The Potential of Trace Amines and Their Receptors for Treating Neurological and Psychiatric Diseases

M.D. Berry*

Department of Chemistry, Brandon University, 270, 18th Street, Brandon, Manitoba, Canada, R7A 6A9

Abstract: Mining of the human genome has revealed approximately 7000 novel proteins, which could serve as potential targets for the development of novel therapeutics. Of these, approximately 2000 are predicted to be G-protein coupled receptors. Within this group of proteins, a family of 18 mammalian receptors has recently been identified that appear to exhibit selectivity toward the so-called trace amines. The trace amines are a family of endogenous compounds with strong structural similarity to classical monoamine neurotransmitters, consisting primarily of 2-phenylethylamine, *m*- and *p*-tyramine, tryptamine, *m*- and *p*-octopamine and the synephrines. The endogenous levels of these compounds are at least two orders of magnitude below those of neurotransmitters such as dopamine, noradrenaline and 5-HT. The effects of these low physiological concentrations have been difficult to demonstrate but it has been suggested that they may serve to maintain the neuronal activity of monoamine neurotransmitters within defined physiological limits. Such an effect of trace amines would make them ideal candidates for the development of novel therapeutics for a wide range of human disorders. Although the demonstration of a trace amine family of receptors has seen a resurgence of interest in these endogenous compounds, with recent articles reviewing trace amine pharmacological and physiological responses, the potential clinical utility of the trace amine receptors has not been specifically addressed. Historically, trace amines have been implicated in a diverse array of human pathologies ranging from schizophrenia to affective disorders to migraine. Recent studies have strengthened some of this historical data by linking trace amine receptor polymorphisms and mutations to distinct clinical conditions. The aim of the current article is to review the previous studies linking trace amines to human pathology in the context of the recently discovered trace amine receptors and evidence of the existence of trace amine receptor polymorphisms and mutations associated with such disorders. In addition, recent evidence linking trace amines to the development of drug dependence will be discussed.

Keywords: Affective disorders, Attention deficit/hyperactivity disorders, Drug abuse/dependence, Migraine, Schizophrenia, Trace amines.

INTRODUCTION

Trace amines are a family of endogenous monoamine substances structurally closely related to the monoamine neurotransmitters. Members of this family include 2-phenylethylamine (PE), *p*- and *m*-tyramine, tryptamine, *p*- and *m*-octopamine and the synephrines. Although the presence of these compounds in all mammalian species has been known for several decades, it is only within the last five years that they have become a focus of the mainstream scientific community. This has coincided with the discovery of a family of receptors [1, 2], at least some of which are selectively activated by the trace amines. This resurgence of interest in the trace amines is evidenced by a number of recent review articles dealing primarily with possible physiological and pharmacological relevance of the trace amines [3-6]. Whilst providing a basis for future studies concerning the basic molecular action and function of trace amines, these reports have largely neglected a large body of historical data linking changes in trace amine metabolism to a number of disorders. The purpose of the current article is to review the historical data linking trace amines to human disorders in the context of the recent discovery of trace amine receptors. Prior to describing the evidence for a role of trace amines in various disorders, the current state of trace amine physiology and pharmacology will briefly be outlined in order to provide a context for subsequent discussions.

Trace Amine Receptors

The trace amine receptor family, initially identified by Borowsky *et al.* [1] and Bunzow *et al.* [2], is a family of G-protein coupled receptors. It is worth emphasizing, however, that thus far only two members of this family have been shown to be responsive to trace amines [1, 2, 7, 8] and an endogenous ligand for each receptor has yet to be unequivocally identified. Suggested endogenous ligands beyond the trace amines include the O-methyl monoamine metabolites [2], thyronamine metabolites of thyroid hormone [9] and imidazoline ligands [10] including the β-carbolines [3]. On this basis, Lindemann *et al.* [11] suggested the receptors to be re-named as trace-amine-associated receptors (TAAR) and considering both phylogenetic relationships and predicted homology of the ligand recognition pocket, proposed a uniform nomenclature. This proposed nomenclature will be used in the current article. Table (**1**) relates this nomenclature to previously used names of the trace amine receptors.

Whilst there are up to 18 TAAR in the rodent genome, two of which are pseudogenes, the human genome contains

*Address correspondence to this author at the Department of Chemistry, Brandon University, 270, 18th Street, Brandon, Manitoba, Canada, R7A 6A9; Tel: +1-204-727-9775; Fax: +1-204-728-7346; E-mail: berrym@brandonu.ca

1574-8871/07 $50.00+.00

Table 1. Relationship of Previous Trace Amine Receptor Names to the Proposed Unified Nomenclature

Unified Nomenclature	Previous Name(s)
TAAR1	TRAR1[a,c], TA1[a,c,d], TAR1[a,c,d]
TAAR2	GPR58[a]
TAAR3	GPR57P[a]
TAAR4	TA2P[a], 5-HT4P[a], TA2[c]
TAAR5	PNR[a]
TAAR6	TRAR4[a,b,c], TA4[a,c]
TAAR7	-
TAAR7a	-
TAAR7b	TA12[c]
TAAR7c	-
TAAR7d	TA15[c]
TAAR7e	TA14[c]
TAAR7f	TA13P[c]
TAAR7g	TA9[c]
TAAR7h	TA6[c]
TAAR7i	-
TAAR8	TRAR5[a], TA5[a], TAR5[a], GPR102[a]
TAAR8a	TA11[c]
TAAR8b	TA7[c]
TAAR8c	TA10[c]
TAAR9	TRAR3[a], TA3[a,c], TAR3[a]

Unified nomenclature is that proposed by Lindemann *et al.* [11].
- Receptor gene not previously named.
[a]Gene nomenclature previously used in human, [b]Gene nomenclature previously used in chimpanzee, [c]Gene nomenclature previously used in rat, [d]Gene nomenclature previously used in mouse

only 9 TAAR genes, out of which 3 are pseudogenes (Table **2**). Indeed, the pronounced inter-species variability documented for TAAR (Table **2**) has prompted the suggestion that they are intricately linked to fundamental species-specific functioning [5, 11], and as such they are of possible relevance to disorders uniquely associated with humans. In each species, however, there appears to be three distinct sub-families of TAAR, with at least one member of each sub-family present in each species so far examined (Table **2**).

Trace Amine Metabolism

The synthesis and metabolism of trace amines are directly analogous to that of the monoamine neurotransmitters (Fig. **1** and **2**). Similar to the classical neurotransmitter amines, dopamine (DA), noradrenaline (NA) and 5-hydroxytryptamine (5-HT), the trace amines are synthesized in neuronal terminals in a process involving decarboxylation of precursor amino acids by the enzyme aromatic L-amino acid decarboxylase (AADC; EC 4.1.1.28) [12]. With respect to DA, NA and 5-HT synthesis, AADC is present in a large excess [13, 14]. Unlike the situation with DA, NA and 5-HT however, AADC is *de facto*, the rate limiting step in trace amine synthesis, being the only enzyme involved in the synthetic process, at least with respect to PE, tyramine (Fig. **1**) and tryptamine (Fig. **2**). As such, whilst alteration of AADC activity is expected to have little effect on brain levels of DA, NA and 5-HT, trace amine levels can be profoundly altered.

Metabolism of trace amines takes place in both glia and neuronal terminals predominantly *via* monoamine oxidases (MAO; EC 1.4.3.4), with PE being one of the few endogenous compounds exhibiting pronounced selectivity toward MAO-B [15]. Other trace amines show markedly reduced selectivity, with approximately equal affinities toward MAO-A and MAO-B [12]. Such metabolism results in the generation of the acid metabolites phenylacetic acid, hydroxyphenylacetic acid and hydroxymandelic acid for PE, the tyramines and octopamines, respectively. Tryptamine is metabolized to the corresponding acid indole-3-acetic acid.

Extraneuronal synthesis and metabolism of trace amines are also possible and indeed probable. For example, it is known that AADC is located outside the neuronal terminals in a number of peripheral tissues (see [13] and references therein). Likewise, MAO-B is well documented to be present in a number of extraneuronal peripheral tissues including platelets (see [16] and references therein). In this respect, it is also worth noting that a number of other amine oxidases are present in the plasma and the trace amines are substrates for at least some of these [17]. The relevance of such extraneuronal synthesis and metabolism of trace amines to their neuronal functioning has not been specifically studied and will not be considered further here. Notwithstanding, the relevant acid metabolites of trace amines remain the major metabolic end-product. Excretion of the unmetabolized trace amines and their acid metabolites occurs *via* the urine, with conjugated and unconjugated derivatives identified [18-21].

Trace Amine Physiology/Pharmacology

A detailed discussion of the physiological and pharmacological functions of trace amines in mammalian species is beyond the scope of the current article and the reader is referred to a number of recent thorough review articles [3-6]. Of note, trace amines do not appear to be released in an activity-dependent manner from neurons, readily crossing cell membranes by simple diffusion [12]. Further, at physiological levels, trace amines do not appear to alter neuronal excitability. Rather, they appear to alter neuronal responsivity primarily to monoamine neurotransmitters [3, 12], although a recent study has suggested a similar effect on GABA [22]. As shown in Table (**3**), there is evidence that selectivity exists with respect to trace amines potentiating neurotransmitter responsivity. This has led to the suggestion that, rather than being neurotransmitters *per se* in mammalian species, the trace amines represent a new class of neuroactive compounds i.e, the neuromodulators [3, 12]. At supra-physiological levels, trace amines, and in particular PE have well documented amphetamine-like effects [23-25]. Indeed, PE has been

Table 2. Variations in the TAAR Present in the Genomes of Mammalian Species

	Human	Chimpanzee	Rat	Mouse
Group 1	TAAR1 TAAR2	TAAR1	TAAR1 TAAR2 TAAR3 TAAR4	TAAR1 TAAR2 TAAR3 TAAR4
Group 2	TAAR5	TAAR5	TAAR5	TAAR5
Group 3	TAAR6 TAAR8 TAAR9	TAAR6	TAAR6 TAAR7a, 7b, 7c, 7d, 7e, 7g, 7h TAAR8a, 8b, 8c TAAR9	TAAR6 TAAR7a, 7b, 7d, 7e, 7f TAAR8a, 8b, 8c TAAR9
Pseudogenes	TAAR3 TAAR4 TAAR7	TAAR2 TAAR3 TAAR4 TAAR7 TAAR8 TAAR9	TAAR7f, 7i	TAAR7c

Although the above receptors have been identified in the genome of various mammalian species, the assumed associated receptor proteins have not necessarily been identified.

