

The Adrenochrome Hypothesis of Schizophrenia Revisited

JOHN SMYTHIES^{a,b,*}

^aDepartment of Psychology, Center for Brain and Cognition, University of California at San Diego, La Jolla, CA 92093-0109, USA; ^bDepartment of Neuropsychiatry, Institute of Neurology, Queen Square, London, UK

(Received 12 April 2001; In final form 18 April 2001)

This paper reviews the current status of the adrenochrome theory of schizophrenia. An account is first given of all the experiments in which adrenochrome was reported to induce psychotomimetic effects in normal volunteers. Then the evidence is presented that adrenochrome may actually occur in the brain as a metabolite of adrenaline in the C2 group of adrenergic neurons in the medulla, together with an account of current ideas of the function of these neurons in higher limbic functions. Lastly the recent evidence is reviewed that the gene for the enzyme glutathione S-transferase is defective in schizophrenia. This enzyme detoxifies adrenochrome.

Keywords: Schizophrenia; adrenochrome; adrenaline; C1–C3 adrenergic nuclei; neuromelanin

Hoffer *et al.* (1954) reported that adrenochrome, the autooxidative product of adrenaline, produced psychological changes in one normal subject (Osmond), who is an experienced subject in such experiments. He gave the most detailed first hand account that we currently possess of its effects. His reaction was characterized by profound introversion, bizarre ideation and minor visual aberrations. We suggested therefore that some cases of schizophrenia might result from the abnormal production of adrenochrome in the brain.

Schwartz *et al.* (1956) gave adrenochrome to two patients with schizophrenia and to one patient with an epileptic psychosis. They reported that one schizophrenic became catatonic and the other developed body-image disturbances and loosening of associations. In contrast, the patient with epilepsy became more relaxed and in better contact. However, the psychological evaluations in this study were very superficial. All three patients developed high voltage

slow waves in depth electrograms similar to those reported by Szatmari *et al.* (1955) in epileptic patients given adrenochrome. Taubman *et al.* (1957) reported that adrenochrome in normal volunteers produced “very impressive” visual illusions of color, movement and distance perception but did not report any thought disorder.

The most complete (and only placebo controlled) study was carried out by Grof *et al.* (1963) on 15 subjects (10 normal and five neurotic or psychopathic patients). They used “adrenochrome” prepared in two different laboratories, one by themselves (AV) and one by a pharmaceutical company (AL). There were clear chemical differences between these samples in that other products of adrenaline oxidation were differentially present. The placebo used a red dye *S*-azorubine. They employed two doses 15 and 30 mg of adrenochrome given by the sublingual route. Their reported results were that, all eight subjects given 30 mg of adrenochrome developed a psychotic reaction, which they characterized as a toxic psychosis of the Bonhoeffer type in five and as schizophreniform in three. At the 15 mg dose AL (in four subjects) produced no psychotic reactions whereas in the case of AV (nine subjects) one developed a toxic psychosis, one a schizophreniform psychosis and the rest failed to react.

During the psychotic reactions the following symptoms were reported:

- Thought disorder (8)
- Bizarre ideation (1)
- Derealization (5)
- Depersonalization (1)
- Body image disturbances (2)

*Address: Department of Psychology, Center for Brain and Cognition, University of California at San Diego, La Jolla, CA 92093-0109, USA. E-mail: smythies@psy.ucsd.edu.

Tactile hallucinations (2)
 Auditory hallucinations (1)
 Visual hallucinations (0)
 Minor visual illusions (3)
 Euphoria (5)
 Forced laughter (3)
 Heboid behavior (5)
 Bizarrely inappropriate behavior (1)
 Disinhibition (1)
 Psychomotor inhibition (1)
 Negativism (1)
 Paranoia (1)
 Complete loss of insight (2)

The authors noted that there were marked individual differences between the responses of different subjects. One normal subject had previously taken psilocybin and reported that the effects were quite different. In particular, the vivid visual hallucinations typically induced by drugs like LSD, mescaline and psilocybin were not reported by any subject.

