Trace Monoamines and Receptors in Mammalian CNS

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Introduction

The trace amines are a class of endogenous neuroactive amines primarily comprising 2-phenylethylamine (PE), tryptamine, the tyramines (ortho-, meta-, and para-), the octopamines, and the synephrines, although other family members may also exist. As can be seen from Figure 1, these amines are structurally related to the classical monoamine neurotransmitters dopamine (DA), noradrenaline, and 5-hydroxytryptamine (5-HT), as well as amphetamine-related drugs of abuse.

Trace amines have been found in all species so far examined, ranging from lower invertebrates such as the starfish *Pycnopodia helianthoides*, up to higher mammals, including humans. Although synthetic and degradative strategies are the same in all species, trace amine functioning appears to be distinct, certainly between invertebrate and vertebrate species. Thus, while trace amines, in particular the tyramines and octopamines, have been established as neurotransmitters in a number of invertebrate species, such a neurotransmitter function has not been established in vertebrates. Indeed, in vertebrate species, trace amines have been suggested to regulate the efficacy of coexisting neurotransmitters, rather than serving as true neurotransmitters. The recent discovery and preliminary characterization of a family of putative G-protein-coupled trace amine receptors has lent some support to this hypothesis. Mammalian trace amine receptors comprise a phylogenetically distinct family only distantly related to their invertebrate counterparts.

This article describes the synthesis and degradation of trace amines and distribution of trace amines and their receptors in the mammalian central nervous system (CNS). The current state of understanding of trace amine physiology and pharmacology is presented in the context of the putative trace amine receptors, along with the possible relevance of trace amines to human neurologic and psychiatric disorders.

Trace Amine Synthesis

As would be expected of such closely related structures, the synthesis of trace amines occurs through the same enzymatic mechanisms as for the monoamine neurotransmitters (Figures 2 and 3). 2-Phenylethylamine, the tyramines, and tryptamine are formed by the decarboxylation of the precursor amino acids L-phenylalanine, L-tyrosine, and L-tryptophan, respectively. This reaction is catalyzed by the enzyme aromatic L-amino acid decarboxylase (EC 4.1.1.28; AADC). Tyramines can be converted into the corresponding octopamines by further hydroxylation via the enzyme dopamine-β-hydroxylase. Synephrines can then be formed following N-methylation of octopamines by the enzyme phenylethanolamine-*N*-methyltransferase. There are thus direct parallels between the synthesis of trace amines and the more abundant monoamine neurotransmitters DA, noradrenaline, adrenaline, and 5-HT.

As would be expected, this synthesis occurs primarily within monoaminergic axonal terminals in the CNS. Unlike neurotransmitters such as DA, however, AADC is of prime importance in trace amine synthesis. With respect to DA, noradrenaline, and 5-HT synthesis, AADC is present in a large excess, and is not rate limiting. This has caused considerable confusion, however, since AADC is regulated in response to dopaminergic and noradrenergic receptor activation in regions throughout the CNS. Such regulation does not, however, alter DA or noradrenaline levels. As can be seen from Figures 2 and 3, AADC is, by default, rate limiting with respect to the synthesis of trace amines. No other enzymatic process is present, at least with respect to 2-phenylethylamine and tyramine synthesis. Further, there is no evidence for regulation of either dopamine-β-hydroxylase or phenylethanolamine-*N*-methyltransferase activity.

In addition to synthesis in monoaminergic neurons, trace amines may also be synthesized in the so-called D cells of the CNS. D cells are neurons, which, while being immunopositive for AADC, are immunonegative for tyrosine hydroxylase, tryptophan hydroxylase, and 5-HT. As such, D cells, while not capable of synthesizing DA, noradrenaline, or 5-HT, can synthesize trace amines. The function of D cells in the mammalian CNS is poorly understood, and whether they function as dedicated trace aminergic neurons requires investigation.

With respect to the ortho-, meta-, and para- forms of the tyramines, octopamines, and synephrines, differential synthesis is present. The para-structural isomers of both tyramine and octopamine predominate, with somewhat lower levels of meta-isomers. In both instances, the ortho-isoform is rarely identified conclusively. Few studies have examined for differences in the structural isomers of synephrines. However, given that synephrines are derived directly from octopamines, which themselves are synthesized from tyramines, it seems likely that the para-isoform will again predominate.