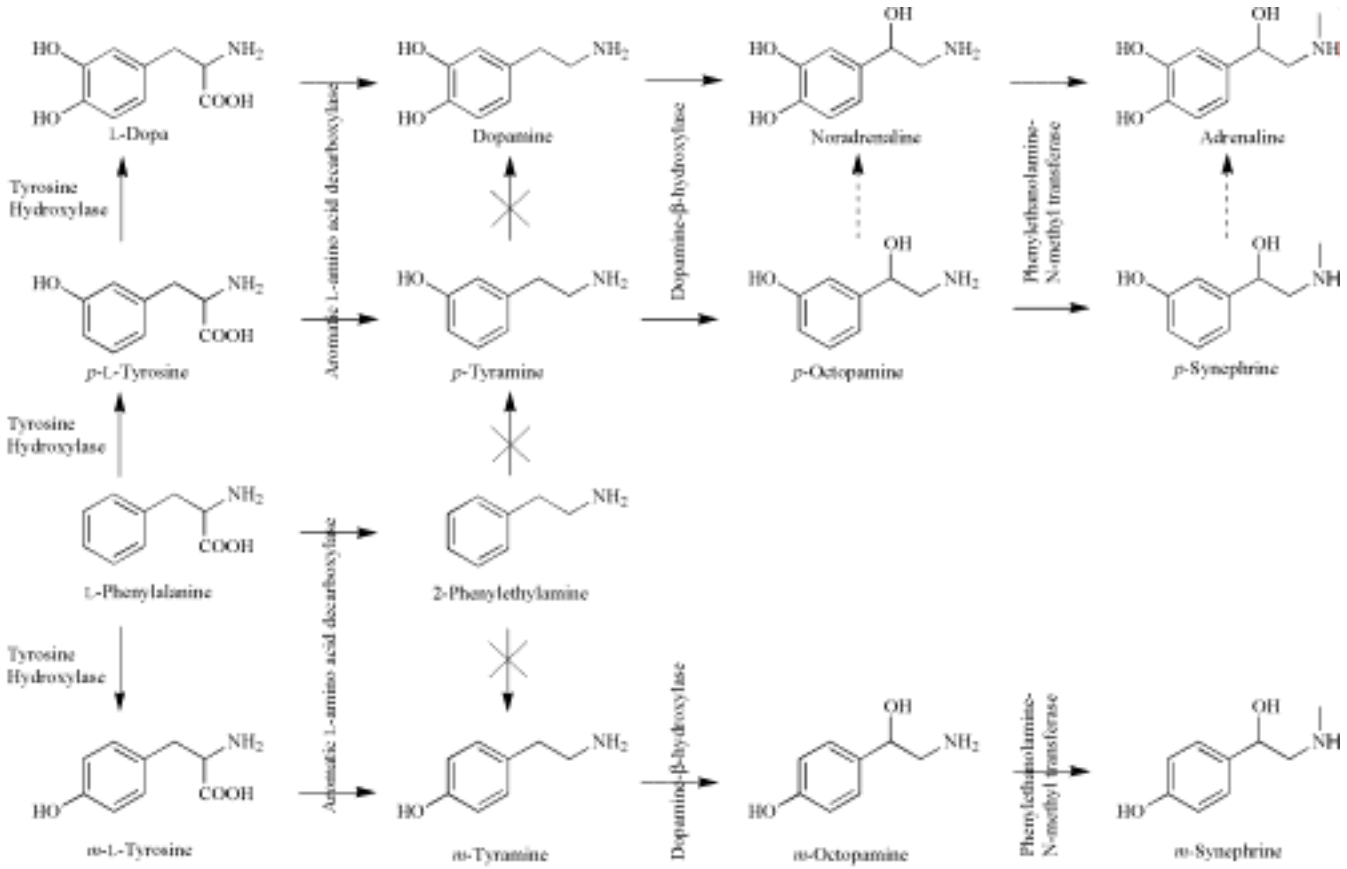

Fig. (1). Relationship between monoamine neurotransmitter and trace amine metabolic pathways. Hydroxylation of L-phenylalanine can yield either *p*- or *m*-isomers of tyrosine. Although not shown in the figure, the same relationship exists between *m*-isomers and monoamine neurotransmitters as that shown for *p*-isomers. Note that in extraneuronal tissue, hydroxylation to tyrosine can also occur *via* the enzyme phenylalanine hydroxylase. Interconversion between subsequent *p*- and *m*-isomers of trace amines does not appear to occur. Interconversion of 2-phenylethylamine to *p*- and *m*-tyramine and the tyramines to dopamine does not appear to occur to a significant degree [197]. The putative interconversion of the octopamines and synephrines to noradrenaline and adrenaline respectively has not been investigated.

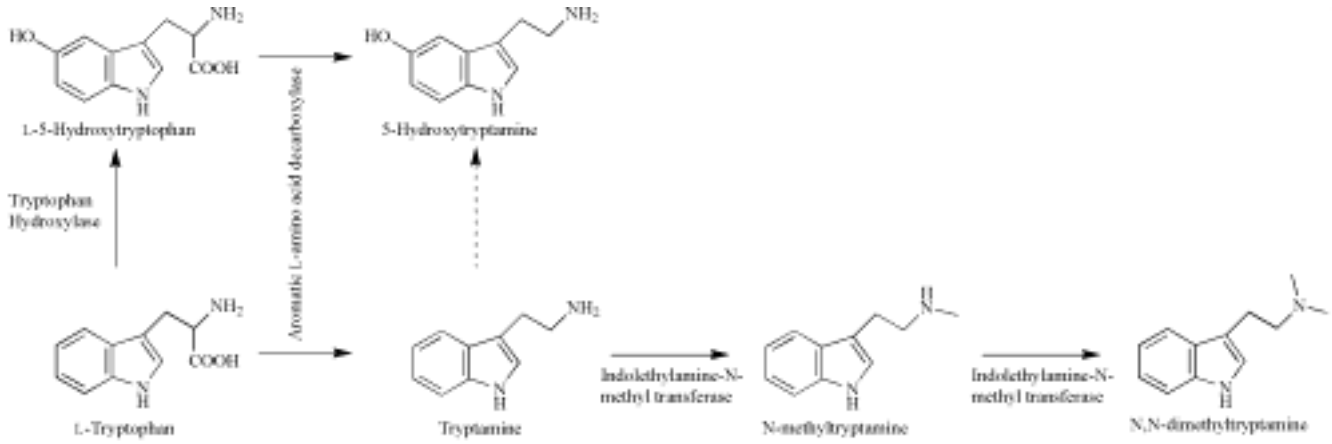

Fig. (2). Relationship between indoleamine neurotransmitter and trace amine metabolic pathways. The putative interconversion of tryptamine and 5-hydroxytryptamine has not been investigated.

Table 3. Summary of the Selectivity of Trace Amines for the Modification of Neurotransmitter Responses

	PE	Tyramine	Tryptamine	Octopamine	Synephrine
Dopamine	+	+		-	
Noradrenaline	+	+		+	
5-HT	-	-	+/-[b]	-	
Acetylcholine	-		-		
GABA	-/+[a]	-/+[a]			
Glutamate	-	-			

+ Neurotransmitter responses potentiated in the presence of trace amine
- Neurotransmitter responses unaffected by the presence of trace amine
Blank cells indicate interactions that have yet to be examined
[a]GABA mediated neurotransmission has been reported to be either unaffected or potentiated in the presence of either PE or tyramine.
[b]Inhibitory effects of 5-HT are potentiated by tryptamine, whilst excitatory responses to 5-HT are either unaffected or converted to inhibitory responses in the presence of tryptamine.
Summary based on [3, 22] and references therein.

suggested to be an endogenous amphetamine [26, 27]. Whether the levels of trace amines can be elevated sufficiently to achieve such effects in any but the most extreme of pathological situations requires further study.

The proposal that trace amines function as endogenous neuromodulators deserves further comment. In invertebrates, there is little doubt that trace amines function as true neurotransmitters [28, 29]. That such a situation is not readily generalizable to mammalian species is supported by studies of the phylogenetic relationships of trace amine receptors between vertebrates and invertebrates. Consistent with trace amines serving a different function in vertebrate species, invertebrate and mammalian trace amine receptors arose independently during evolution [1, 11, 30]. As indicated above, the high species variability in trace amine receptors has prompted the suggestion that the endogenous ligands for these receptors may be involved in species-specific functioning/adaptation [5, 11]. In agreement with this, it has recently been reported that TAAR present in the olfactory epithelium function in the recognition of urinary behavioral cues in the mouse [8]. Such a situation intuitively suggests that trace amines may be implicated in higher cognitive functions in humans and as such disorders associated with such functioning. As will be seen, this provides an interesting link to older studies examining changes in trace amine metabolism in various disease states. The strongest evidence for such a link was found in patients diagnosed with either affective or schizophrenic disorders (see later sections). Finally, if trace amine receptors are proven to be targets for endogenous neuromodulators, rather than neurotransmitter substances, this may have implications for the identification of the endogenous ligand(s). A neuromodulator substance, as previously defined [3], requires the presence of a suitable neurotransmitter for its effect to be seen. Thus, when examining for substances that cause activation of trace amine receptors, traditional second messenger-related assays may be unsuitable, unless combined with activation of a partner neurotransmitter receptor. Further, such a situation has implications for the way in which trace amines are viewed with respect to disease conditions. Under a neuromodulator model, a given trace amine may be therapeutically useful in any disorder associated with an alteration in the partner neurotransmitter functioning, in addition to disorders associated with a

primary alteration in trace aminergic functioning. As such, alterations in trace amine functioning as the underlying cause of a disorder are not necessarily required in order for receptor ligands to be therapeutically important. Thus, trace amine receptor ligands may be useful in alleviating symptomatology without addressing the underlying disease pathology.

Such therapeutic potential of TAAR has been recognized by a number of pharmaceutical companies conducting active trace amine research projects [6, 11]. At present, however, information on novel ligands showing selectivity at TAAR is not available through either the patent databases or within the scientific literature. The one exception to this is the demonstration that putative thyroid hormone metabolites and their synthetic derivatives are good TAAR ligands [9, 31]. Such activity was initially suggested to be of importance for the non-genomic actions of thyroid hormone, although the authors have recently presented an alternative explanation of such effects that do not appear to involve trace amines [32]. In addition, the compounds previously described by Knoll and colleagues [33, 34], along with a series of trace amine derivatives synthesized by Ling *et al.* [35] are potential TAAR ligands. Although neither of these classes of compound appear to have been examined for efficacy at TAAR, their strong structural similarity to trace amines suggests that such studies are warranted.

Trace Amine Detection Assays

The following sections contain, in part, a review of older literature in which changes in trace amines and their metabolites were examined in various body tissues. Due to their trace concentrations and close structural similarity to the much more abundant monoamine neurotransmitters, assays for such measurements require a very high degree of selectivity and sensitivity. Although such assays have subsequently been developed (for example [36, 37]), most of the earlier studies relied on assays with insufficient sensitivity and selectivity, resulting in a considerable overestimation of trace amine levels, confounding the interpretation of data. A discussion of the advantages and disadvantages of the various procedures that have been used to estimate trace amine levels in body tissues is beyond the scope of the current article and the reader is referred to previous review articles for a more detailed discussion [38, 39]. Although some of these earlier studies have been included in the following sections, care has been taken to limit this to studies which have subsequently been verified with more selective and sensitive assay procedures. While techniques for the determination of trace amine levels at the level of a single cell have not yet been described, those described by Durden and Davis [37] and Henry and colleagues [36] appear sufficiently sensitive and selective to allow the determination of trace amine levels in discrete brain nuclei through the use of *in vivo* microdialysis.

The following sections will review evidence and the rationale behind the potential utility of TAAR ligands in various disorders. Fig. (**3**) shows a schematic of the relevant trace amine associated proteins and compounds that will be discussed in subsequent sections.

PHENYLKETONURIA

Phenylketonuria is the most frequent of the so-called inborn errors of metabolism. It is an autosomal recessive condition characterized by a deficiency in phenylalanine hydroxylase activity, with a resultant marked elevation of peripheral phenylalanine and decreases in tyrosine levels. If left untreated, the disease results in a pronounced mental retardation, seizures and neurological and psychiatric dysfunction [40]. Although all of these may be related to the perturbation of normal CNS monoaminergic neurotransmitters due to the alteration of phenylalanine metabolism as a result of increased CNS phenylalanine availability (see Fig. **1**), the mechanism of cognitive abnormalities remains unresolved [40]. As can be seen in Fig. (**1**), increased brain levels of phenylalanine also result in an increase in PE levels. Such changes in PE levels result in altered neuronal functioning. Since PE exists in a steady state, with release from neuronal terminals occurring by simple diffusion, there is no opportunity for such increases in PE to be buffered by storage mechanisms, resulting in an increase in PE mediated stimulation of TAAR. Indeed, a marked increase in PE turnover has been observed [41, 42], which was previously suggested as a possible cause of at least some of the neurological/psychiatric symptomatology observed [41]. Further, changes in other trace amine levels may also occur [43]. The possible relevance of trace amines to the development of seizure activity and epilepsy is detailed in subsequent sections.

Current treatment of phenylketonuria is restricted to dietary restriction of phenylalanine and supplementation with tyrosine. Even with early diagnosis and instigation of such a dietary regime, evidence of abnormal cortical functioning persists. Further, patients are required to maintain such a diet for life [40]. Although initially relaxation of dietary restriction was recommended beyond early childhood, evidence now exists that such dietary relaxation may be contraindicated and associated with subtle changes in cognitive functioning [40]. Antagonists or partial agonists of the cognate PE receptor may allow for such dietary relaxation whilst preventing the subsequent decline in functioning. Whether such PE receptor ligands could improve daily functioning beyond that currently seen with dietary restriction warrants investigation upon the development of such ligands.

