biol Psychiatry (2001) 2, 99 - 102

BRIEF REPORT ▸

Movement Disorder, Memory, Psychiatric Symptoms and Serum DHEA Levels in Schizophrenic and Schizoaffective Patients

Debra S. Harris, Owen M. Wolkowitz, Victor I. Reus

Department of Psychiatry, University of California, San Francisco, California, USA

Summary

Objective: *Reports of low levels of dehydroepiandrosterone (DHEA) or its sulphate (DHEA-S) in some schizophrenic patients and in some persons with poorer motoric and cognitive functioning led us to examine clinical correlates of serum DHEA and DHEA-S levels in schizophrenic patients.*

Method: *Ratings of abnormal movements, memory and psychiatric symptoms in 17 medicated chronic schizophrenic or schizoaffective inpatients at a state hospital were correlated with serum DHEA and DHEA-S levels, and their ratios with serum cortisol.*

Results: *Controlling for age, higher DHEA levels and/or higher DHEA/cortisol ratios were significantly correlated with lower symptom ratings on the Brief Psychiatric Rating Scale, better performance on some measures of memory, and lower ratings of parkinsonian symptoms.*

Conclusion: *Relatively low DHEA levels or DHEA/cortisol ratios may identify a particularly impaired subgroup of medicated patients with chronic schizophrenia. Potential implications are discussed.*

Key words: *dehydroepiandrosterone (DHEA), cortisol, schizophrenia, movement disorder, memory.*

Correspondence:
Debra S. Harris, M.D.
Department of Psychiatry
Box CPR-0984
University of California
San Francisco Medical Center
401 Parnassus Ave.
San Francisco
CA 94143-0984
USA
Tel: + 1 415 476 7491
Fax: + 1 415 476 7690
E-mail: dharris@itsa.ucsf.edu

Acknowledgements
Supported by grants from the National Alliance for Research in Schizophrenia and Depression (NARSAD), the National Alliance for the Mentally Ill (NAMI), the Stanley Foundation, the California Department of Mental Health and Napa State Hospital. We thank Scott Espinosa for his phlebotomy assistance and Dr William Raum for conducting the hormone assays.

This work was previously presented as a poster in the New Research Session, Annual Meeting of the American Psychiatric Association, Washington, DC, 1999

Introduction

Dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S) [together referred to as DHEA(S)], the major circulating steroids in humans, are neuroprotective and memory-enhancing, and enhance neuronal plasticity and adaptive responses to neuronal injury in animal models (Bologa et al 1987; Herbert 1998). Whether similar effects are seen in humans is unknown. However, low levels of DHEA(S) have been reported in some demented patients (for review see Wolkowitz and Reus 2000) as well as in community-dwelling elderly with poor memory, gait and balance (Berkman et al 1993; Wolkowitz and Reus 2000). Patients with schizophrenia have variably been reported to have increased or decreased levels of DHEA(S) (Erb et al 1981; Oades and Schepker 1994; Wolkowitz and Reus 2000), and early clinical trials in this population reported favourable treatment effects with DHEA (Strauss et al 1952). Nonetheless, the clinical correlates of DHEA(S) levels in schizophrenic populations have not been studied.

DHEA(S) levels decrease with advancing age in humans, are generally lower in women than in men, may be lower in some affectively ill patients, and are reduced in patients with diabetes mellitus [(Ganzini et al 1992; Jeste and Caligiuri 1993; Woerner et al 1993) for review see (Wolkowitz and Reus 2000)]. Since all of these are risk factors for developing tardive dyskinesia, it is possible that low DHEA(S) levels confer vulnerability to its development. We hypothesized, based on the above data, that lower levels of DHEA(S) would identify patients with increased psychiatric symptomatology, more severe movement disorder and decreased memory. Since the biological activity of DHEA(S) may be related to circulating cortisol levels (Herbert 1998; Wolkowitz and Reus 2000), we also assessed behavioural correlations with DHEA(S)/cortisol ratios.

Methods

Adult inpatients at Napa State Hospital (Napa, CA) were recruited. Inclusion criteria were a DSM-III-R diagnosis of schizophrenia or schizoaffective disorder, age 18 to 95, and a history of ≥ one year of continuous neuroleptic use. Neuroleptic doses were stabilized (defined as no more than 50% change in dose for at least three months and no neuroleptic dosage changes at all

for one month before testing), no changes in non-neuroleptic medication doses for two weeks, and no additional psychotropic medications (PRNs) for 48 hours. Menstruating women were assessed between days four and 12 of their menstrual cycle.

Exclusion criteria were significant acute medical illness, pregnancy, and current clozapine or hormone use (including oestrogen replacement therapy and birth control pills). Subjects who were taking adjunctive benzodiazepines or anticonvulsants were not excluded (see below). After complete description of the study to the subjects and guardian, if applicable, written informed consent was obtained.