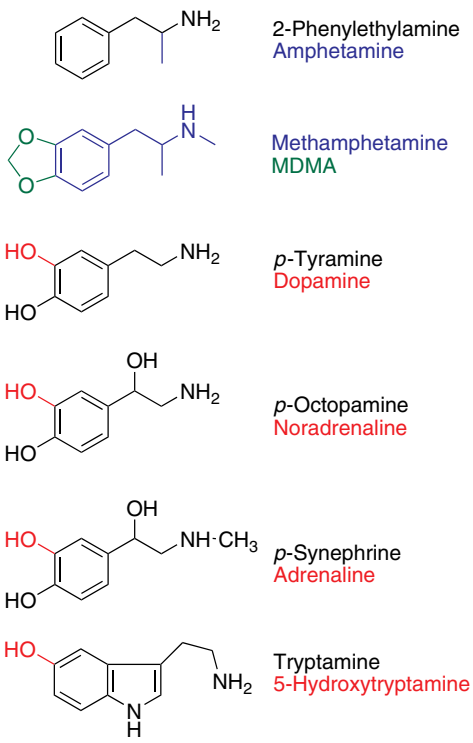

Figure 1 Similarity of trace amines to neurotransmitter monoamines and amphetamine. Structures in black represent the base trace amine structures. Minor additions to these structures give neurotransmitters (red) or amphetamine (blue). Methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) are also shown for comparison.

A further difference between trace amines and the monoamine neurotransmitters is seen when their tissue levels are compared. While whole brain levels of DA, noradrenaline, and 5-HT approximate 300–600 ng g^{-1} tissue in a number of mammalian species, the levels of the trace amines are at least two orders of magnitude lower, in the region of 1–5 ng g^{-1} of tissue. Notwithstanding such low levels, the trace amines are heterogeneously distributed within the mammalian CNS (see later). Further, their rate of synthesis is equivalent to that of neurotransmitter monoamines. As such, trace amines have an exceedingly rapid turnover rate, in the region of 30 s. Such a turnover is consistent with the apparent lack of storage of trace amines. Finally, in comparison to monoamine neurotransmitters, trace amines show a markedly elevated lipophilicity. Indeed, the trace amines so far studied do not appear to undergo storage and active release via exocytosis. Rather, trace amines appear to be 'released' by simple diffusion across cell membranes. As such, their endogenous levels within the CNS are a reflection of the steady state existing between synthetic and degradative pathways.

Trace Amine Degradation

Trace amine metabolism, with the exception of interconversion, proceeds primarily via oxidative deamination. As with monoamine neurotransmitters, this is