The subjects were also given a word association test. In the subjects given adrenochrome there was an incidence of 25.5% of abnormal associations (mostly clang) whereas, in these subjects given the placebo this incidence was 6.7%. In six subjects an EEG was carried out and in five of these slow theta waves developed.

In the only reported negative non-anecdotal study in the literature (Rinkel and Solomon 1957) the experimenters used adrenochrome semicarbazone, which is a different substance altogether.

With regards to the pathological introversion vividly recorded by Osmond (which would not readily be detectable by purely objective studies), an old paper by Lindemann (1935) is of great interest. He injected 1 cm³ of a 0.1% solution of adrenaline intramuscularly into 48 subjects. He noted that their actions changed and became "...directed mainly towards inner experiences, the body, his own acts, and less towards outside objects, tasks, and other persons... The subject becomes less accessible, more self-absorbed, and his activities are colored more by fears and desires... We have an increase in inner tension, an exaggeration of instinctual needs with aggravation of conflicts, and increased awareness of restrictions and taboos." He noted that the "dynamic process" induced by adrenaline is very similar to that produced by mescaline. He continued "De Jong has called attention to the fact that the latter drug has a chemical structure similar to adrenaline itself... The question arises... whether or not under certain circumstances mescaline may appear in the body as a product of adrenaline metabolism." Seventeen years later Osmond and Smythies (1952) resurrected this hypothesis and supplied more biochemical details

with respect to the importance of transmethylation in such reactions.

Reviewing this evidence, it seems that adrenochrome, at an adequate dose, induces some form of psychosis—either "toxic" or "schizophreniform"—in some normal and neurotic subjects. Moreover, its reported effects are more like those seen in schizophrenia than are those produced by mescaline and related drugs. Why, then, did all research in this area cease abruptly in the early 1960s? The answer is what has come to be called "The Great Adrenochrome Fiasco". Hoffer (1957) published a paper in the *American Journal of Psychiatry* claiming to have detected adrenochrome in normal human blood. Six months later Szara *et al.* (1958) reported in the same journal that they could not detect adrenochrome in normal human blood. Hence the fiasco. However, there are two odd points about this controversy. The first is, if adrenochrome does occur in normal blood, why does no psychosis result? The second is that it seems more important to discover whether adrenochrome occurs in the brain (rather than in the blood) and if so under what circumstances. Macarthur *et al.* (2000) report that rat blood contains 200 nM "aminochrome". This is a mixture of adrenochrome and noradrenochrome but the proportion of each could not be ascertained. This level was doubled by the oxidative stress induced by bacterial toxins related to septic shock.

So the question today is whether there is any evidence that adrenochrome occurs in the brain? It has certainly been established that its two close relatives—noradrenochrome and dopaminochrome—occur in the brain, as they are obligatory metabolic precursors of neuromelanin which is abundant in the noradrenergic neurons of the locus coeruleus and in the dopaminergic neurons of the SNpc, respectively (Smythies 1996; Smythies and Galzigna 1998). Moreover 5-cysteinyl dopamine—a metabolite of dopamine quinone—has been detected in the human brain (Fornstedt *et al.* 1989). However, no psychological studies have been carried out on these two compounds. Their chemical instability would make any such studies difficult to carry out. The phenylethanolamine-*N*-methyltransferase-positive (PNMT⁺) adrenergic cell bodies in the brain are located in the C1–C3 group in the medulla. Some 20% of these neurons in the C2 group are pigmented (Gai *et al.* 1993). This makes it possible that adrenochrome may be present in these neurons. However, this pigment has never been formally identified as neuromelanin. Moreover, even if it is, it might have derived from dopamine or norepinephrine, which are necessary metabolic precursors of adrenaline, although kinetic considerations make this unlikely (Gai, personal communication).

At one time it was thought that the adrenergic system in the brain was involved only in low level

visceral functions. However, it now appears in primates that these nuclei project robustly to the medial thalamus, in particular to the paraventricular, parafascicular and mediodorsal nuclei (Rico and Cavada 1998) as well as to the amygdala, several hypothalamic nuclei, periaqueductal gray and other limbic areas (Herbert and Saper, 1992; Otake *et al.*, 1995; Nagatsu *et al.*, 1996; Lew *et al.*, 1997). This system has been linked to psychological stress (Otake *et al.* 1995). Adrenochrome secreted by adrenergic terminals in such basic limbic nuclei might well have deleterious effects.