Abnormal movements were rated using the St. Hans Rating Scale (Gerlach and Korgard 1993). Psychiatric symptoms were assessed with the 24-item Brief Psychiatric Rating Scale (BPRS) (Faustman and Overall 1999). A verbal memory test (Weingartner et al 1992) assessed attention and working memory, episodic vs. semantic memory, free recall vs. recognition memory, and effort-demanding vs. automatic processing. All assessment procedures were performed by the same rater (DSH). Subjects had blood drawn between 8:00 a.m. and 12 noon for assay of DHEA, DHEA-S, and cortisol. All blood samples were assayed in the same batch. Hormones were assayed in triplicate by double antibody, I-125 based radioimmunoassay (Dr. William Raum, UCLA; reagents from ICN/RLS).

DHEA(S) and DHEA(S)/cortisol ratios were correlated with the behavioural measures using partial correlation coefficients, controlling for age, which is a possible confound (SPSS software). In order to assess whether neuroleptic doses were directly correlated with DHEA(S) levels and, hence, introduced spurious correlations with clinical measures, we also correlated neuroleptic doses in chlorpromazine equivalents (Hollister 1973; Physicians Desk Reference 1997; Bezchlibnyk-Butler and Jeffries 1997) with hormone levels. Since benzodiazepines and certain anticonvulsants may alter DHEA levels, we assessed correlations between DHEA(S) levels and clinical ratings in the whole subject sample as well as in only those subjects not receiving these drugs (n = 13). Since results were comparable, we report correlations using all subjects to conserve power. Similarly, data from male and female subjects were not different and were therefore combined. All subjects were taking typical neuroleptics, except one who was receiving risperidone. Her measures were similar to those of the rest of the group and included in the analysis.

Results

• Subjects

Nine male and eight female patients were recruited. Their average age was 48 years (range = 31-66). Fourteen subjects had schizophrenia and three schizoaffective disorder. The median daily dose of neuroleptic in chlorpromazine equivalents was 1000 mg (range 50-4000 mg).

The mean ± SD total BPRS rating for the group was 75 ± 16.4, cortisol level 13.0 mcg/dl ± 3.4, DHEA level 5.2 ng/ml ± 4.3, and DHEA-S level 1448 ng/ml ± 682. The mean hormone values were within normal limits for the laboratory used, though individual subjects had values outside the normal range.

• DHEA and psychopathology (Table 1)

The DHEA/cortisol ratio (but not the individual hormones, DHEA, DHEA-S, or cortisol) was significantly negatively correlated with total BPRS ratings ($p < 0.05$). Statistically significant BPRS subscales which contributed to this finding were: positive symptoms ($p < 0.01$), negative symptoms ($p < 0.05$), thinking disturbance ($p < 0.05$), and withdrawal-retardation ($p < 0.05$). Specifically, higher DHEA/cortisol ratios were associated with less severe symptomatology.

Table 1
Correlations of hormone levels with measures of psychiatric symptoms, memory, and movement (values are correlation coefficients)

Controlling for age:

	DHEA	DHEA-S	Cortisol	DHEA/ Cortisol	DHEA-S/ Cortisol
Psychopathology (BPRS)					
BPRS Total	-0.38	-0.20	-0.07	-0.56*	-0.18
Memory					
Attention and Working Memory	+0.55*	+0.12	+0.29	+0.63†	+0.07
Free Recall Total	+0.45	+0.10	+0.22	+0.52*	+0.08
Automatic Processing	+0.26	-0.07	+0.09	+0.30	-0.06
Semantic Memory	+0.03	+0.51*	-0.08	+0.27	+0.57*
Movement					
Global Parkinsonism	-0.66†	+0.07	-0.23	-0.70†	+0.18
Global Hyperkinesia	-0.22	+0.20	-0.17	-0.19	+0.29

* = $p<0.05$ † = $p<0.01$

• DHEA and memory (Table 1)

DHEA was significantly positively correlated with attention and working memory ($p < 0.05$) and the DHEA/cortisol ratio with attention and working memory ($p < 0.01$) and total free recall ($p<0.05$). DHEA-S and the DHEA-S/cortisol ratio were significantly positively correlated with semantic memory ($p < 0.05$).

• Correlations between DHEA and movement disorder measures (Table 1)

DHEA and the DHEA/cortisol ratios (but not DHEA-S or the DHEA-S/cortisol ratios) were

significantly negatively correlated with ratings of global parkinsonism ($p < 0.01$). Statistically significant specific parkinsonian items which contributed to this finding were: posture ($p < 0.001$) and rigidity ($p < 0.05$) (DHEA and the DHEA/cortisol ratio), and bradykinesia ($p < 0.05$) and gait ($p < 0.05$) (the DHEA/cortisol ratio only). Correlations between hormone levels and the hyperkinetic ratings (e.g. tardive dyskinesia) were nonsignificant.

• Hormone levels and neuroleptic dose

Cortisol levels were significantly correlated with chlorpromazine equivalent doses ($r=+0.65$, $p=0.007$) (i.e. subjects receiving higher neuroleptic doses had higher cortisol levels) but DHEA ($r=+0.24$, $p=0.39$) and DHEA-S levels ($r=-0.20$, $p=0.45$) were not. Also, chlorpromazine equivalent doses were not significantly correlated with clinical variables.