SCHIZOPHRENIA

The potential role of trace amines in schizophrenia is one of the most well documented of the putative pathological indications. Indeed, the similarity of some phenylketonuric symptoms to those of paranoid schizophrenia has previously been documented [44]. As previously stated, TAAR has been suggested to be involved in responses unique to the human lifestyle [5] and anectodal evidence suggests that psychoses show a vastly greater preponderance in humans than in other primate species [45]. Much of the early interest in the possible role of trace amines in schizophrenic conditions stemmed from the close structural similarity of trace amines and in particular PE, to amphetamine. Amphetamine overdose and chronic use are known to induce paranoid schizophrenia-like symptoms. PE is structurally similar and has well documented amphetaminergic effects in animals,

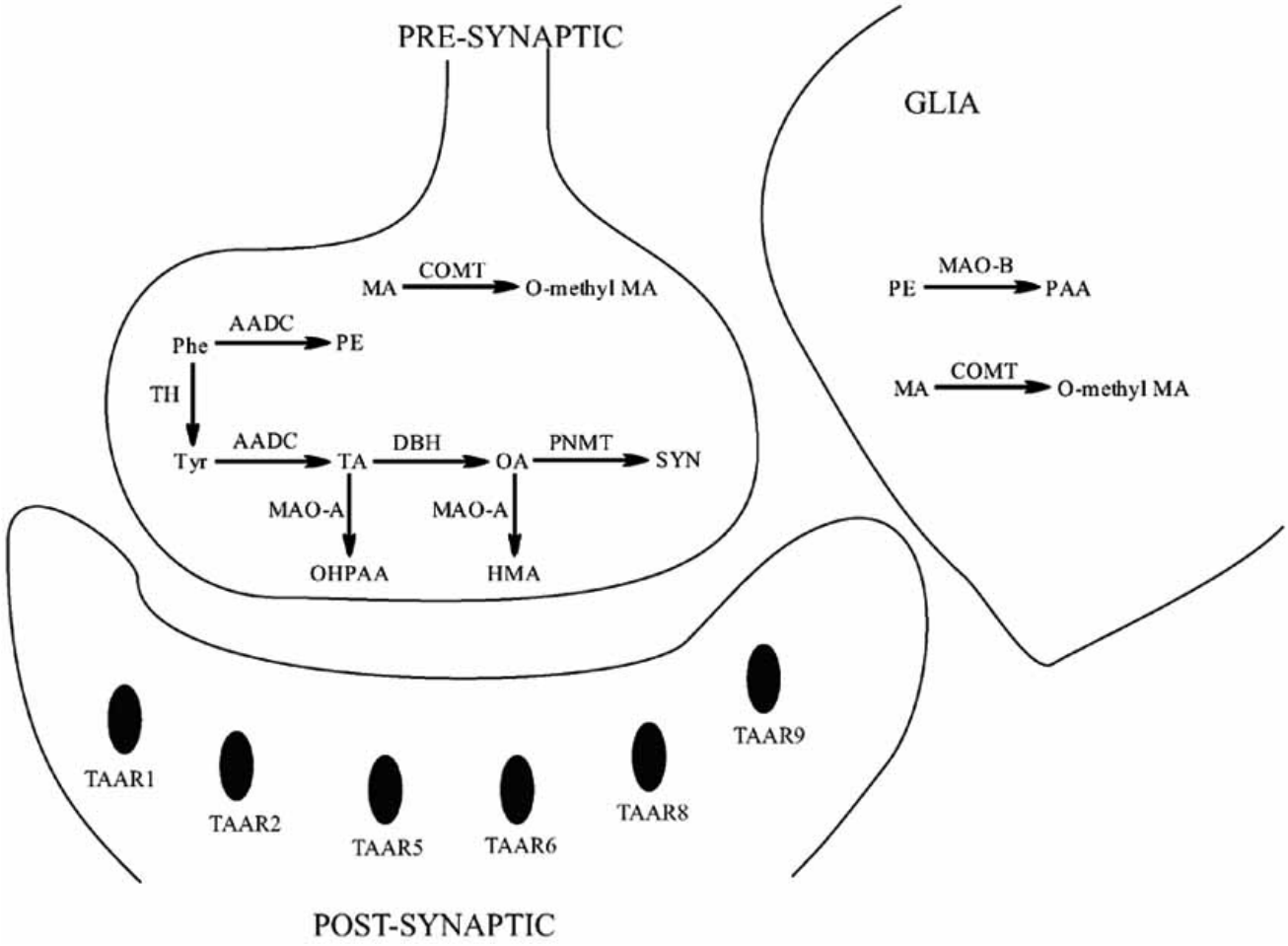

Fig. (3). Schematic representation of trace amine associated proteins and compounds. Abbreviations: Phe – L-phenylalanine, MA – monoamine, COMT – catechol-O-methyltransferase, TH – tyrosine hydroxylase, Tyr – tyrosine, TA – tyramine, OHPAA – hydroxyphenyl-acetic acid, DBH – dopamine-β-hydroxylase, OA – octopamine, PNMT – phenylethanolamine-N-methyl transferase, SYN – synephrine, PAA – phenylacetic acid. Other abbreviations are as defined in the text. For purposes of clarity, tryptamine specific pathways have been omitted. While some enzymes may exist in multiple cellular locations, for clarity only the predominant location has been shown. Although TAAR has the expected 7 putative transmembrane domains, available evidence suggests that TAAR may be primarily intracellular receptors.

including induction of similar stereotyped behaviors [46-48]. On this basis, PE has been suggested to be an endogenous amphetamine [26, 27, 49]. This observation has been reinforced in recent years with the demonstration that amphetamine-type hallucinogens activate TAAR family members [2]. It is worth remembering, however, that in order for amphetaminergic effects to be seen with PE, levels need to be far in excess of those seen physiologically [3, 50], which calls into question the likelihood of the involvement of TAAR. Further there is evidence that behavioral responses to such supra-physiological levels of PE are not identical to those seen with amphetamine [50]. The possibility, however, that some of the effects of the amphetamines may be mediated through an interaction with one or more TAAR deserves further study.

There is a wealth of older literature implicating alterations in trace amine metabolism and, in particular PE, to schizophrenia. A comprehensive review of these studies is beyond the scope of the current article and the reader is referred to the extensive tabulations previously compiled by Davis [18]. Here the salient features of these studies will be outlined to provide a historical context to the more recent studies implicating mutations in various proteins of relevance to trace amine metabolism to schizophrenia. A word of caution is warranted before beginning. Studies involving detection of changes in the levels of endogenous compounds such as the trace amines and their metabolites are inherently difficult to interpret. For instance, an increase in urinary excretion of a compound can equally easily be argued to represent a functional deficit in that compound (due to the increased excretion) or to represent a functional overactivity of the same compound (with the increased excretion reflecting the increased circulatory levels, due to the body being 'flooded' with the molecule of interest). Thus, changes in body fluid levels of trace amines are presented here merely to be indicative that an alteration in trace amine metabolic processes appears to be occurring. Where possible, corollary evidence will be outlined to indicate in which direction this change in metabolism may occur. The situation is complicated further in schizophrenia. It is now accepted that schizophrenia represents a complex family of disorders [51] rather than a single disease entity.

As such, multiple causative factors are likely and even a common symptomatology cannot necessarily be taken to represent a common underlying pathology. Further, studies of patients with schizophrenia are difficult to control with respect to medication status. Indeed, studies often do not report the medication status of the patients involved. This further complicates attempts to interpret various studies with respect to each other.

An increased urinary excretion of PE has most frequently been reported in paranoid schizophrenia [18, 42, 52, 53], although urinary PE changes appear less clear in non-paranoid forms of schizophrenia [18, 54]. A corresponding decrease in the urinary level of the main PE metabolite phenylacetic acid (PAA) has also been observed. However, other studies have reported increases in cerebrospinal fluid (CSF) PAA [18, 44]. Plasma PE levels have also been reported to be increased during acute phases of the disease [55, 56]. The sum total of such effects has been taken as supportive of the hypothesis that an increased PE activity plays a role in schizophrenia [49]. Similarly, altered metabolism of tyramine and tryptamine in schizophrenia has been suggested [43]. Indeed, urinary tryptamine levels have been shown to correlate with disease severity [18, 57]. Further, the plasma levels of the tyramine metabolite hydroxyphenylacetic acid have been reported to be decreased [18]. Trace amines other than PE, and their metabolites have, however, received relatively little investigation and some of the results have been questioned [58].

Methylated tryptamines have also been implicated as playing a role in the onset of schizophrenia (see [59] for a historical perspective). N,N-dimethyltryptamine (DMT), a known, potent hallucinogen is produced endogenously in humans (see Fig. **2**), although the physiological role of this trace amine derivative has been the subject of much debate [59]. Of interest is the fact that DMT is a good ligand for TAAR [2]. A number of studies have provided evidence for an increased urinary level of DMT associated with at least a sub-group of schizophrenia patients [60-62]. Such results promoted suggestions that acute episodes of schizophrenia were associated with endogenous DMT production. Lack of progress in defining a physiological role and the site of action for DMT, however, has hindered further research.

The relevance of trace amines to schizophrenia received considerable theoretical support following mapping of the TAAR genes. All TAAR map to chromosome 6q.23 [1, 2]. This region is within the previously identified SCZD5 schizophrenia locus, which is one of the most frequently replicated schizophrenia susceptibility loci [63-67]. TAAR genes appear to be rapidly evolving (mutating) [5] and TAAR polymorphisms have been identified [5, 11]. One such polymorphism in the TAAR2 gene has, in a preliminary study, been suggested to be associated with schizophrenia [68]. The TAAR6 gene maps particularly close to the SCZD5 locus [5, 11] and has received particular attention. Although initial studies suggested a linkage of TAAR6 polymorphisms to schizophrenia in patients of European and African-American ancestry [69], this was not replicated in subsequent studies with patients of different ethnicities [70-72]. Further supporting a possible role for trace amines and their receptors in schizophrenia is the observation that TAAR6 is preferentially localized to the brain regions implicated in schizophrenia [69].

Alterations in the activity and expression of enzymes involved in trace amine metabolic pathways have also been implicated in the etiology of schizophrenia. In particular, catechol-O-methyl transferase (COMT; EC 2.1.1.6) and AADC have been implicated. With respect to COMT, an enzyme variant associated with decreased activity, which shows a high transmittance in schizophrenia has been identified [73-77]. These observations take on greater significance with the observation that the O-methyl metabolites of monoamine neurotransmitters are particularly effective TAAR ligands [2] and are candidates to act as endogenous ligands at one or more TAAR. Consistent with such a role of COMT in the etiology of schizophrenia, the O-methyl metabolites of monoamines have been reported to be altered in the CSF of patients with various psychiatric conditions including schizophrenia [78].

Numerous reports have linked schizophrenia with alterations in the trace amine synthetic enzyme AADC. A splice variant in AADC has been reported [79], which has been hypothesized to be related to schizophrenia [6]. Polymorphisms of the AADC gene have been reported to be associated with the age of onset of schizophrenic disorders [80], although a later study reported no association between AADC polymorphisms and schizophrenia [81]. More direct evidence has been provided of increased AADC activity present in various brain regions of drug-naïve schizophrenia patients [82, 83]. Similarly, the A1 allele of the D2 receptor, which has been suggested to be a risk factor for schizophrenia [84], is associated with an increase in AADC activity [85]. As previously described, such increases in AADC activity would be expected to result in an increase in the steady state levels of trace amines without affecting the levels of the monoamine neurotransmitters. This provides a consistent link to the previously described hypothesis of increased PE levels causing schizophrenia. It is interesting to note that, at least in rodents, brain AADC levels are reported to increase from birth up to adulthood and then subsequently decrease [86, 87]. Whether a similar ontogeny of AADC expression occurs in humans requires investigation, but it raises the intriguing possibility of the maximal AADC level correlating to the age of maximal risk of developing schizophrenia. It should be noted however that genetic deficiencies in the PE metabolism enzyme MAO-B, which, in experimental animals, markedly elevate steady state PE levels whilst leaving monoamine neurotransmitter levels unaffected [88, 89], are not associated with a human clinical phenotype [90].

The preceding studies are in general, consistent with an over-activity of trace amine systems being involved in the pathogenesis of schizophrenia (Fig. **4**). Other studies, however, appear contradictory, in particular to the findings of increased AADC in patients with schizophrenia. Numerous studies from independent groups have reported that administration of a number of neuroleptic compounds results in acute increases in AADC activity in multiple brain regions in experimental animals [13, 91, 92]. Similarly, chronic administration of neuroleptics results in an increase in AADC mRNA [93, 94], whilst various pharmacologically

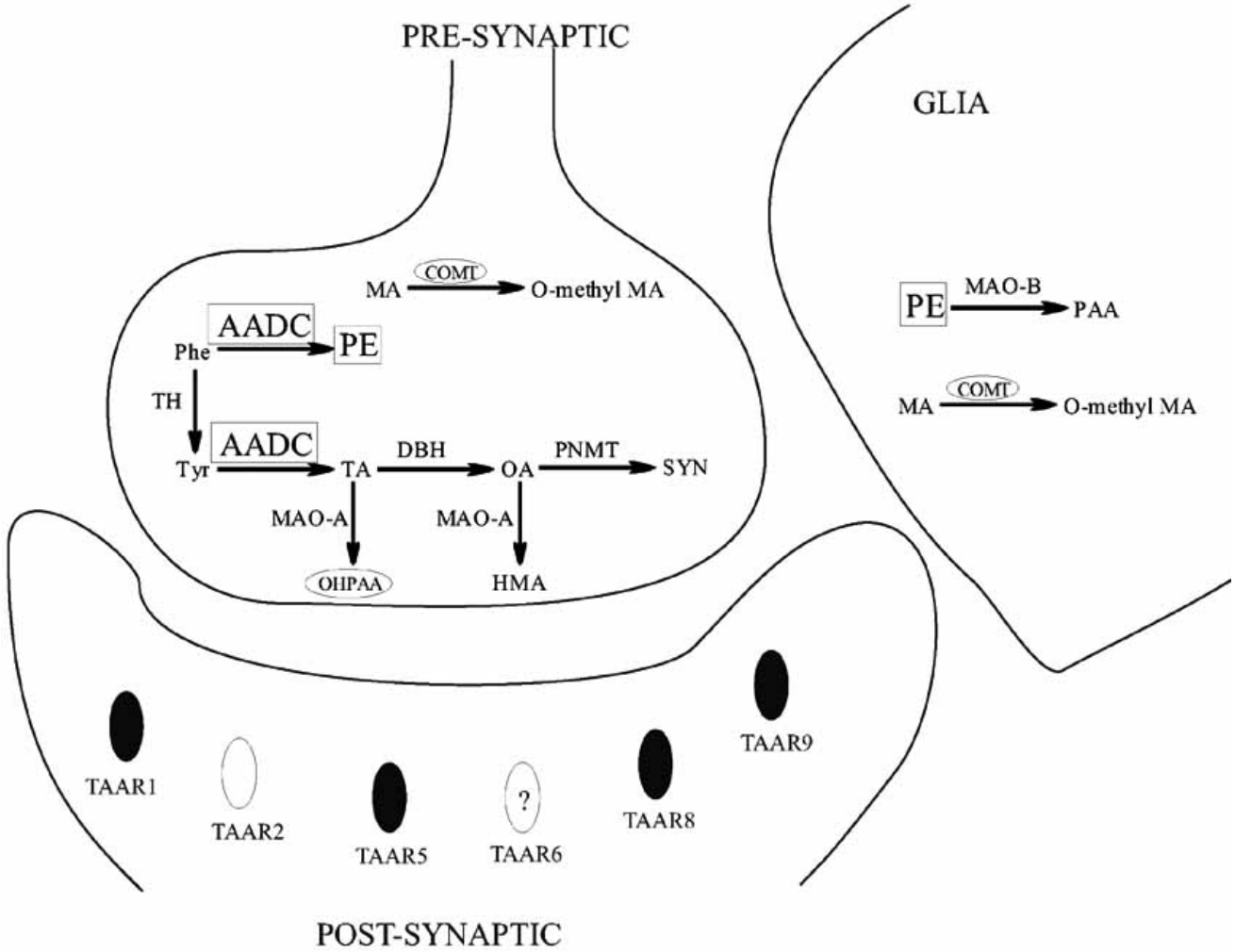

Fig. (4). Schematic summary of trace amine related changes suggested to occur in schizophrenia. For an explanation of abbreviations see Fig. (**3**). Boxed text in an enlarged font indicates an increase in enzyme activity or concentration, encircled text in a smaller font indicates a decrease in enzyme activity or concentration. Non-shaded TAAR indicates a receptor for which a polymorphism associated with schizophrenia has been suggested. ? – The initial suggestion of a schizophrenia associated polymorphism was not observed in a subsequent study.