Some very preliminary accounts report abnormalities of neuromelanin in the brain in some cases of schizophrenia. Kaiya (1980) found in one case of fatal catatonia very low levels of neuromelanin in the SNpc and very high levels in the locus coeruleus. One patient who died from neuroleptic malignant syndrome showed very low levels of neuromelanin in the SNpc and normal levels in the locus coeruleus (Gertz and Schmidt 1991). However, most cases of schizophrenia did not show hypopigmentation in the SNpc (Gertz and Schmidt 1991). Greiner and Nicholson (1965) reported increased general melanogenesis in prephenothiazine schizophrenia. Levels of 5-cysteinyldopamine are elevated in the caudate in schizophrenia (Carlsson *et al.*, 1994).

Recently, the first item of empirical evidence supporting the adrenochrome hypothesis has been presented by Harada *et al.* (2001). Catecholamine *o*-quinones (including adrenochrome) are, in part, detoxified by 5-conjugation with glutathione. This reaction is promoted by glutathione *S*-transferases 1 and 2 (GTM 1 and 2). Harada *et al.* (2001) studied DNA samples from 87 schizophrenics and 176 normal controls. They found an increased frequency of deletion of this gene (frequency of the GSTM1*O allele) in the schizophrenic group ($p = 0.0075$) and an even higher rate in the subgroup of disorganized schizophrenics ($p = 0.0008$). They suggested that the GSTM1 gene deletion may constitute a risk factor for schizophrenia associated with an increased toxic action of catecholamine *o*-quinones, including possibly adrenochrome, in the brain.

CONCLUSION

Of the generally accepted psychotomimetic agents only dimethyltryptamine and *O*-methylbufotenin have been detected *in vivo* (in the CSF in this case) (Smythies *et al.* 1979) but only in minute amounts. Moreover, we did not find increased levels of either in CSF from schizophrenic patients. The recent evidence that adrenochrome may occur in strategic areas of the brain related to anxiety and to basic limbic functions suggests that further research in this area is indicated. We need to know the identity of the

pigment of the C2 group and how it is formed and whether there are any abnormalities in the adrenergic system in the brain in schizophrenia. Very little is known about the basic neuropharmacology of adrenochrome (for a review of what is known see Smythies 1999). An enormous amount of attention has been paid to the dopamine and noradrenergic systems of the brain—very little to the adrenergic system. This imbalance needs to be corrected.