Discussion

In this study, lower DHEA levels and/or DHEA/cortisol ratios were associated with higher ratings of psychopathology, poorer memory performance, and more severe parkinsonian movements. These data raise the possibility that, at least in a medicated, severely treatment refractory state hospital population, lower DHEA levels (or ratios to cortisol) identify a particularly impaired subpopulation of patients with schizophrenia or schizoaffective disorder.

Several mechanisms exist which might account for the relationships observed, including DHEA's effects on dopamine and serotonin transmission and on GABA-A, sigma and NMDA receptor activity (Baulieu 1997). It is challenging to explain the observed inverse correlations of DHEA/cortisol ratios with both psychosis and parkinsonian ratings, since these clinical phenomena have been related to increased and decreased dopamine activity, respectively. However, preclinical data demonstrate DHEA(S)'s ability to both increase and decrease regional brain dopamine content as well as to have both GABA agonist and GABA antagonist effects (Demirgören et al 1991; Spivak 1994; Garcia de Yebenes et al 1995; Porter et al 1995; Imamura and Prasad 1998). In any event, the association of lower DHEA/cortisol ratios with higher psychosis ratings may be consistent with the beneficial effects of DHEA supplementation in schizophrenic patients noted by Strauss et al (1952).

Higher DHEA levels and higher DHEA/cortisol ratios were related to better attention and working memory and free recall, and higher DHEA-S levels and DHEA-S/cortisol ratios were related to better semantic memory. This is consistent with the finding of Reus et al (1993) that higher DHEA-S/cortisol ratios were correlated with better automatic processing and semantic memory in normals. However, these relationships were not seen with all facets of cognition tested in the present study, so the clinical significance of this finding is unclear.

DHEA levels and the DHEA/cortisol ratio were also inversely related to parkinsonian symptom severity. This may be consistent with findings in healthy elderly subjects that higher DHEA-S levels are associated with better gait and balance (Berkman et al 1993), although in that study DHEA-S rather than DHEA levels were assessed. The relationship in our study cannot be explained by the fact that higher neuroleptic doses were correlated with higher cortisol levels (thereby yielding a lower DHEA/cortisol ratio), since DHEA levels alone were similarly correlated with the parkinsonian ratings (and cortisol was not). Also, neuroleptic dose was not related to clinical variables, so the inverse relationship between DHEA and parkinsonian ratings and psychopathology ratings was unlikely to be a result of neuroleptic treatment. Contrary to our hypothesis, hormone levels did not show any consistent relationship with measures of tardive dyskinesia.

Conclusions from this study are limited by its small sample size and by the simultaneous assessment of multiple correlations. Furthermore, the findings may not generalize to less treatment refractory schizophrenic patients or to unmedicated patients. Nonetheless, these results suggest that low DHEA levels and low DHEA to cortisol ratios are associated with more severe illness in chronic schizophrenic patients, and they raise the possibility that DHEA treatment may have beneficial effects in this population (Strauss et al 1952; Wolkowitz and Reus 2000).

References

Baulieu EE (1997) Neurosteroids: of the nervous system, by the nervous system, for the nervous system. Recent Prog Horm Res 52: 1-32.

Berkman LF, Seeman TE, Albert M, Blazer D, Kahn R, Mohs R, Finch C, Schneider E, Cotman C, McClearn G, Nesselroade J, Featherman D, Garmezy N, McKhann G, Brim G, Prager D, Rowe J (1993) High, usual and impaired functioning in community-dwelling older men and women: findings from the MacArthur Foundation Research Network on Successful Aging. J Clin Epidemiol 46 (10): 1129-1140.

Bezchlibnyk-Butler KZ, Jeffries JJ (1997) Clinical Handbook of Psychotropic Drugs. Hogrefe & Huber Publishers, Seattle.

Bologa L, Sharma J, Roberts E (1987) Dehydroepiandrosterone and its sulphate derivative reduce neuronal death and enhance astrocytic differentiation in brain cell cultures. J Neurosci Res 17: 225-234.

Demirgören S, Majewska MD, Spivak CE, London ED (1991) Receptor binding and electrophysiological effects of dehydroepiandrosterone sulfate, an antagonist of the GABAA receptor. Neuroscience 45(1): 127-135.

Erb JL, Kadane JB, Tourney G, Mickelsen R, Trader D, Szabo R, Davis V (1981) Discrimination between schizophrenic and control subjects by means of plasma dehydroepiandrosterone measurements. J Clin Endocrinol Metab 52 (2): 181-186.

Faustman WO, Overall JE (1999) The Brief Psychiatric Rating Scale. In: Maurish M (ed) Use of Psychological Testing for Treatment Planning and Outcome Assessment. Lawrence Erlbaum Associates, Hillsdale, NJ, pp 791-830.

Ganzini L, Casey DE, Hoffman WF, Heintz RT (1992) Tardive dyskinesia and diabetes mellitus. Psychopharmacol Bull 28 (3): 281-286.