unrelated chemicals, all of which are associated with the onset of psychoses in humans, result in a decrease in AADC mRNA [94]. How such discrepancies can be resolved is unclear, although they may simply reflect species differences.

It has been reported that there is a decrease in the number of CNS D-neurons associated with schizophrenia [95]. D-neurons are groups of neurons that whilst containing AADC, appear neither to contain tyrosine hydroxylase, nor to synthesize 5-HT [96-98]. Such neurons are ideally suited to synthesize trace amines. Interestingly, reports suggest that there is a greater preponderance of D-neurons in humans than in rodents and they are particularly enriched in brain regions implicated in schizophrenia [99]. Such observations would appear to be consistent with the suggestion that TAAR are involved in species-specific adaptation responses. These reports of decreases in D-neuron numbers are suggestive of a decrease in trace aminergic functioning, playing a role in schizophrenia. Notwithstanding the apparent discrepancies, the above studies emphasize the importance of conducting studies in drug-naïve patients. The demonstration that neuroleptics alter AADC activity and levels in experimental animals makes it difficult to interpret studies conducted in patients receiving neuroleptic therapy.

ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Although there is little direct evidence, changes in trace amines, in particular PE, have been identified as a possible factor for the onset of attention deficit/hyperactivity disorder (ADHD) [5, 27, 43, 78]. PE has been shown to induce hyperactivity and aggression, two of the cardinal clinical features of ADHD, in experimental animals [100]. Hyperactivity is also a symptom of phenylketonuria, which as discussed above is associated with a markedly elevated PE turnover [44]. Further, amphetamines, which have clinical utility in ADHD, are good ligands at trace amine receptors [2]. Of possible relevance in this aspect is modafanil, which has shown beneficial effects in ADHD patients [101] and has been reported to enhance the activity of PE at TAAR1 [102]. Conversely, methylphenidate, which is also clinically useful in ADHD, showed poor efficacy at the TAAR1 receptor [2]. In this respect it is worth noting that the enhancement of functioning at TAAR1 seen with

modafanil was not a result of a direct interaction with TAAR1 [102].

More direct evidence has been obtained recently for a role of trace amines in ADHD. Urinary PE levels have been reported to be decreased in ADHD patients in comparison to both controls and patients with autism [103-105]. Evidence for a decrease in PE levels in the brain of ADHD patients has also recently been reported [4]. In addition, decreases in the urine and plasma levels of the PE metabolite phenylacetic acid and the precursors phenylalanine and tyrosine have been reported along with decreases in plasma tyramine [103]. Following treatment with methylphenidate, patients who responded positively showed a normalization of urinary PE, whilst non-responders showed no change from baseline values [105]. However, there did not appear to be a direct link between urinary PE levels and ADHD severity [105]. Phenylalanine administration alone does not appear to be beneficial to these patients [106].

Direct evidence for altered AADC activity has been obtained from positron emission tomography studies of ADHD patients [107], with increases in AADC reported to be correlated with symptom severity [108]. There is also evidence indicating an increased paternal transmission of AADC alleles in ADHD in an Irish population [109]. Further, the AADC gene maps to a region of chromosome 7p that was recently identified as a susceptibility locus for ADHD [110].

Although these studies require replication, they support further investigation of the role of trace amines and their metabolic pathways in ADHD. In general, the results so far obtained seem to suggest that there may be a decrease in trace aminergic functioning, which may be normalized by currently available therapeutics. The reports of increased AADC activity correlating with disease severity, however, would seem to contradict such a hypothesis.

DRUG ABUSE/DEPENDENCE

Trace amines have also been suggested to play a role in the neural mechanisms underlying drug abuse and dependence. Indeed, as previously described, PE has been proposed to be an endogenous amphetamine [26, 49]. These historical observations are seemingly supported by the observations that amphetamines, along with a number of other drugs of abuse, are some of the more potent ligands at TAAR1 [2]. Caution is required, however. Although amphetamine is a ligand at TAAR1, it has previously been shown that amphetamine does not displace radiolabeled trace amines from their binding sites [111].

Behavioral responses to PE also resemble those seen with amphetamine. Behavioral sensitization to PE has been shown to occur [112] and PE has been suggested to be involved in the neural mechanisms underlying reward and reinforcement [50, 113]. Experimental animals also self-administer PE [50, 113, 114]. Further, animals maintaining electrical self-stimulation show a decreased MAO inhibitor-induced elevation of PE [50], indicating that stimulation is associated with altered PE metabolism. Such effects are consistent with PE mediating the behavioral phenotype induced by amphetamine. Differences have been observed, however, between the behavioral phenotypes induced by PE and amphetamine [50, 115]. In particular, exogenously administered PE does not induce aversive stimulus properties. In contrast, most drugs of abuse, including amphetamine, induce pronounced aversive stimulus properties [50]. Further, differences in amphetamine- and PE-induced self-stimulation have been noted [115]. While such observations do not preclude a role for PE and trace amines in inducing behavioral phenotypes associated with drugs of abuse and dependence, they do suggest a level of complexity beyond the initial hypothesis that PE acts as an endogenous amphetamine. It is also worth noting that PE brain levels have been suggested to require elevation above 70ng/g tissue in order for self stimulation properties to be observed [50]. Such levels are approximately 20-30 fold above normal trace amine levels [3].

Trace amines have also been implicated in the abuse/dependence of other substances. The requirement for tyramine in order for Drosophila to develop sensitization to cocaine [116] has often been cited in recent years [2, 6, 43]. Considerable caution is required in generalizing species-specific results, however, in particular between vertebrates and invertebrates. In this aspect, it should be borne in mind that in invertebrates, trace amines serve a traditional neurotransmitter function [117]. Further, mammalian trace amine receptors appear to have evolved only following the divergence of vertebrates and invertebrates [1, 11, 30]. As such, studies conducted in invertebrates may be of limited relevance to elucidating the functional consequences and clinical utility of trace aminergic systems in mammals.

The previously described A1 allele of the D2 dopamine receptor, which is associated with an increased AADC activity [85], has been suggested to be associated with an increased risk of alcoholism [84, 118], although these results have been questioned [119]. Of interest in this respect are the independent reports of increased AADC activity seen in alcohol-dependent patients, as assessed by PET scans [120]. As described elsewhere, AADC is not rate limiting for monoamine neurotransmitter synthesis and changes in its activity do not appear to affect neurotransmitter levels. In contrast, levels of the trace amines are considerably changed in response to changes in AADC activity. Single nucleotide polymorphisms within the AADC gene have also been linked to nicotine dependence, at least in European populations [121]. The 7p11 chromosome region, which contains the AADC gene, was previously linked to smoking quantity [122], whilst dopaminergic activity has been hypothesized to play a role in nicotine dependence [123]. Of interest in this respect, the A1 allele of the D2 receptor has also been frequently associated with nicotine dependence [84, 124-126]. Again, altered AADC activity can result in changes in dopaminergic activity *via* regulation of trace amine levels and their subsequent modulation of dopaminergic functioning.

In addition to alcoholism and nicotine dependence, the A1 allele of the D2 dopamine receptor has also been suggested to be a risk factor for a number of other addictions including those to psychostimulants [84, 127], opioids [128], polysubstance abuse [129-131] and gambling [132] in at least a subset of the population. Although such studies have not always been replicated (see [84] and references therein),

they do raise the possibility that the allele may be a more generic risk factor for addiction/drug dependence, rather than acting in a substance-specific manner. An ethnic- and sex-specific association has also been reported between COMT haplotypes and nicotine dependence [133]. As described previously, O-methyl metabolites of monoamine neurotransmitters are particularly potent ligands at TAAR [2]. Two further drugs of abuse have been linked to trace amines in individual reports. γ-hydroxybutyric acid, the so called 'date rape drug' has also been suggested as a possible ligand for TAAR [43]. Finally, Δ^9-tetrahydrocannabinol has been shown to cause increases in central PE [100].

ANOREXIA/EATING DISORDERS

Although few studies have been conducted, there is interest in the role of trace amines in anorexia and other eating disorders due to the close similarity between PE and amphetamine. Amphetamine has well documented anorectic effects [134], an effect that can also be demonstrated with PE, and appears to be due to a decreased food intake [135]. Further, the TAAR1 protein is found in brain regions suggested to be involved in the control of appetite [6]. Finally, the ability to displace amphetamine from its binding sites within the brain has been shown to correlate with anorectic activity [136]. The degree with which such binding sites overlap with the more recently identified TAAR receptors requires further study. Although trace amines, notably tyramine and octopamine, have been documented to regulate feeding behavior in invertebrates [137], this again is likely to be of limited relevance to mammalian species.

AFFECTIVE DISORDERS

Trace amines have received much attention with respect to a pathological relevance in the etiology of affective disorders. Once again, most of this attention has focused on a role for PE. Unlike other disorders, however, a much more cohesive theory has been put forth, whereby deficits in PE functioning/turnover are associated with depression, whilst elevated PE functioning is associated with mania [5, 6, 44, 138]. Indeed, trace amines have been suggested to function to maintain mental functions within "normal" limits [44], a hypothesis strikingly similar to the neuromodulator hypothesis for trace amine functioning at the cellular level [3, 12].

Older studies examining the levels of PE in a variety of body fluids have in general supported this so-called PE hypothesis. These studies have been comprehensively reviewed elsewhere [18, 19], and the reader is referred to these tabulations for further details. In summary, the most robust changes observed are a decrease in urinary, plasma and CSF PE and/or phenylacetic acid [19, 139-141]. Adding further weight to the theory, a number of clinically effective antidepressant treatments (including tricyclic antidepressants, MAO inhibitors and electroconvulsive shock therapy) have been shown to elevate PE levels/functioning [142-145], whilst phenelzine has been shown to be metabolized to PE [146]. Further, chronic treatment of experimental animals with antidepressants has been reported to decrease β-adrenergic receptor number [147], an effect mirrored by chronic PE administration [148]. Finally reserpine, which can precipitate episodes of depression [149], also decreases central trace amine levels [150].

More recently, MAO-B knock-out mice, whose only documented neurochemical change is a pronounced elevation of central PE, have been shown to exhibit a behavioral phenotype that is indistinguishable from that induced by clinically effective antidepressants [88]. It has also been suggested that the antidepressant effects of exercise are due to an exercise-induced elevation of PE [151]. Two studies have directly sought to elevate endogenous PE levels in patients with depressive disorders. In the first, a combination of (-)deprenyl to inhibit MAO-B and phenylalanine, the precursor of PE, was reported to be beneficial in 70% of patients [152]. A more recent study reported a decrease in depressive symptomatology in 60% of patients treated with either L-phenylalanine or PE [153]. Such results are consistent with earlier studies where phenylalanine was reported to be as effective as imipramine in treating depression [154].

Other trace amines, notably tyramine [43, 155], tryptamine [43, 58] and octopamine [155], have also been suggested to play a role in depressive symptomatology. Few additional studies have been performed however. TAAR appears to be appropriately distributed in the CNS to play a role in the control of affect, receptors having been localized in particular to the amygdala [1]. Genetically, a susceptibility locus for bipolar disorder has been suggested on chromosome 6q22 [156-158], close to the chromosomal location of all TAAR. Variants in the AADC gene have also been suggested to be linked to both unipolar and bipolar disorder [159], although such results are not without controversy. In a follow-up study, the original association could not be replicated, although there was evidence for a paternal transmission that may increase susceptibility [160]. An association between bipolar disorder and COMT polymorphisms has also recently been reported [161]. Thus, as was seen in schizophrenia, there is evidence of genetic susceptibility factors, which are linked to normal trace amine metabolic pathways playing a role in affective disorders.