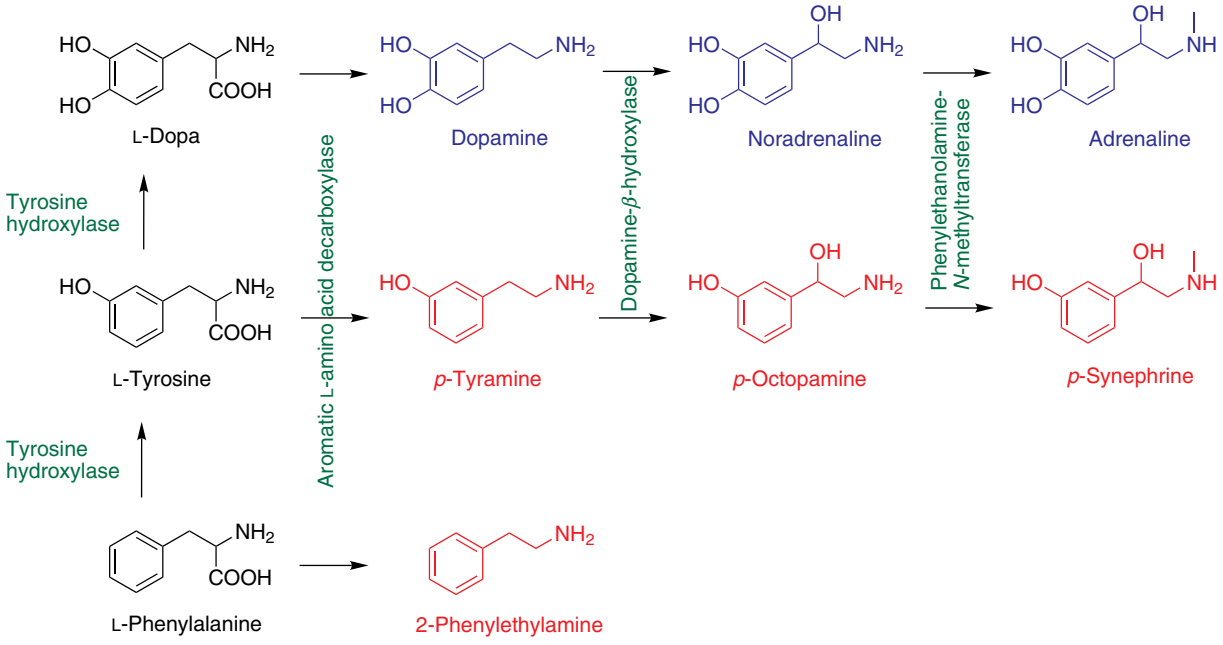

Figure 2 Relationship between trace amine and neurotransmitter synthetic pathways. Precursor amino acids are shown in black, trace amines in red, and neurotransmitter amines in blue. Enzymes common to the synthetic pathways are shown in green.

mediated by monoamine oxidase (EC 1.4.3.4; MAO). In general, the trace amines are rather nonselective substrates for both MAO types A and B. The exception to this is 2-phenylethylamine, which is the prototypical MAO-B selective substrate. Additional metabolic routes, such as deamination through the cytochrome P450 system, and O-methylation via catechol-O-methyltransferase (COMT), are minor fates of trace amine metabolism.

Tissue Distribution

Although trace amines are present in low levels, and readily cross cell membranes, they are heterogeneously distributed throughout the mammalian CNS (Table 1). In the rat, 2-phenylethylamine is particularly enriched in the olfactory tubercles, globus pallidus, and nucleus accumbens, while lower levels are seen in various brain stem regions. The tyramines and tryptamine, in contrast, are also enriched within the caudate putamen, with the cerebellum and cortical regions in addition to the brain stem showing low levels. Octopamine, meanwhile, shows higher levels in the hypothalamus and cerebellum, in comparison to other trace amines.

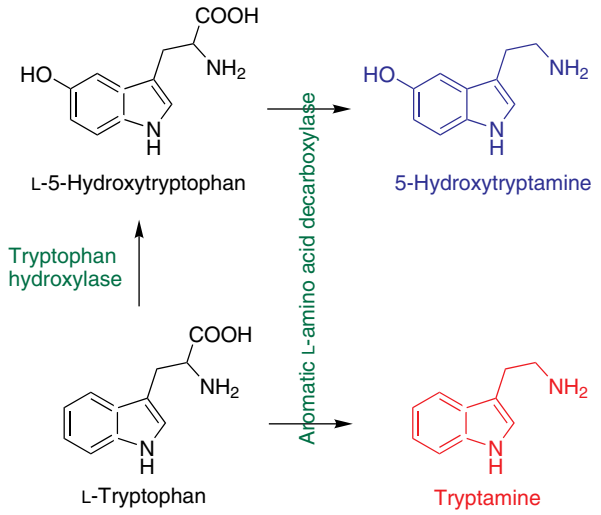

Figure 3 Relationship between tryptamine and 5-HT biosynthesis. Precursor amino acids are shown in black, trace amines in red, and neurotransmitter amines in blue. Enzymes common to the synthetic pathways are shown in green.

Trace Amine Receptors

Although the existence and distribution of invertebrate trace amine receptors is well established, mammalian equivalents were only identified in 2001. Somewhat surprisingly, the mammalian trace amine receptors do not show a close phylogenetic relationship to their invertebrate counterparts, suggesting a possible divergence in the physiological function of trace amines between invertebrates and mammals. The mammalian trace amine receptors form a distinct family of receptor protein termed trace amine-associated receptors (TAARs). A remarkable variability is present between mammalian species with respect to the numbers of receptors present within the genome (Table 2). The human and chimpanzee genomes each contain nine family members, while the rat has 19 members and the mouse, 16. In each instance, this number includes one or more pseudogenes; three in humans, six in chimpanzee, two in rat, and a single pseudogene in mouse. Phylogenetic and ligand-binding pocket analyses have identified three subclasses of TAAR, with each species so far studied containing at least one representative of each subclass (Table 2). All TAAR receptors show seven putative transmembrane domains consistent with the functional receptors being G-protein coupled. Both TAAR1 and TAAR4 appear to couple to the G_s protein, resulting in a stimulation of