Garcia de Yebenes E, Hong M, Pelletier G (1995) Effects of dehydroepiandrosterone (DHEA) on pituitary prolactin and arcuate nucleus neuron tyrosine hydroxylase mRNA levels in the rat. J Neuroendocrinol 7 (8): 589-595.

Gerlach J, Korgard S (1993) The St. Hans Rating Scale for extrapyramidal syndromes: reliability and validity. Acta Psychiatr Scand 87 (4): 244-252.

Herbert J (1998) Neurosteroids, brain damage, and mental illness. Exp Gerontol 33 (7/8): 713-727.

Hollister LE (1973) Clinical Use of Psychotherapeutic Drugs. Charles C. Thomas, Springfield, IL.

Imamura M, Prasad C (1998) Modulation of GABA-gated chloride ion influx in the brain by dehydroepiandrosterone and its metabolites. Biochem Biophys Res Commun 243 (3): 771-775.

Jeste DV, Caligiuri MP (1993) Tardive dyskinesia. Schizophr Bull 19 (2): 303-315.

Oades RD, Schepker R (1994) Serum gonadal steroid hormones in young schizophrenic patients. Psychoneuroendocrinology 19 (4): 373-385.

Physicians Desk Reference (1997) Medical Economics Company, Inc, Montvale, NJ.

Porter JR, Abadie JM, Wright BE, Browne ES, Svec F (1995) The effect of discontinuing dehydroepiandrosterone supplementation on Zucker rat food intake and hypothalamic neurotransmitters. Int J Obes Relat Metab Disord 19 (7): 480-488.

Reus VI, Wolkowitz OM, Roberts E, Chan T, Turetsky N, Manfredi F, Weingartner H (1993) Dehydroepiandrosterone (DHEA) and memory in depressed patients. Neuropsychopharmacology 9: 66S.

Spivak CE (1994) Desensitization and noncompetitive blockade of GABAA receptors in ventral midbrain neurons by a neurosteroid dehydroepiandrosterone sulfate. Synapse 16 (2): 113-122.

Strauss EB, Sands DE, Robinson AM, Tindall WJ, Stevenson WAH (1952) Use of dehydroisoandrosterone in psychiatric treatment: a preliminary survey. Br Med J 2: 64-66.

Weingartner HJ, Eckardt M, Molchan S, Sunderland T, Wolkowitz O (1992) Measurement and interpretation of changes in memory in response to drug treatments. Psychopharmacol Bull 28 (4): 331-340.

Woerner MG, Saltz BL, Kane JM, Lieberman JA, Alvir JM (1993) Diabetes and development of tardive dyskinesia. Am J Psychiatry 150 (6): 966-968.

Wolkowitz OM, Reus VI (2000) Neuropsychiatric Effects of Dehydroepiandrosterone (DHEA). In: Kalimi M, Regelson W (eds) Dehydroepiandrosterone (DHEA): Biochemical, Physiological and Clinical Aspects. Walter De Gruyter, Berlin, pp 271-298.

World J Biol Psychiatry (2001) 2, 103 - 105

CASE REPORT/CASE SERIES ▸

Attenuation of HPA Axis Hyperactivity and Simultaneous Clinical Deterioration in a Depressed Patient treated with Mirtazapine

Cornelius Schüle, Thomas Baghai, Peter Zwanzger, Rainer Rupprecht

Department of Psychiatry, Ludwig-Maximilians-University, Munich, Germany

Summary

It has been suggested that hypothalamic-pituitary-adrenal (HPA) system dysregulation plays an important role in the pathophysiology of depression and that normalization of HPA axis hyperactivity precedes successful treatment with antidepressants. We report the case of a 61-year-old patient suffering from a major depressive episode who underwent the combined dexamethasone suppression/CRH stimulation test (DEX/CRH test) before and again after one week of mirtazapine treatment. While the patient showed a marked decrease of cortisol and ACTH secretion during the DEX/CRH test within one week, a pronounced and ongoing deterioration of depressive symptoms with suicidal thoughts occurred that was resistant to antidepressant medication and had to be treated with electroconvulsive therapy. Apparently, mirtazapine rapidly attenuates HPA axis hyperactivity in depressed patients via direct pharmacoendocrinological effects. However, this amelioration of HPA system dysregulation is not necessarily accompanied by clinical improvement.

Key words: *mirtazapine, major depression, dexamethasone/corticotropin-releasing hormone test, cortisol, adrenocorticotropic hormone.*

Correspondence:
Cornelius Schüle, M.D.
Department of Psychiatry
Ludwig-Maximilians-University
Nussbaumstrasse 7
80336 Munich
Germany
Tel: +49 89 5160 5810
Fax: +49 89 5160 5391
E-mail:
Cornelius.Schuele@psy.med.uni-muenchen.de

Introduction

Preclinical and clinical studies suggest that hypothalamic-pituitary-adrenal (HPA) system dysregulation is related to the occurrence of depression (Holsboer 2001). Moreover, there is evidence that antidepressants may act in part through normalization of HPA system activity. Heuser and colleagues performed serial dexamethasone suppression/CRH stimulation tests (DEX/CRH tests) in depressed patients treated with amitriptyline and found a gradual normalization of the cortisol response during the DEX/CRH test throughout the clinical course towards remission (Heuser et al 1996). Furthermore, in patients who responded clinically to antidepressant therapy but had a substantially increased cortisol response in the DEX/CRH test at discharge, a higher risk for relapse within the following six months was demonstrated (Zobel et al 1999).