The above studies are summarized in Fig. (**5**). Taken together, the above described studies provide a fairly uniform view for a deficit of trace aminergic functioning being associated with depressive disorders in at least a sub-set of patients. The recent discovery of a family of TAAR provides a new target to which novel molecules can be designed with a view to investigating their potential utility for the treatment of affective disorders.

MIGRAINE/CLUSTER HEADACHE

Suggestions of a potential link between trace amines and the etiology of pathological headache, in particular migraine, have long circulated in the scientific literature. Initially proposed by Hanington [162], the hypothesis garnered considerable support from the observations that foods known to precipitate migraine attacks in susceptible individuals contain high levels of trace amines [163]. In particular, chocolate contains high levels of PE, whilst aged cheeses and red wine have a high tyramine content [163-166]. Such foods are also known to increase blood pressure and this has also been suggested to be the causative effect in precipitating

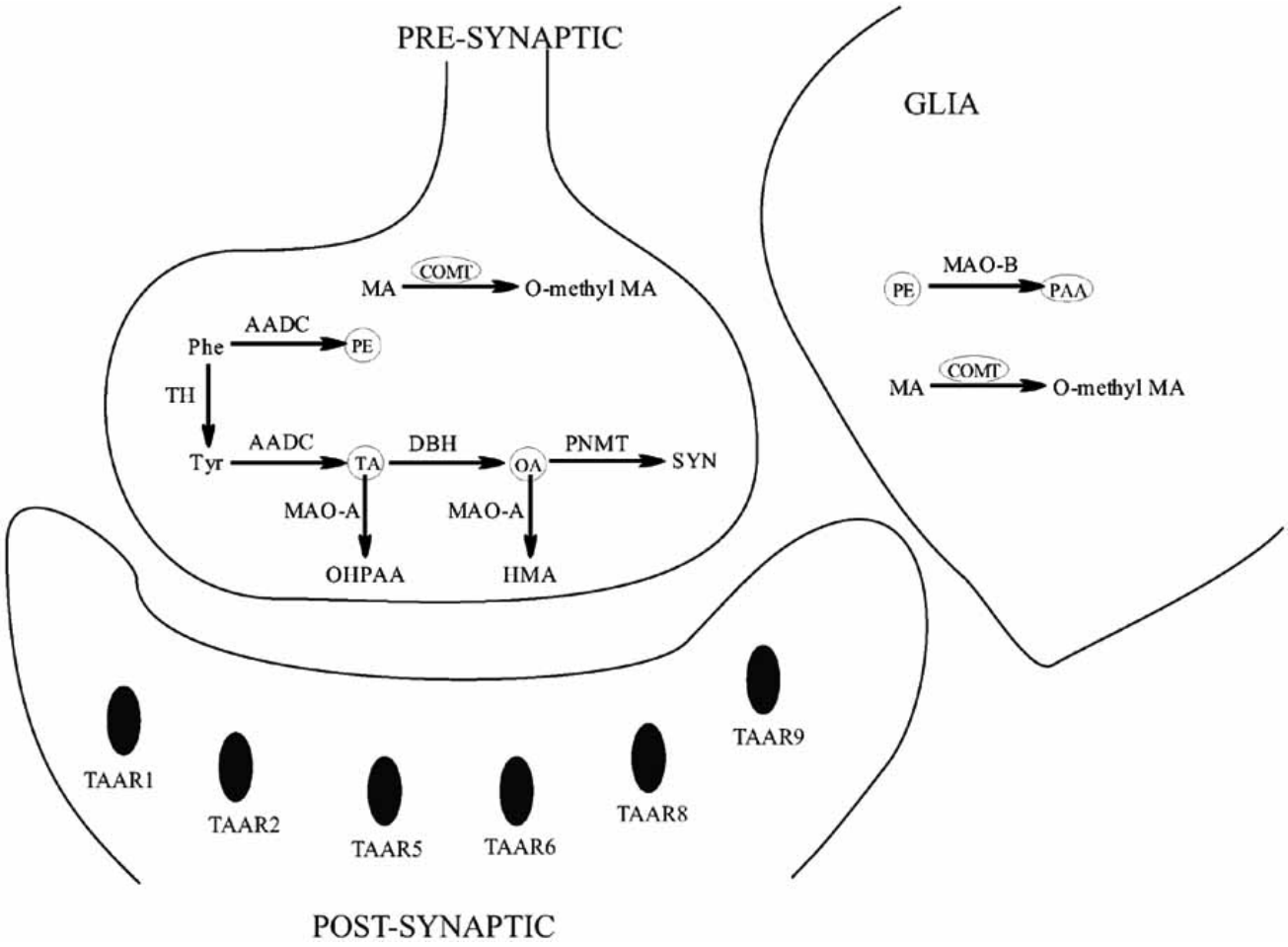

Fig. (5). Schematic summary of trace amine related changes suggested to occur in depression. For an explanation of abbreviations see Fig. (**3**). Encircled text in a smaller font indicates a decrease in enzyme activity or concentration.

attacks [167]. In this respect, it is interesting to note that trace amine receptors are present both in the kidney [1] and vasculature [168]. The basis behind individual susceptibility is not understood and early suggestions that migraine attacks may be due to a deficit in MAO-B [162] have not generally been supported clinically [169], although a decreased platelet MAO activity has been reported to be associated with menstrual migraine [170]. Further, it has been suggested that conversion of tyramine to octopamine (see Fig. **1**) is required for precipitation of migraine attacks [171].

Given the frequency with which links between migraine and elevated trace amines continue to be cited [5, 6, 43, 172, 173], it is surprising to note how little evidence supportive of such a link is available. Elevations in plasma octopamine and synephrine have been reported in patients suffering migraines in comparison to controls [174], while no difference was observed in plasma tyramine levels [174]. This study was recently extended, with elevated octopamine reported to be associated with migraine with aura patients, whilst in patients suffering migraine without aura synephrine was significantly elevated [175]. Of possible interest, it was recently reported that gelatin capsules used during oral administration of placebos during clinical trials contain high levels of tyramine [176], possibly explaining reports of headache amongst migraineurs following placebo administration. Similarly a single study has reported elevations in tyramine, octopamine and synephrine in both the plasma and platelets of patients with cluster headaches [174], although no differences were noted between patients in the active and remission phases. Of possible relevance are suggestions that cluster headaches are hypothalamic in origin [177, 178], the hypothalamus containing the highest concentrations of octopamine [3]. In the one study conducted, no evidence of a genetic link between cluster headache and trace amine receptors was found in the two families examined [179]. Similarly there was no change in AADC allele frequency observed in migraine patients compared to controls [180].

In summary, although an attractive hypothesis on the basis of food-induced migraine, there is little direct evidence at present supporting a role of trace amines in pathological headache. Evidence for changes in monoamine neurotransmitter metabolism has led to suggestions that such headaches are due to an imbalance between excitatory and inhibitory neurotransmitters [181]. Although trace amines may be involved in the generation of such an imbalance by virtue of their suggested role in maintaining basal neuronal tone within defined physiological limits [3], additional studies are required.

STRESS/ANXIETY DISORDERS

Stress is a possible precipitating factor for acute schizophrenic episodes. Due to the possible role of PE in schizophrenia, Paulos and Tessel [182] investigated the excretion of PE following stressful experiences. Using parachuting as the stress-inducer, it was reported that urinary PE excretion was markedly increased in the hours post parachuting. These changes were not correlated with changes in urinary pH or creatinine excretion [182], suggesting that the results do not merely represent a global change in metabolism. Although intriguing, replication studies do not appear to have been attempted.

PE has also been proposed to be an endogenous anxiogen in experimental animals [183]. At doses below those usually required to elicit amphetamine-like responses, PE was reported to cause behavioral changes indicative of an anxiogen. Further, the effects were prevented by the anxiolytic agent diazepam [183]. In agreement with these findings, genetic deficiency in MAO-B was associated with an exaggerated stress response in mice [88]. Biochemically, these animals were notable for a pronounced elevation in PE, with few consistent changes in other biogenic amines [88].

As previously described, N,N-dimethyltryptamine (DMT), a known hallucinogen produced endogenously, has historically been suggested to play a role in the etiology of schizophrenia. These studies have recently been re-interpreted. At non-hallucinogenic doses, DMT elicited responses consistent with an anxiolytic agent [59], leading to a suggestion that DMT and other endogenous tryptamines are endogenous anxiolytic compounds [59]. Here the increased DMT production associated with schizophrenia is regarded as an attempt by the body to regain emotional control [59].

Finally, endogenous β-carbolines are putative ligands at one or more TAAR [10]. These agents also interact with benzodiazepine binding sites [184, 185] and have been suggested to play both anxiogenic and anxiolytic roles [186]. Whilst an interaction of endogenous β-carbolines with TAAR requires definitive demonstration, such a demonstration would classify TAAR as a target to which novel anxiolytic agents can be designed.

REYE'S SYNDROME

Reye's Syndrome has been defined as an unexplained, non-inflammatory encephalopathy, which is associated with elevated aspartate or alanine aminotransferases, hyperammonemia and fatty degeneration of the liver and mitochondrial dysfunction in children [187]. Such mitochondrial dysfunction could cause pronounced changes in endogenous trace amine levels, as metabolism *via* MAO would be expected to be compromised. Although there has been much conjecture regarding the possible role of aspirin in initiating Reye's Syndrome [188], a definitive cause remains elusive. Octopamine and tryptamine have been suggested to play a role in hepatic encephalopathy [43, 189, 190], whilst post-mortem brain octopamine levels have been reported to be elevated 700% in Reye's Syndrome patients [191]. The cause and effect relationship of such observations requires clarification, although it is interesting that similarities have been noted between tyramine-induced coma in experimental animals with concomitant liver damage and the coma associated with Reye's Syndrome [192]. Evidence has also been presented for markedly elevated tyramine levels in patient urine and plasma [193]. Of note, the increased tyramine levels were reported to be correlated to the subsequent length of coma and hyperammonemia [193].

Such elevated tyramine levels would be expected to also result in an increase in octopamine levels (see Fig. **1**). Whether correction of trace amine functioning alone, without addressing the underlying hepatic failure and mitochondrial dysfunction, would be beneficial in Reye's Syndrome patients requires further investigation.

EPILEPSY

Administration of high doses of PE have been shown to induce seizure activity in mice [194]. Such epileptiform activity was antagonized by standard benzodiazepine anti-epileptics in a manner suggesting that the high doses of PE interacted with the GABAergic system [194]. In this respect it is interesting to note that PE and tyramine were recently demonstrated to modulate GABAergic responses [22] in a manner similar to that previously described for dopaminergic and noradrenergic responses [3]. Neither PE, tyramine nor octopamine appear to interact directly with flunitrazepam binding sites however [195]. β-carbolines, which are known to decrease seizure threshold, have been thought to do so due to an interaction with benzodiazepine binding sites associated with GABA receptors [184, 185, 196]. As described previously, endogenous β-carbolines have been suggested as putative endogenous ligands at one or more TAAR [10]. As such, there are preliminary indications suggesting an investigation of a role for TAAR in the genesis and control of seizure activity may be warranted.

CONCLUDING STATEMENTS

As can be seen from the preceding sections, although little is known about the basic functioning of the trace aminergic system, there is a large body of literature linking alterations in trace amines and their metabolism to a variety of clinical conditions. As progress continues to be made in elucidating the molecular mechanisms of trace amine functioning, selective ligands for each TAAR will be developed. The first such ligands for TAAR have recently been described [31] and these will likely aid considerably in the elucidation of the basic mechanisms of trace amines and their clinical relevance. Further, it is becoming apparent that existing therapeutics and drugs of abuse may interact with TAAR, either directly [2] or indirectly [102], providing an additional explanation for the observed clinical effects of such compounds. The high species variation present in trace amine receptors is, however, a considerable complicating factor. This high variation, along with the proposed species-dependant relevance of TAAR, makes generalizations of results from animal studies to humans difficult. The discovery of TAAR has also provided an additional target for the modification of central neuronal processes. The proposed function of trace amines in maintaining central neuronal functioning within defined physiological limits means that a primary deficit in trace aminergic functioning may not be required for TAAR ligands to be of therapeutic relevance. For example, although not discussed here, trace amine ligands are also likely to be useful in disorders such as

Parkinson's disease. Here a synthetic ligand that mimics the potentiation of dopaminergic responses observed following elevation of PE levels could realistically be expected to provide symptomatic relief. In summary, the discovery of the TAAR family of receptors has rejuvenated interest in the trace amines, an endogenous family of compounds with therapeutic implications in a number of human neurologic and psychiatric conditions.

ACKNOWLEDGEMENTS

The author wishes to thank Dr. P. Jackson for his helpful comments and critical appraisal of the manuscript.