References

- Carlsson, A., Waters, A. and Hansson, L.O. (1994) "Neurotransmitter aberrations in schizophrenia: new findings", In: Fog, R., Gerlach, J. and Hemmingston, R., eds, *Schizophrenia. An Integrated View* (Munksgard, Copenhagen), pp 332–343.
- Fornstedt, B., Brun, A., Rosengren, E. and Carlsson, A. (1989) "The apparent autoxidation rate of catechols in dopamine-rich areas of the brain increases with the degree of depigmentation of substantia nigra", *J. Neural. Trans. Park. Dis. Den. Sect.* **1**, 279–295.
- Gai, W.P., Geffen, L.B., Denoroy, L. and Blessing, W.W. (1993) "Loss of C1 and C3 epinephrine-synthesizing neurons in the medulla oblongata in Parkinson's disease", *Ann. Neurol.* **33**, 357–367.
- Gertz, H-J. and Schmidt, L.G. (1991) "Low melanin content of substantia nigra in a case of neuroleptic malignant syndrome", *Pharmacopsychiatry* **24**, 93–95.
- Greiner, A.C. and Nicholson, G.A. (1965) "Schizophrenia-melaninism", *Lancet* **ii**, 1165.
- Grof, S., Vojtechovsky, M., Vitek, V. and Prankova, S. (1963) "Clinical and experimental study of central effects of adrenochrome", *J. Neuropsychiatr.* **5**, 33–50.
- Harada, S., Tachikawa, H. and Kawanishi, Y. (2001) "Glutathione *S*-transferase M1 gene deletion may be associated with susceptibility to certain forms of schizophrenia", *Biochem. Biophys. Res. Comm.* **281**, 267–271.
- Herbert, H. and Saper, C.B. (1992) "Organization of medullary adrenergic and noradrenergic projections to medullary periaqueductal gray matter in the rat", *J. Comp. Neurol.* **315**, 34–52.
- Hoffer, A. (1957) "Adrenochrome in blood plasma", *Am. J. Psychiat.* **114**, 0.
- Hoffer, A., Osmond, H. and Smythies, J. (1954) "Schizophrenia: a new approach part 2", *J. Ment. Sci.* **100**, 29–45.
- Kaiya, H. (1980) "Neuromelanin, neuroleptics and schizophrenia", *Neuropsychobiology* **6**, 241–248.
- Lew, J.Y., Matsumoto, Y., Pearson, J., Goldstein, M., Hokfelt, T. and Fuxe, K. (1977) "Localization and characterization of phenylethanolamine-*N*-methyltransferase in the brain of various mammalian species", *Brain Res.* **119**, 199–210.
- Lindemann, E. (1935) "The psychopathological effects of drugs affecting the vegetative system", *Am. J. Psychiat.* **91**, 983–1008.
- Macarthur, H., Westfall, T.C., Riley, D.P., Misko, T.P. and Salvemini, D. (2000) "Inactivation of catecholamines by superoxide gives new insights on the pathogenesis of septic shock", *Proc. Natl Acad. Sci. USA* **97**, 9753–9758.
- Nagutsu, I., Ikemoto, K., Takeuchi, T., Arai, T., Karasawa, N., Fujii, T. and Nagatsu, T. (1996) "Phenylethanolamine-*N*-methyltransferase-immunoreactive nerve terminals afferent to the mouse substantia nigra", *Neurosci. Lett.* **245**, 41–44.
- Osmond, H. and Smythies, J. (1952) "Schizophrenia: a new approach", *J. Ment. Sci.* **98**, 309–320.
- Otake, K., Ruggiero, D.A. and Nakamura, Y. (1995) "Adrenergic innervation of forebrain neurons that project to the paraventricular thalamic nucleus in the rat", *Brain Res.* **697**, 17–26.

- Rico, B. and Cavada, C. (1998) "Adrenergic innervation of the monkey thalamus; an immunohistochemical study", *Neuroscience* **84**, 839–847.
- Rinkel, M. and Solomon, A.C. (1957) "Chemical theories of psychosis", *J. Clin. Exp. Psychopath.* **18**, 323–334.
- Schwartz, B.E., Sem-Jacobsen, C. and Petersen, M.C. (1956) "Effects of mescaline, LSD-25 and adrenochrome on depths electrograms in man", *Arch. Neurol. Psychiat.* **75**, 579–587.
- Smythies, J. (1996) "On the function of neuromelanin", *Proc. R Soc. London B* **263**, 487–489.
- Smythies, J. (1999) "The neurotoxicity of glutamate, dopamine, iron and reactive oxygen species: functional interrelationships in health and disease: a review", *Neurotox. Res.* **1**, 27–39.
- Smythies, J. and Galzigna, L. (1998) "The oxidative metabolism of catecholamines in the brain: a review", *Biochim. Biophys Acta* **1380**, 19–162.
- Smythies, J.R., Morin, R.D. and Brown, G.B. (1979) "Identification of dimethyltryptamine and *o*-methylbufotenin in human cerebrospinal fluid by combined gas chromatography/mass spectrometry", *Biol. Psychiatr.* **14**, 549.
- Szara, S., Axelrod, J. and Perlin, S. (1958) "Is adrenochrome present in the blood?", *Am. J. Psychiatr.* **115**, 162–163.
- Szatmari, A., Hoffer, A. and Schneider, R. (1955) "The effect of adrenochrome and niacin on the electroencephalogram in epilepsy", *Am. J. Psychiat.* **111**, 603–616.
- Taubman, G. and Jantz, H. (1957) "Untersuchung über die dem adrenochrom zugeschriebenen psychotoxischen wirkungen", *Nervenarzt* **28**, 485–488.