The new antidepressant agent mirtazapine acts as an antagonist at presynaptic α_2-receptors and at postsynaptic 5-HT_2 and 5-HT_3 receptors. Mirtazapine enhances the release of noradrenaline (NA) by blocking α_2 autoreceptors (De Boer 1995) and increases serotonergic neurotransmission, especially in the hippocampus, via an increase of serotonin (5-HT) cell firing and a blockade of α_2-adrenergic heteroreceptors at the 5-HT nerve terminals (Haddjeri et al 1997). In contrast to reuptake inhibitors of NA or 5-HT, mirtazapine showes no evidence of noradrenergic or serotonergic stimulatory effects on anterior pituitary hormones but acutely inhibits cortisol secretion in healthy subjects when given as a single dose of 15 mg. This acute cortisol inhibition by mirtazapine is presumably a result of 5-HT_2 receptor antagonism (Laakmann et al 1999). To further assess the impact of mirtazapine treatment on HPA system activity in depression, we studied a male depressed patient who underwent the DEX/CRH test before and again after one week of mirtazapine treatment.

Case report

A 61-year-old farmer was admitted to an open ward of our Department of Psychiatry. He was suffering from his second depressive episode according to DSM-IV criteria and had been treated with doxepine and trimipramine for several months without any treatment response. At admission, he was moderately depressed and had a

score of 23 on the 21-item version of the Hamilton Rating Scale for Depression (21-HRSD; Hamilton 1960). His main complaints were depressed mood, loss of energy, slight psychomotor agitation, insomnia, and loss of libido and appetite. There were neither paranoid ideas nor hallucinations. Moreover, the patient had no suicidal thoughts.

After a drug-free interval of five days (chloralhydrate was applied in case of sleep difficulties), the first DEX/CRH test was performed (Test 1). The patient received an oral dose of 1.5 mg dexamethasone (DEX) at 11:00 p.m. the night before the CRH challenge. On the following day an intravenous catheter was inserted into an anticubital vein at 2:00 p.m. At 3:02 p.m. 100 µg hCRH was injected within 30 seconds. Blood samples were collected at 2:00, 3:00, 3:15, 3:30, 3:45, 4:00 and 4:15 p.m. for cortisol and ACTH measurements. During the first DEX/CRH test (Test 1) the patient showed elevated postdexamethasone cortisol and ACTH levels (before CRH challenge) and a pronounced CRH-induced cortisol and ACTH stimulation (Figure 1). Subsequently, the patient was treated with mirtazapine at a dosage of 45 mg per day. During the first four days of mirtazapine treatment a marked deterioration of depressive symptoms occurred. The patient developed hypochondriac delusions in that he was convinced he was infected with the HIV virus. He thought he was going to die of AIDS. Moreover, he had the feeling that he was not able to swallow and would starve as a consequence. The patient became extremely agitated and could not sleep any more. He became suicidal and even wrote a farewell letter announcing his intention, which fortunately was found by staff. Thus, he had to be transferred to a closed ward to prevent a suicide attempt. After one week of mirtazapine treatment, the DEX/CRH test was carried out for a second time. In contrast to the clinical deterioration, the patient showed an amelioration of HPA dysregulation in the second DEX/CRH test (Test 2) (Figure 1). The postdexamethasone cortisol and ACTH levels (before CRH application) were markedly lower than in Test 1. Furthermore, the CRH-induced cortisol and ACTH stimulation were also attenuated. However, the 21-HRSD score was 36 on the day of Test 2.

During the following eight weeks the patient received two different antidepressants (mirtazapine, clomipramine) at high dosages, two neuroleptics (haloperidol, risperidone), benzodiazepines, and lithium. Nethertheless, depressive symptoms, hypochondriac delusions and suicidal thoughts were resistant to psychopharmacological treatment. Therefore, the patient was subsequently treated with electroconvulsive therapy (ECT). After nine sessions of unilateral ECT within three weeks, the patient showed a pronounced alleviation of both depressive and delusional symptoms and was distanced from suicidality.