REFERENCES

[1] Borowsky B, Adham N, Jones KA, *et al.* Trace amines: identification of a family of mammalian G protein-coupled receptors. Proc Natl Acad Sci USA 2001; 98: 8966-71.

[2] Bunzow JR, Sonders MS, Arttamangkul S, *et al.* Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. Mol Pharmacol 2001; 60: 1181-8.

[3] Berry MD. Mammalian central nervous system trace amines. Pharmacologic amphetamines, physiologic neuromodulators. J Neurochem 2004; 90: 257-71.

[4] Lewin AH. Receptors of mammalian trace amines. AAPS J 2006; 8: E138-45.

[5] Lindemann L, Hoener MC. A renaissance in trace amines inspired by a novel GPCR family. Trends Pharmacol Sci 2005; 26: 274-81.

[6] Branchek TA, Blackburn TP. Trace amine receptors as targets for novel therapeutics: legend, myth and fact. Curr Opin Pharmacol 2003; 3: 90-97.

[7] Navarro HA, Gilmour BP, Lewin AH. A rapid functional assay for the human trace amine--associated receptor 1 based on the mobilization of internal calcium. J Biomol Screen 2006; e-pub July 10: doi:10.1177/1087057106289891 Accessed August 10, 2006.

[8] Liberles SD, Buck LB. A second class of chemosensory receptors in the olfactory epithelium. Nature 2006; 442: 645-50.

[9] Scanlan TS, Suchland KL, Hart ME, *et al.* 3-Iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. Nat Med 2004; 10: 638-42.

[10] Holt A. Imidazoline binding sites on receptors and enzymes: emerging targets for novel antidepressant drugs? J Psychiatry Neurosci 2003; 28: 409-14.

[11] Lindemann L, Ebeling M, Kratochwil NA, *et al.* Trace amine-associated receptors form structurally and functionally distinct subfamilies of novel G protein-coupled receptors. Genomics 2005; 85: 372-85.

[12] Paterson IA, Juorio AV, Boulton AA. 2-Phenylethylamine: a modulator of catecholamine transmission in the mammalian central nervous system? J Neurochem 1990; 55: 1827-37.

[13] Berry MD, Juorio AV, Li XM, Boulton AA. Aromatic L-amino acid decarboxylase: a neglected and misunderstood enzyme. Neurochem Res 1996; 21: 1075-87.

[14] Bowsher RR, Henry DP. Aromatic L-amino decarboxylase. In: Boulton AA, Baker GB, Yu PH, Ed, Neuromethods: Neurotransmitter Enzymes. Clifton, New Jersey, Humana Press, Inc. 1986; 33-78.

[15] Yang HY, Neff NH. The monoamine oxidases of brain: selective inhibition with drugs and the consequences for the metabolism of the biogenic amines. J Pharmacol Exp Ther 1974; 189: 733-40.

[16] Berry MD, Juorio AV, Paterson IA. The functional role of monoamine oxidases A and B in the mammalian central nervous system. Prog Neurobiol 1994; 42: 375-91.

[17] Holt A, Todd KG, Baker GB. The effects of chronic administration of inhibitors of flavin and quinone amine oxidases on imidazoline I(1) receptor density in rat whole brain. Ann N Y Acad Sci 2003; 1009: 309-22.

[18] Davis BA. Biogenic amines and their metabolites in body fluids of normal, psychiatric and neurological subjects. J Chromatogr 1989; 466: 89-218.

[19] Davis BA, Boulton AA. The trace amines and their acidic metabolites in depression--an overview. Prog Neuropsychopharmacol Biol Psychiatry 1994; 18: 17-45.

[20] McQuade PS. Analysis and the effects of some drugs on the metabolism of phenylethylamine and phenylacetic acid. Prog Neuropsychopharmacol Biol Psychiatry 1984; 8: 607-14.

[21] Huebert ND, Dulery BD, Schoun J, *et al.* Kinetics and metabolism of *p*-tyramine during monoamine oxidase inhibition by mofegiline. Clin Pharmacol Ther 1994; 56: 537-42.

[22] Berretta N, Giustizieri M, Bernardi G, Mercuri NB. Trace amines reduce GABA(B) receptor-mediated presynaptic inhibition at GABAergic synapses of the rat substantia nigra pars compacta. Brain Res 2005; 1062: 175-8.

[23] Fuxe K, Grobecker H, Jonsson J. The effect of β-phenylethylamine on central and peripheral monoamine-containing neurons. Eur J Pharmacol 1967; 2: 202-7.

[24] Raiteri M, Del Carmine R, Bertollini A, Levi G. Effect of sympathomimetic amines on the synaptosomal transport of noradrenaline, dopamine and 5-hydroxytryptamine. Eur J Pharmacol 1977; 41: 133-43.

[25] Parker EM, Cubeddu LX. Comparative effects of amphetamine, phenylethylamine and related drugs on dopamine efflux, dopamine uptake and mazindol binding. J Pharmacol Exp Ther 1988; 245: 199-210.

[26] Janssen PA, Leysen JE, Megens AA, Awouters FH. Does phenylethylamine act as an endogenous amphetamine in some patients? Int J Neuropsychopharmcol 1999; 2: 229-240.

[27] Borison RL, Mosnaim AD, Sabelli HC. Brain 2-phenylethylamine as a major mediator for the central actions of amphetamine and methylphenidate. Life Sci 1975; 17: 1331-43.

[28] Roeder T. Octopamine in invertebrates. Prog Neurobiol 1999; 59: 533-61.

[29] Roeder T. Tyramine and octopamine: ruling behavior and metabolism. Annu Rev Entomol 2005; 50: 447-77.

[30] Gloriam DE, Bjarnadottir TK, Schioth HB, Fredriksson R. High species variation within the repertoire of trace amine receptors. Ann N Y Acad Sci 2005; 1040: 323-7.

[31] Hart ME, Suchland KL, Miyakawa M, *et al.* Trace amine-associated receptor agonists: synthesis and evaluation of thyronamines and related analogues. J Med Chem 2006; 49: 1101-12.

[32] Hiroi Y, Kim HH, Ying H, *et al.* Rapid nongenomic actions of thyroid hormone. Proc Natl Acad Sci USA 2006; 103: 14104.

[33] Knoll J. Antiaging compounds: (-)deprenyl (selegeline) and (-)1-(benzofuran-2- yl)-2-propylaminopentane, [(-)BPAP], a selective highly potent enhancer of the impulse propagation mediated release of catecholamine and serotonin in the brain. CNS Drug Rev 2001; 7: 317-45.

[34] Knoll J, Yoneda F, Knoll B, Ohde H, Miklya I. (-)1-(Benzofuran-2-yl)-2-propylaminopentane, [(-)BPAP], a selective enhancer of the impulse propagation mediated release of catecholamines and serotonin in the brain. Br J Pharmacol 1999; 128: 1723-32.

[35] Ling L, Urichuk LJ, Sloley BD, *et al.* Synthesis of N-propargylphenelzine and analogues as neuroprotective agents. Bioorg Med Chem Lett 2001; 11: 2715-7.

[36] Henry DP, Russell WL, Clemens J, Plebus LA. Phenylethylamine and *p*-tyramine in the extracellular space of the rat brain: quantification using a new radioenzymatic assay and in situ microdialysis. In: Boulton AA, Juorio AV, Downer RG, Ed, Trace Amines: Comparative and Clinical Neurobiology. Clifton, New Jersey, Humana Press, Inc. 1988; 239-250.

[37] Durden DA, Davis BA. Determination of regional distributions of phenylethylamine and meta- and para-tyramine in rat brain regions and presence in human and dog plasma by an ultra-sensitive negative chemical ion gas chromatography-mass spectrometric (NCI-GC-MS) method. Neurochem Res 1993; 18: 995-1002.

[38] Davis BA, Durden DA. Quantitative high resolution mass spectrometry of biogenic amines. In: Baker GB, Coutts RT, Ed, Analysis of biogenic amines, Part A: Evaluation of analytical methods in biological systems. Amsterdam, Elsevier. 1982; 129-149.

[39] Durden DA, Boulton AA. Mass spectrometric analysis of some neurotransmitters and their precursors and metabolites. In: Lajtha A, Ed, Handbook of neurochemistry, Vol 2. New York, Plenum press. 1982; 103-132.

[40] Kahler SG, Fahey MC. Metabolic disorders and mental retardation. Am J Med Genet C Semin Med Genet 2003; 117: 31-41.

[41] Reynolds GP, Seakins JW, Gray DO. The urinary excretion of 2-phenylethylamine in phenylketonuria. Clin Chim Acta 1978; 83: 33-9.

[42] Wolf ME, Mosnaim AD. Phenylethylamine in neuropsychiatric disorders. Gen Pharmacol 1983; 14: 385-90.

[43] Premont RT, Gainetdinov RR, Caron MG. Following the trace of elusive amines. Proc Natl Acad Sci USA 2001; 98: 9474-5.

[44] Reynolds GP. Phenylethylamine - a role in mental illness. Trends Neurosci 1979; 2: 265.

[45] Olson MV, Varki A. Sequencing the chimpanzee genome: insights into human evolution and disease. Nat Rev Genet 2003; 4: 20-8.

[46] Moja EA, Stoff DM, Gillin JC, Wyatt RJ. Dose-response effects of beta-phenylethylamine on stereotyped behavior in pargyline-pretreated rats. Biol Psychiatry 1976; 11: 731-42.

[47] Dourish CT. An observational analysis of the behavioural effects of β - phenylethylamine in isolated and grouped mice. Prog Neuropsychopharmacol Biol Psychiatry 1982; 6: 143-58.

[48] Greenshaw AJ, Juorio AV, Boulton AA. Behavioral and neurochemical effects of deprenyl and β-phenylethylamine in Wistar rats. Brain Res Bull 1985; 15: 183-9.

[49] Sandler M, Reynolds GP. Does phenylethylamine cause schizophrenia? Lancet 1976; 1: 70-1.

[50] Greenshaw AJ. β-Phenylethylamine and reinforcement. Prog Neuropsychopharmacol Biol Psychiatry 1984; 8: 615-20.

[51] Mueser KT, McGurk SR. Schizophrenia. Lancet 2004; 363: 2063-72.

[52] O'Reilly RL, Davis BA. Phenylethylamine and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 1994; 18: 63-75.

[53] Potkin SG, Karoum F, Chuang LW, *et al.* Phenylethylamine in paranoid chronic schizophrenia. Science 1979; 206: 470-1.

[54] Potkin SG, Wyatt RJ, Karoum F. Phenylethylamine (PEA) and phenylacetic acid (PAA) in the urine of chronic schizophrenic patients and controls. Psychopharmacol Bull 1980; 16: 52-4.

[55] O'Reilly R, Davis BA, Durden DA, *et al.* Plasma phenylethylamine in schizophrenic patients. Biol Psychiatry 1991; 30: 145-50.

[56] Shirkande S, O'Reilly R, Davis B, Durden D, Malcolm D. Plasma phenylethylamine levels of schizophrenic patients. Can J Psychiatry 1995; 40: 221.

[57] Gilka L. Schizophrenia, a disorder of tryptophan metabolism. Acta Psychiatr Scand Suppl 1975; 258: 1-83.

[58] Anderson GM, Gerner RH, Cohen DJ, Fairbanks L. Central tryptamine turnover in depression, schizophrenia, and anorexia: measurement of indoleacetic acid in cerebrospinal fluid. Biol Psychiatry 1984; 19: 1427-35.

[59] Jacob MS, Presti DE. Endogenous psychoactive tryptamines reconsidered: an anxiolytic role for dimethyltryptamine. Med Hypotheses 2005; 64: 930-7.

[60] Murray RM, Oon MC, Rodnight R, Birley JL, Smith A. Increased excretion of dimethyltryptamine and certain features of psychosis: a possible association. Arch Gen Psychiatry 1979; 36: 644-9.

[61] Checkley SA, Murray RM, Oon MC, Rodnight R, Birley JL. A longitudinal study of urinary excretion of N,N,-dimethyltryptamine in psychotic patients. Br J Psychiatry 1980; 137: 236-9.

[62] Tanimukai H, Ginther R, Spaide J, Bueno JR, Himwich HE. Detection of psychotomimetic N,N-dimethylated indoleamines in the urine of four schizophrenic patients. Br J Psychiatry 1970; 117: 421-30.

[63] Cao Q, Martinez M, Zhang J, *et al.* Suggestive evidence for a schizophrenia susceptibility locus on chromosome 6q and a confirmation in an independent series of pedigrees. Genomics 1997; 43: 1-8.

[64] Kaufmann CA, Suarez B, Malaspina D, *et al.* NIMH Genetics Initiative Millenium Schizophrenia Consortium: linkage analysis of African-American pedigrees. Am J Med Genet 1998; 81: 282-9.

[65] Levinson DF, Holmans P, Straub RE, *et al.* Multicenter linkage study of schizophrenia candidate regions on chromosomes 5q, 6q, 10p, and 13q: schizophrenia linkage collaborative group III. Am J Hum Genet 2000; 67: 652-63.