Discussion

The present case report describes a patient with moderate depressive symptoms and a hyperactivity of the HPA system in the DEX/CRH test at admission to hospital. During the first week of mirtazapine treatment there was a clinical worsening and simultaneous attenuation of HPA axis dysregulation. In this case, amelioration of HPA axis dysregulation was not followed by a favourable therapeutic outcome because the patient was refractory to psychopharmacological medication and had to be treated with ECT. Apparently, amelioration of HPA axis hyper-

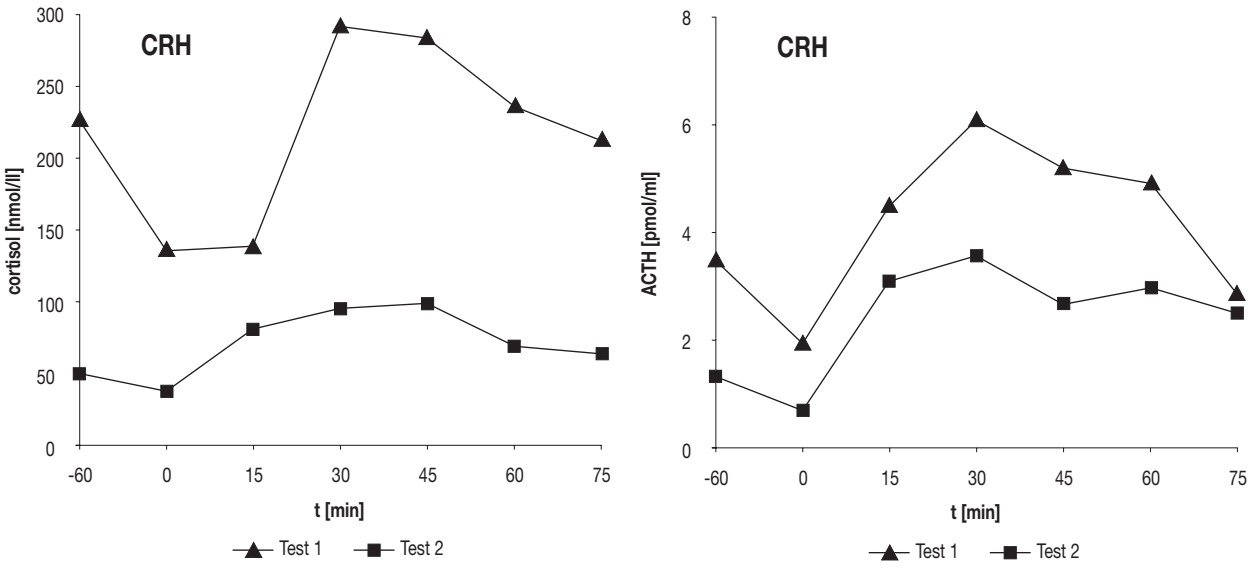

Figure 1
Combined dexamethasone suppression/CRH stimulation test (DEX/CRH test) in a depressed patient before mirtazapine treatment (Test 1) and after one week of mirtazapine treatment at a dosage of 45 mg per day (Test 2)

activity in the DEX/CRH test does not necessarily predict responsiveness to psychopharmacological treatment. However, it has to be considered that in our patient HPA system activity was still increased after one week of mirtazapine treatment (DEX/CRH Test 2), in spite of the marked reduction of cortisol and ACTH secretion.

In contrast to reuptake inhibitors, which are known to acutely stimulate cortisol secretion via noradrenergic and serotonergic mechanisms, mirtazapine is an acute inhibitor of cortisol and ACTH secretion (Laakmann et al 1999). Obviously, the rapid attenuation of HPA axis dysregulation in the patient described here is due to a direct pharmacoendocrinological effect of mirtazapine which may be different from the normalization of the hyperactive HPA system observed in depressed patients who have been successfully treated with reuptake inhibitors such as amitriptyline (Heuser et al 1996). Whereas mirtazapine presumably acts as an inhibitor of cortisol secretion via blockade of central 5-HT_2 receptors and acute reduction of hypothalamic CRH release, reuptake inhibitors may normalize HPA axis hyperactivity in depressed patients by means of enhancement of glucocorticoid receptor function (Barden et al 1995). Nethertheless, the downregulation of the hyperactive HPA system may contribute to the antidepressant efficacy of mirtazapine.

References

Barden N, Reul JM, Holsboer F (1995) Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system? Trends Neurosci 18: 6-11.

De Boer T (1995) The effects of mirtazapine on central noradrenergic and serotonergic neurotransmission. Int Clin Psychopharmacology 10 (Suppl 4): 19-23.

Haddjeri N, Blier P, De Montigny C (1997) Effects of long-term treatment with the α_2-adrenoceptor antagonist mirtazapine on 5-HT neurotransmission. Naunyn Schmied Arch Pharmacol 355: 20-29.

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23: 66-62.

Heuser IJ, Schweiger U, Gotthardt U, Schmider J, Lammers CH, Dettling M, Yassouridis A, Holsboer F (1996) Pituitary-adrenal-system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects. Am J Psychiatry 153: 93-99.

Holsboer F (2001) Stress, hypercortisolism and corticosteroid receptors in depression: implicatons for therapy. J Affect Disord 62: 77-91.

Laakmann G, Schule C, Baghai T, Waldvogel E (1999) Effects of mirtazapine on growth hormone, prolactin, and cortisol secretion in healthy male subjects. Psychoneuroendocrinology 24: 769-784.

Zobel AW, Yassouridis A, Frieboes RM, Holsboer F (1999) Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. Am J Psychiatry 156: 949-951.

Reponse to Yaryura-Tobias et al (2000) Negative outcome after neurosurgery for refractory obsessive-compulsive spectrum disorder, World J Biol Psychiatry 1: 197-203.

Stephen Curran
Specialist Registrar in Psychiatry
Keith Matthews
Professor of Psychiatry
Dundee Neurosurgery for Mental Disorder Programme
Department of Psychiatry, Ninewells Hospital & Medical School, Dundee, United Kingdom

The importance of diligent, comprehensive and valid assessment of the clinical outcome following destructive neurosurgery for intractable mental disorder cannot be overstated. Without doubt, crude destructive procedures have been used despite an absence of critical appraisal of their efficacy and adverse effects. Nevertheless, considerable evidence has accrued to support the use of irreversible focal tissue ablation in the management of a restricted population of severely disabled patients with defined psychopathology. Given the rarity of such procedures within modern psychiatric practice, the report by Yaryura-Tobias and colleagues is timely and welcome. However, it is important that we require equivalent academic rigour when confronted with reports of negative or positive outcome.

Yaryura-Tobias and colleagues have presented brief clinical details for a series of five patients who received neurosurgical intervention for intractable obsessive compulsive disorder (OCD). Presenting a series of five patients with globally negative outcomes potentially casts a shadow over neurosurgical treatment. Unfortunately, it is difficult to consider these data within the necessary context. Were these five patients from a series of eight or 80? No pre-operative measures are available for two of these patients. Only one was followed up for over a year. One had a cingulotomy, three had capsulotomies, and one had both. How are we to evaluate such heterogeneous data? If we take Case 3, for example, we are informed of the apparent unresponsiveness of her obsessional symptoms to capsulotomy and of her subsequent severe depression and suicidal ideation. How do we know that this reflects a change from her pre-surgical status? Similarly, Case 4 must be considered without the benefit of essential pre-operative information. Indeed, the clinical description suggests a pervasive, severe and disabling neurological condition. Interpretation of the contribution of capsulotomy to his subsequent clinical course seems fraught with difficulty. Are we now considering a case series of three? These are, of course, the entirely legitimate criticisms that we would face if presenting a case series of five positive outcomes.

For Case 1, we do have some pre-operative data, but a short follow-up period (seven months) and no information at all about treatment post-surgery. Neurosurgery, of course, should never be proposed as a curative intervention - it is a treatment augmentation strategy. Which psychological and pharmacological treatments were applied in the post-operative period when symptomatic improvement was evident? Did these change? Were lesion placements and sizes confirmed by MRI? Was the early improvement due to the effects of acute brain oedema that subsequently resolved? With respect to the data presented, there was no significant change in Beck Depression Inventory (BDI) scores (Figure 2). Beck Anxiety Inventory (BAI) scores were not presented, and there were no attempts to quantify suicidality or self-harm. The appearance of generalised cerebral atrophy is acknowledged as a potentially clinically insignificant observation. Were there any attempts to assess its functional significance? Case 2 appears to have experienced a brief improvement in symptoms that was not sustained. Again, where were the lesions? Were they of adequate size? Could cerebral oedema have brought about the transient improvement? Substance misuse is frequently co-morbid with major depression and it is difficult to relate the cocaine use to surgery.

These comments ought not to be misinterpreted. We agree unreservedly with Yaryura-Tobias and colleagues that there is a duty to report the outcome of all neurosurgical operations for mental disorder. Only then can we make informed clinical judgements about the efficacy and acceptability of these treatments. Only then can we provide adequate advice to our patients. However, the presentation of negative outcome data from a small, heterogeneous and potentially unrepresentative series of patients serves no better purpose than the exaggerated, selective and uncritical reports of positive outcome.

Stephen Curran
Keith Matthews

Letters published in this Journal do not necessarily reflect the opinions of the Editors or the Editorial Board.

Suicide: An Unnecessary Death

Danuta Wasserman, M.D., Ph. D. (Ed), (Martin Dunitz Ltd, London, 2001, pp 250, £ 29.95)

Reviewed by Dan Rujescu and Ina Giegling, Department of Psychiatry, Ludwig-Maximilians-University, Munich, Germany

Danuta Wasserman has succeeded in editing an outstanding and important book on suicide. Suicide and attempted suicide are rather complex issues. It is therefore a pleasure to see how this book manages to be clear in extracting the essentials while at the same time avoiding oversimplifications. It performs a major service by providing an up-to-date source of information on this important topic.

A considerable number of people who commit suicide have had prior contact with staff from the health care sector. Under these circumstances, it is surprising that many health care professionals are not sufficiently aware of this problem. This book is based on work and research carried out by people who are well known in this field, and it addresses those clinicians who take care of suicidal patients. The book also gives a good overview and is a good introduction for those who want to begin work as researchers in the field of suicidology.