[66] Lindholm E, Ekholm B, Shaw S, *et al.* A schizophrenia-susceptibility locus at 6q25, in one of the world's largest reported pedigrees. Am J Hum Genet 2001; 69: 96-105.

[67] Lewis CM, Levinson DF, Wise LH, *et al.* Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. Am J Hum Genet 2003; 73: 34-48.

[68] Bly M. Examination of the trace amine-associated receptor 2 (TAAR2). Schizophr Res 2005; 80: 367-8.

[69] Duan J, Martinez M, Sanders AR, *et al.* Polymorphisms in the trace amine receptor 4 (TRAR4) gene on chromosome 6q23.2 are associated with susceptibility to schizophrenia. Am J Hum Genet 2004; 75: 624-38.

[70] Ikeda M, Iwata N, Suzuki T, *et al.* No association of haplotype-tagging SNPs in TRAR4 with schizophrenia in Japanese patients. Schizophr Res 2005; 78: 127-30.

[71] Duan S, Du J, Xu Y, *et al.* Failure to find association between TRAR4 and schizophrenia in the Chinese Han population. J Neural Transm 2006; 113: 381-5.

[72] Amann D, Avidan N, Kanyas K, *et al.* The trace amine receptor 4 gene is not associated with schizophrenia in a sample linked to chromosome 6q23. Mol Psychiatry 2006; 11: 119-21.

[73] Li T, Ball D, Zhao J, *et al.* Family-based linkage disequilibrium mapping using SNP marker haplotypes: application to a potential locus for schizophrenia at chromosome 22q11. Mol Psychiatry 2000; 5: 77-84.

[74] Egan MF, Goldberg TE, Kolachana BS, *et al.* Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA 2001; 98: 6917-22.

[75] Shifman S, Bronstein M, Sternfeld M, *et al.* A highly significant association between a COMT haplotype and schizophrenia. Am J Hum Genet 2002; 71: 1296-302.

[76] Shifman S, Levit A, Chen ML, *et al.* A complete genetic association scan of the 22q11 deletion region and functional evidence reveal an association between DGCR2 and schizophrenia. Hum Genet 2006; 120: 160-70.

[77] Palmatier MA, Pakstis AJ, Speed W, *et al.* COMT haplotypes suggest P2 promoter region relevance for schizophrenia. Mol Psychiatry 2004; 9: 859-70.

[78] Kim K-A, von Zastrow M. Old drugs learn new tricks: insights from mammalian trace amine receptors. Mol Pharmacol 2001; 60: 1165-7.

[79] O'Malley KL, Harmon S, Moffat M, Uhland-Smith A, Wong S. The human aromatic L-amino acid decarboxylase gene can be alternatively spliced to generate unique protein isoforms. J Neurochem 1995; 65: 2409-16.

[80] Borglum AD, Hampson M, Kjeldsen TE, *et al.* Dopa decarboxylase genotypes may influence age at onset of schizophrenia. Mol Psychiatry 2001; 6: 712-7.

[81] Zhang B, Jia Y, Yuan Y, *et al.* No association between polymorphisms in the DDC gene and paranoid schizophrenia in a northern Chinese population. Psychiatr Genet 2004; 14: 161-3.

[82] Reith J, Benkelfat C, Sherwin A, *et al.* Elevated dopa decarboxylase activity in living brain of patients with psychosis. Proc Natl Acad Sci USA 1994; 91: 11651-4.

[83] Lindstrom LH, Gefvert O, Hagberg G, *et al.* Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. Biol Psychiatry 1999; 46: 681-8.

[84] Noble EP. D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. Am J Med Genet B Neuropsychiatr Genet 2003; 116: 103-25.

[85] Laakso A, Pohjalainen T, Bergman J, *et al.* The A1 allele of the human D2 dopamine receptor gene is associated with increased activity of striatal L-amino acid decarboxylase in healthy subjects. Pharmacogenet Genomics 2005; 15: 387-91.

[86] David JC, Coulon JF, Cavoy A, Delacour J. Effects of aging on *p*- and *m*-octopamine, catecholamines, and their metabolizing enzymes in the rat. J Neurochem 1989; 53: 149-54.

[87] Brus R. Activity of some enzymes which synthesize and metabolize catecholamines in the brain and peripheral organs in developing rats. Arch Immunol Ther Exp (Warsz) 1975; 23: 449-57.

[88] Grimsby J, Toth M, Chen K, *et al.* Increased stress response and beta-phenylethylamine in MAOB-deficient mice. Nat Genet 1997; 17: 206-10.

[89] Holschneider DP, Chen K, Seif I, Shih JC. Biochemical, behavioral, physiologic, and neurodevelopmental changes in mice deficient in monoamine oxidase A or B. Brain Res Bull 2001; 56: 453-62.

[90] Lenders JW, Eisenhofer G, Abeling NG, *et al.* Specific genetic deficiencies of the A and B isoenzymes of monoamine oxidase are

characterized by distinct neurochemical and clinical phenotypes. J Clin Invest 1996; 97: 1010-9.

[91] Zhu MY, Juorio AV, Paterson IA, Boulton AA. Regulation of striatal aromatic L-amino acid decarboxylase: effects of blockade or activation of dopamine receptors. Eur J Pharmacol 1993; 238: 157-64.

[92] Hadjiconstantinou M, Wemlinger TA, Sylvia CP, Hubble JP, Neff NH. Aromatic L-amino acid decarboxylase activity of mouse striatum is modulated *via* dopamine receptors. J Neurochem 1993; 60: 2175-80.

[93] Buckland PR, O'Donovan MC, McGuffin P. Changes in dopa decarboxylase mRNA but not tyrosine hydroxylase mRNA levels in rat brain following antipsychotic treatment. Psychopharmacology 1992; 108: 98-102.

[94] Buckland PR, Spurlock G, McGuffin P. Amphetamine and vigabatrin down regulate aromatic L-amino acid decarboxylase mRNA levels. Brain Res Mol Brain Res 1996; 35: 69-76.

[95] Ikemoto K, Nishimura A, Oda T, Nagatsu I, Nishi K. Number of striatal D-neurons is reduced in autopsy brains of schizophrenics. Leg Med (Tokyo) 2003; 5 (Suppl 1): S221-4.

[96] Jaeger CB, Teitelman G, Joh TH, *et al.* Some neurons of the rat central nervous system contain aromatic-L-amino-acid decarboxylase but not monoamines. Science 1983; 219: 1233-5.

[97] Nagatsu I, Sakai M, Yoshida M, Nagatsu T. Aromatic L-amino acid decarboxylase-immunoreactive neurons in and around the cerebrospinal fluid-contacting neurons of the central canal do not contain dopamine or serotonin in the mouse and rat spinal cord. Brain Res 1988; 475: 91-102.

[98] Jaeger CB, Ruggiero DA, Albert VR, Joh TH, Reis DJ. Immunocytochemical localization of aromatic L-amino acid decarboxylase. In: Bjorklund A, Hokfelt T, Ed, Handbook of Chemical Neuroanatomy Vol. 2. Classical transmitters in the CNS. Amsterdam, Elsevier. 1984; 387-408.

[99] Ikemoto K. Significance of human striatal D-neurons: implications in neuropsychiatric functions. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 429-34.

[100] Sabelli HC, Vazquez AJ, Mosnaim AD, Madrid-Pedemonte L. 2-Phenylethylamine as a possible mediator for Δ^9- tetrahydro-cannabinol-induced stimulation. Nature 1974; 248: 144-5.

[101] Turner D. A review of the use of modafinil for attention-deficit hyperactivity disorder. Expert Rev Neurother 2006; 6: 455-68.

[102] Madras BK, Xie Z, Lin Z, *et al.* Modafinil occupies dopamine and norepinephrine transporters *in vivo* and modulates the transporters and trace amine activity *in vitro*. J Pharmacol Exp Ther 2006; e-pub August 2: doi:10.1124/jpet.106.106583 Accessed August 10, 2006.

[103] Baker GB, Bornstein RA, Rouget AC, *et al.* Phenylethylaminergic mechanisms in attention-deficit disorder. Biol Psychiatry 1991; 29: 15-22.

[104] Zametkin AJ, Karoum F, Rapoport JL, Brown GL, Wyatt RJ. Phenylethylamine excretion in attention deficit disorder. J Am Acad Child Psychiatry 1984; 23: 310-4.

[105] Kusaga A, Yamashita Y, Koeda T, *et al.* Increased urine phenylethylamine after methylphenidate treatment in children with ADHD. Ann Neurol 2002; 52: 372-4.

[106] Zametkin AJ, Karoum F, Rapoport JL. Treatment of hyperactive children with D-phenylalanine. Am J Psychiatry 1987; 144: 792-4.

[107] Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. J Neurosci 1998; 18: 5901-7.

[108] Ernst M, Zametkin AJ, Matochik JA, *et al.* High midbrain [18F]DOPA accumulation in children with attention deficit hyperactivity disorder. Am J Psychiatry 1999; 156: 1209-15.

[109] Hawi Z, Foley D, Kirley A, *et al.* Dopa decarboxylase gene polymorphisms and attention deficit hyperactivity disorder (ADHD): no evidence for association in the Irish population. Mol Psychiatry 2001; 6: 420-4.

[110] Bakker SC, van der Meulen EM, Buitelaar JK, *et al.* A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. Am J Hum Genet 2003; 72: 1251-60.

[111] Hauger RL, Skolnick P, Paul SM. Specific [^{3}H] β-phenylethylamine binding sites in rat brain. Eur J Pharmacol 1982; 83: 147-8.

[112] Borison RL, Diamond BI. A new animal model for schizophrenia: interactions with adrenergic mechanisms. Biol Psychiatry 1978; 13: 217-25.

[113] Shannon HE, Thompson WA. Behavior maintained under fixed-interval and second-order schedules by intravenous injections of endogenous noncatecholic phenylethylamines in dogs. J Pharmacol Exp Ther 1984; 228: 691-5.

[114] Risner ME, Jones BE. Characteristics of beta-phenethylamine self-administration by dog. Pharmacol Biochem Behav 1977; 6: 689-96.

[115] Greenshaw AJ, Sanger DJ, Blackman DE. Effects of *d*-amphetamine and of β-phenylethylamine on fixed interval responding maintained by self-regulated lateral hypothalamic stimulation in rats. Pharmacol Biochem Behav 1985; 23: 519-23.

[116] McClung C, Hirsh J. The trace amine tyramine is essential for sensitization to cocaine in Drosophila. Curr Biol 1999; 9: 853-60.

[117] Blenau W, Baumann A. Molecular and pharmacological properties of insect biogenic amine receptors: lessons from Drosophila melanogaster and Apis mellifera. Arch Insect Biochem Physiol 2001; 48: 13-38.

[118] Blum K, Noble EP, Sheridan PJ, *et al.* Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA 1990; 263: 2055-60.

[119] Gelernter J, Goldman D, Risch N. The A1 allele at the D2 dopamine receptor gene and alcoholism. A reappraisal. JAMA 1993; 269: 1673-7.

[120] Tiihonen J, Vilkman H, Rasanen P, *et al.* Striatal presynaptic dopamine function in type 1 alcoholics measured with positron emission tomography. Mol Psychiatry 1998; 3: 156-61.

[121] Ma JZ, Beuten J, Payne TJ, *et al.* Haplotype analysis indicates an association between the DOPA decarboxylase (DDC) gene and nicotine dependence. Hum Mol Genet 2005; 14: 1691-8.

[122] Wang D, Ma JZ, Li MD. Mapping and verification of susceptibility loci for smoking quantity using permutation linkage analysis. Pharmacogenomics J 2005; 5: 166-72.

[123] Uhl GR, Vandenbergh DJ, Rodriguez LA, Miner L, Takahashi N. Dopaminergic genes and substance abuse. Adv Pharmacol 1998; 42: 1024-32.

[124] Comings DE, Ferry L, Bradshaw-Robinson S, *et al.* The dopamine D2 receptor (DRD2) gene: a genetic risk factor in smoking. Pharmacogenetics 1996; 6: 73-9.

[125] Spitz MR, Shi H, Yang F, *et al.* Case-control study of the D2 dopamine receptor gene and smoking status in lung cancer patients. J Natl Cancer Inst 1998; 90: 358-63.

[126] Bierut LJ, Rice JP, Edenberg HJ, *et al.* Family-based study of the association of the dopamine D2 receptor gene (DRD2) with habitual smoking. Am J Med Genet 2000; 90: 299-302.

[127] Persico AM, Bird G, Gabbay FH, Uhl GR. D2 dopamine receptor gene TaqI A1 and B1 restriction fragment length polymorphisms: enhanced frequencies in psychostimulant-preferring polysubstance abusers. Biol Psychiatry 1996; 40: 776-84.

[128] Lawford BR, Young RM, Noble EP, *et al.* The D(2) dopamine receptor A(1) allele and opioid dependence: association with heroin use and response to methadone treatment. Am J Med Genet 2000; 96: 592-8.

[129] Comings DE, Comings BG, Muhleman D, *et al.* The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. JAMA 1991; 266: 1793-800.