The book gives a good description of the editor, Danuta Wasserman, who wrote or co-authored several chapters, and of the contributors. The structure of the book, in eight major sections, helps with orientation. "Epidemiology" by José M. Bertolote is written from the global WHO perspective and gives an epidemiological overview of suicide in the world for the years 1959-2000. It seems a good chapter to start with since it points out the whole extent of the problem; among others, one million people take their own life every year and at least ten times as many attempt suicide. The section "Theoretical model of suicidal behaviour" has a chapter presenting an elaborated stress-vulnerability model for the development of the suicidal process. Danuta Wasserman succeeds in integrating the various neuropsychobiological permissive and protective factors into one model, including a plausible graph. The neurobiology of suicide and attempted suicide, an emerging field in suicidology, is highlighted by John Mann and Victoria Arango in the subsequent chapter. Family, twin and adoption studies, molecular genetic studies and studies on the serotonin metabolite 5-HIAA in cerebrospinal fluid and post-mortem brains are summarized. The third section elaborates on important risk groups for suicide and addresses psychiatric disorders and somatic diseases as well as social conditions in several chapters by Danuta Wasserman, Jan Fawcett, Alec Roy, Jouko Lönnqvist and Ilkka Henrik Mäkinen. The chapters on affective disorders and alcoholism give detailed reflections on the importance of these risk factors. The section "Risk situations for suicide and risk assessment" starts with two chapters by Danuta Wasserman which describe a wide range of negative life events that are associated with elevated suicide risk and the patients' distinctive experiences of them. For the clinician, the chapter by Nils Retterstøl and Lars Mehlum on attempted suicide as a risk factor for suicide should be especially important. What makes this chapter so interesting is that it uses epidemiological data, but is written from a clinical perspective. Two chapters by Danuta Wasserman, one on suicide risk assessment and one on the suicidal patient-doctor relationship, describe very nicely this sensitive topic. Suicide risk assessment is the most difficult kind of assessment in psychiatric practice, since it is about life and death, as stated by Danuta Wasserman. These chapters are also of immediate use for everyday clinical practice since the particularities and pitfalls in the management of the suicidal patient are described. Per Bech, Lis Raabaek Olsen and Anders Niméus contribute with a chapter on psychometric scales in suicide risk assessment. They concentrate on short and thus applicable scales, which measure different facets of this complex behaviour, and elaborate on the quality of the scales. The next section is dedicated to treatment. While there are an overwhelming number of different psychotherapeutic approaches to the suicidal patient, until now only cognitive-behavioural and dialectical behaviour therapy have proven to be effective in controlled clinical trials. These therapies are described in the chapter by Paul Salkovskis, including the two prominent cognitive mechanisms identified in suicide attempters: problem-solving deficits and hopelessness. The chapter on pharmacotherapy by Hans-Jürgen Möller gives a clear overview of the treatment of suicidal patients and should be of special interest for the clinician. It deals with both the management of suicidal patients after psychosocial stress conditions and suicidal patients with a comorbid psychiatric diagnosis. It delineates the important distinctions of these patient groups and the appropriate treatment. The next section deals with two particular age groups: adolescents, written by Alan Apter, and the elderly, written by Diego De Leo and Gaia Meneghel. In many ways, both chapters are a book in a book as they cover all aspects of the respective topic. The next section is devoted to prevention, the ultimate

goal. In the introductory chapter, Danuta Wasserman describes the two major approaches to prevention, the health care and the public health approach. Next, she writes on suicide prevention in psychiatric patients by optimisation of treatment. Wolfgang Rutz gives an impressive example of reduction of suicide rates by adequate training of general practitioners, who often do not recognize the signs and symptoms of depression and suicidality and are not trained to give efficient pharmacotherapy. Jean-Pierre Soubrier highlights the cooperation with other physicians, Danuta Wasserman the impact on and of the psychiatric staff. Karen Dunne-Maxim and Edward Dunne emphasize the role of the family. In a surprising chapter, Danuta Wasserman and Airi Värnik help to understand why Peristroika in the former USSR was history's most effective suicide–prevention programme for men. Antoon Leenaars describes how controlling the environment, e.g. by controlling the availability of fire arms, can be an effective method to prevent suicide. Armin Schmidtke, Sylvia Schaller and Danuta Wasserman present guidelines for media communication of suicide, to prevent imitation, and the prevention of clustered suicide on psychiatric wards. And last but not least, Danuta Wasserman and Véronique Narboni give examples of suicide prevention in schools.

In summary, this book is written by outstanding experts in their field for "busy clinicians" who are interested in a compact, but comprehensive, overview of different aspects of suicide. It is designed for a broad audience who should profit immediately in the everyday treatment of patients. Thus, it is also of benefit for the patients, which is why this book should be of interest to a broad audience, and a great success.

Correspondence:
Dan Rujescu, M.D.
Molecular Neurobiology
Department of Psychiatry
Ludwig-Maximilians-University
Nussbaumstrasse 7
80336 Munich
Germany
Tel: +49 89 5160 5756
Fax: +49 89 5160 5779
E-mail: Dan.Rujescu@psy.med.uni-muenchen.de