[130] O'Hara BF, Smith SS, Bird G, *et al.* Dopamine D2 receptor RFLPs, haplotypes and their association with substance use in black and Caucasian research volunteers. Hum Hered 1993; 43: 209-18.

[131] Comings DE, Muhleman D, Ahn C, Gysin R, Flanagan SD. The dopamine D2 receptor gene: a genetic risk factor in substance abuse. Drug Alcohol Depend 1994; 34: 175-80.

[132] Comings DE, Rosenthal RJ, Lesieur HR, *et al.* A study of the dopamine D2 receptor gene in pathological gambling. Pharmacogenetics 1996; 6: 223-34.

[133] Beuten J, Payne TJ, Ma JZ, Li MD. Significant association of catechol-O-methyltransferase (COMT) haplotypes with nicotine dependence in male and female smokers of two ethnic populations. Neuropsychopharmacology 2006; 31: 675-84.

[134] Cole SO. Brain mechanisms of amphetamine-induced anorexia, locomotion and stereotypy: a review. Neuroscience Biobehav Rev 1978; 2: 89-100.

[135] Dourish CT, Boulton AA. The effects of acute and chronic administration of β- phenylethylamine on food intake and body weight in rats. Prog Neuropsychopharmacol 1981; 5: 411-4.

[136] Paul SM, Hulihan-Giblin B, Skolnick P. (+)-Amphetamine binding to rat hypothalamus: relation to anorexic potency for phenylethylamines. Science 1982; 218: 487-90.

[137] Blenau W, Balfanz S, Baumann A. Amtyr1: characterization of a gene from honeybee (Apis mellifera) brain encoding a functional tyramine receptor. J Neurochem 2000; 74: 900-8.

[138] Sabelli HC, Mosnaim AD. Phenylethylamine hypothesis of affective behavior. Am J Psychiatry 1974; 131: 695-9.

[139] Sandler M, Ruthven CR, Goodwin BL, Coppen A. Decreased cerebrospinal fluid concentration of free phenylacetic acid in depressive illness. Clin Chim Acta 1979; 93: 169-71.

[140] Kawabata M, Kobayashi K, Shohmori T. Determination of phenylacetic acid in cerebrospinal fluid by gas chromatography-mass spectrometry. Acta Med Okayama 1986; 40: 271-6.

[141] DeLisi LE, Murphy DL, Karoum F, *et al.* Phenylethylamine excretion in depression. Psychiatry Res 1984; 13: 193-201.

[142] Philips SR, Boulton AA. The effect of monoamine oxidase inhibitors on some arylalkylamines in rat striatum. J Neurochem 1979; 33: 159-67.

[143] Greenshaw AJ. Functional interactions of 2-phenylethylamine and of tryptamine with brain catecholamines: implications for psychotherapeutic drug action. Prog Neuropsychopharmacol Biol Psychiatry 1989; 13: 431-43.

[144] Sabelli HC, Giardina WJ, Mosnaim AD, Sabelli NH. A comparison of the functional roles of norepinephrine, dopamine, and phenylethylamine in the central nervous system. Acta Physiol Pol 1973; 24: 33-40.

[145] Fischer E, Spatz H, Heller B, Reggiani H. Phenethylamine content of human urine and rat brain, its alterations in pathological conditions and after drug administration. Experientia 1972; 28: 307-8.

[146] Dyck LE, Durden DA, Boulton AA. Formation of β-phenylethylamine from the antidepressant, β-phenylethylhydrazine. Biochem Pharmacol 1985; 34: 1925-9.

[147] Baker GB, Greenshaw AJ. Effects of long-term administration of antidepressants and neuroleptics on receptors in the central nervous system. Cell Mol Neurobiol 1989; 9: 1-44.

[148] Paetsch PR, Baker GB, Greenshaw AJ. Induction of functional down-regulation of β-adrenoceptors in rats by 2-phenylethylamine. J Pharm Sci 1993; 82: 22-4.

[149] Baumeister AA, Hawkins MF, Uzelac SM. The myth of reserpine-induced depression: role in the historical development of the monoamine hypothesis. J Hist Neurosci 2003; 12: 207-20.

[150] Boulton AA, Juorio AV, Philips SR, Wu PH. The effects of reserpine and 6-hydroxydopamine on the concentrations of some arylalkylamines in rat brain. Br J Pharmacol 1977; 59: 209-14.

[151] Szabo A, Billett E, Turner J. Phenylethylamine, a possible link to the antidepressant effects of exercise? Br J Sports Med 2001; 35: 342-3.

[152] Birkmayer W, Riederer P, Linauer W, Knoll J. L-deprenyl plus L-phenylalanine in the treatment of depression. J Neural Transm 1984; 59: 81-7.

[153] Sabelli H, Fink P, Fawcett J, Tom C. Sustained antidepressant effect of PEA replacement. J Neuropsychiatry Clin Neurosci 1996; 8: 168-71.

[154] Beckmann H, Strauss MA, Ludolph E. DL-phenylalanine in depressed patients: an open study. J Neural Transm 1977; 41: 123-34.

[155] Sandler M, Ruthven CR, Goodwin BL, *et al.* Deficient production of tyramine and octopamine in cases of depression. Nature 1979; 278: 357-8.

[156] Dick DM, Foroud T, Flury L, *et al.* Genomewide linkage analyses of bipolar disorder: a new sample of 250 pedigrees from the National Institute of Mental Health Genetics Initiative. Am J Hum Genet 2003; 73: 107-14.

[157] Pato CN, Middleton FA, Gentile KL, *et al.* Genetic linkage of bipolar disorder to chromosome 6q22 is a consistent finding in Portuguese subpopulations and may generalize to broader populations. Am J Med Genet B Neuropsychiatr Genet 2005; 134: 119-21.

[158] Middleton FA, Pato MT, Gentile KL, *et al.* Genomewide linkage analysis of bipolar disorder by use of a high-density single-nucleotide-polymorphism (SNP) genotyping assay: a comparison with microsatellite marker assays and finding of significant linkage to chromosome 6q22. Am J Hum Genet 2004; 74: 886-97.

[159] Borglum AD, Bruun TG, Kjeldsen TE, *et al.* Two novel variants in the DOPA decarboxylase gene: association with bipolar affective disorder. Mol Psychiatry 1999; 4: 545-51.

[160] Borglum AD, Kirov G, Craddock N, *et al.* Possible parent-of-origin effect of Dopa decarboxylase in susceptibility to bipolar affective disorder. Am J Med Genet B Neuropsychiatr Genet 2003; 117: 18-22.

[161] Shifman S, Bronstein M, Sternfeld M, *et al.* COMT: a common susceptibility gene in bipolar disorder and schizophrenia. Am J Med Genet B Neuropsychiatr Genet 2004; 128: 61-4.

[162] Hanington E. Preliminary report on tyramine in headache. Brit Med J 1967; 2: 550-551.

[163] Coutts RT, Baker GB, Pasutto FM. Foodstuffs as sources of psychoactive amines and their precursors: content significance and identification. Adv Drug Res 1986; 15: 169-232.

[164] Yigit M, Ersoy L. Determination of tyramine in cheese by LC-UV. J Pharm Biomed Anal 2003; 31: 1223-8.

[165] Lange J, Thomas K, Wittmann C. Comparison of a capillary electrophoresis method with high-performance liquid chromatography for the determination of biogenic amines in various food samples. J Chromatogr B Analyt Technol Biomed Life Sci 2002; 779: 229-39.

[166] Baker GB, Wong JT, Coutts RT, Pasutto FM. Simultaneous extraction and quantitation of several bioactive amines in cheese and chocolate. J Chromatogr 1987; 392: 317-31.

[167] Davenport AP. Peptide and trace amine orphan receptors: prospects for new therapeutic targets. Curr Opin Pharmacol 2003; 3: 127-134.

[168] Maguire JJ, Barriocanal FP, Davenport AP. Are vasoconstrictor responses to tyramine in human blood vessels, *in vitro*, mediated by the orphan trace amine receptor, TA1. Br J Pharmacol 2002; 131: 71P.

[169] D'Andrea G, Terrazzino S, Fortin D, *et al.* Elusive amines and primary headaches: historical background and prospectives. Neurol Sci 2003; 24 (Suppl 2): S65-S67.

[170] Fioroni L, D'Andrea G, Alecci M, Cananzi A, Facchinetti F. Platelet serotonin pathway in menstrual migraine. Cephalalgia 1996; 16: 427-30.

[171] Sever PS. False transmitters and migraine. Lancet 1979; 1: 333.

[172] Balbi T, Fusco M, Vasapollo D, *et al.* The presence of trace amines in postmortem cerebrospinal fluid in humans. J Forensic Sci 2005; 50: 630-2.

[173] Shimazu S, Miklya I. Pharmacological studies with endogenous enhancer substances: beta-phenylethylamine, tryptamine, and their synthetic derivatives. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 421-7.

[174] D'Andrea G, Terrazzino S, Leon A, *et al.* Elevated levels of circulating trace amines in primary headaches. Neurology 2004; 62: 1701-5.

[175] D'Andrea G, Granella F, Leone M, *et al.* Abnormal platelet trace amine profiles in migraine with and without aura. Cephalalgia 2006; 26: 968-72.

[176] Strong FC, 3rd. Why do some dietary migraine patients claim they get headaches from placebos? Clin Exp Allergy 2000; 30: 739-43.

[177] May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. PET and MRA findings in cluster headache and MRA in experimental pain. Neurology 2000; 55: 1328-35.

[178] Leone M, Franzini A, Bussone G. Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. N Engl J Med 2001; 345: 1428-9.

[179] Aridon P, D'Andrea G, Rigamonti A, *et al.* Elusive amines and cluster headache: mutational analysis of trace amine receptor cluster on chromosome 6q23. Neurol Sci 2004; 25 (Suppl 3): S279-80.

[180] Johnson MP, Griffiths LR. A genetic analysis of serotonergic biosynthetic and metabolic enzymes in migraine using a DNA pooling approach. J Hum Genet 2005; 50: 607-10.

[181] D'Andrea G, Perini F, Terrazzino S, Nordera GP. Contributions of biochemistry to the pathogenesis of primary headaches. Neurol Sci 2004; 25 (Suppl 3): S89-92.

[182] Paulos MA, Tessel RE. Excretion of β-phenethylamine is elevated in humans after profound stress. Science 1982; 215: 1127-9.

[183] Lapin IP. Beta-phenylethylamine (PEA): an endogenous anxiogen? Three series of experimental data. Biol Psychiatry 1990; 28: 997-1003.

[184] Braestrup C, Nielsen M. GABA reduces binding of 3H-methyl beta-carboline-3-carboxylate to brain benzodiazepine receptors. Nature 1981; 294: 472-4.

[185] Oakley NR, Jones BJ. Differential pharmacological effects of beta-carboline-3-carboxylic acid esters. Neuropharmacology 1982; 21: 587-9.

[186] File SE, Baldwin HA. Effects of beta-carbolines in animal models of anxiety. Brain Res Bull 1987; 19: 293-9.

[187] Glasgow JF, Middleton B. Reye syndrome--insights on causation and prognosis. Arch Dis Child 2001; 85: 351-3.

[188] van Bever HP, Quek SC, Lim T. Aspirin, Reye syndrome, Kawasaki disease, and allergies; a reconsideration of the links. Arch Dis Child 2004; 89: 1178.

[189] Manghani KK, Lunzer MR, Billing BH, Sherlock S. Urinary and serum octopamine in patients with portal-systemic encephalopathy. Lancet 1975; 2: 943-6.

[190] Fischer JE, Baldessarini RJ. False neurotransmitters and hepatic failure. Lancet 1971; 2: 75-80.

[191] Lloyd KG, Davidson L, Price K, McClung HJ, Gall DG. Catecholamine and octopamine concentrations in brains of patients with Reye syndrome. Neurology 1977; 27: 985-8.

[192] Faraj BA, Caplan DB, Malveaux EJ, Camp VM, Ali FM. Similarity between tyramine-induced neurotoxicity and the coma of Reye's syndrome. J Pharmacol Exp Ther 1983; 226: 608-15.

[193] Faraj BA, Newman SL, Caplan DB, *et al.* Evidence for hypertyraminemia in Reye's syndrome. Pediatrics 1979; 64: 76-80.

[194] Dourish CT, Cooper SJ. Pharmacology of β-phenylethylamine-induced seizures in mice. Prog Neuropsychopharmacol Biol Psychiatry 1983; 7: 787-90.

[195] Smith TM. [^{3}H]-Flunitrazepam binding in the presence of β-phenylethylamine and its metabolites. Pharmacol Biochem Behav 1985; 23: 965-7.

[196] Braestrup C, Schmiechen R, Neef G, Nielsen M, Petersen EN. Interaction of convulsive ligands with benzodiazepine receptors. Science 1982; 216: 1241-3.

[197] Dyck LE, Yang CR, Boulton AA. The biosynthesis of *p*-tyramine, *m*-tyramine, and β-phenylethylamine by rat striatal slices. J Neurosci Res 1983; 10: 211-20.

Received: August 16, 2006 Revised: September 22, 2006 Accepted: October 17, 2006