Table 1 Regional distribution of trace amines in mammalian CNS

	2-Phenylethylamine	*p-Tyramine*	*Tryptamine*	*p-Octopamine*
Amygdala		+		
Brainstem	+/++	+	–	+++
Caudate putamen	++/+++	++++	++	++++
Cerebellum	++	+	–	+++
Cortex	+/++	+	–	
Globus pallidus	+++	+++	+	
Hippocampus		–		
Hypothalamus	++	+/++	+	+++
Nucleus accumbens	+++/++++	++++	+	+
Olfactory tubercles	++++	++++	+	

Average levels of trace amines in various brain regions of mammalian species.
– = < 0.1 ng g^{-1} tissue; + = 0.1–1 ng g^{-1} tissue; ++ = 1–3 ng g^{-1} tissue; +++ = 3–5 ng g^{-1} tissue; ++++ = >5 ng g^{-1} tissue.
Blank cells indicate conclusive data are not available for the relevant amine in that region.

Table 2 Comparison of trace amine receptors present in mammalian species

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

Trace amine receptors present in the genome of various mammalian species. Note that the receptor protein has not necessarily been identified.

adenylate cyclase and resultant cellular increase in cAMP levels.

In each species, all TAARs cluster around a narrow chromosomal region. In humans, the nine TAAR genes are located at chromosome 6q23.1, chromosome 1p12 in the rat, and within chromosome 5 in the chimpanzee. All TAARs are coded by a single exon with the exception of TAAR2, where coding is split between two exons. Although TAAR orthologs show the expected high degree of homology, the marked divergence in the number of pseudogenes and receptor subtypes between species of close phylogenetic relationship (e.g., human vs. chimpanzee; rat vs. mouse) has led to suggestions that TAARs represent a rapidly evolving receptor family, involved in adaptation responses to evolutionary events. This raises the intriguing possibility of TAAR representing novel targets for pharmacotherapy of diseases that are uniquely human in nature.

The CNS distribution of the majority of TAARs is unknown, with only TAAR1 studied in any detail so far. The greatest CNS levels of TAAR1 mRNA in humans are found in the amygdala, with lower levels present in the cerebellum, hippocampus, hypothalamus, and medulla. This correlates well with both the distribution of endogenous trace amines, and preliminary reports of TAAR protein distribution. TAAR6 mRNA shows a similar distribution, with highest levels seen in the amygdala and hippocampus, while TAAR8 also appears to be particularly located to the amygdala. In mouse, high levels of TAAR1 mRNA are seen in a number of regions, including the olfactory bulb, piriform cortex, various trigeminal nuclei, and the cerebellum. The thalamus, hippocampus, and hypothalamic and raphe nuclei show lower mRNA levels, whereas the lowest levels are seen in the septum, basal ganglia, and amygdala. Of particular interest, TAAR1 mRNA is associated with the major monoamine neurotransmitter neuron groups within the raphe nucleus (5-HT), locus coeruleus (noradrenaline), and ventral tegmental area (DA).

The cellular localization of expressed TAAR1 and TAAR4 appears to be consistent with the lipophilicity of the potential endogenous ligand trace amines. As such, both receptor subtypes have been shown to be primarily intracellular, with little, if any, expressed protein appearing within the extracellular membrane. In this aspect, it is noteworthy that TAAR1 and -4 are the only TAAR members so far shown to be responsive to trace amines. The cognate endogenous ligand(s) for the additional TAAR members awaits identification.

Receptor Pharmacology

As indicated, the only TAAR members shown to be activated by trace amines are TAAR1 and TAAR4. TAAR1 from all species is activated by low to submicromolar concentrations of 2-phenylethylamine and *p*-tyramine. In addition, rat TAAR1 is similarly stimulated by octopamine and tryptamine. In contrast, mouse and human TAAR1 show a much lower affinity for both octopamine, and, in the case of human TAAR1, tryptamine. Of note, however, there appears to be a marked disparity with respect to affinity assessed by functional assay of cAMP production, and binding affinity (K_i) value obtained from competition experiments. For example, 2-phenylethylamine displacement of tyramine binding at human TAAR1 occurs at concentrations at least one order of magnitude below those required for receptor activation by 2-phenylethylamine. The basis for this disparity is unclear. Whether it represents additional, as yet unidentified, trace amine receptors/binding sites requires further investigation.

In contrast, classical neuroactive biogenic amines are either ineffective at activating TAAR1, or show at best, partial agonist properties. Histamine, noradrenaline, and 5-HT show limited efficacy to activate TAAR1 from a number of species, although 5-HT can act as a partial agonist at the rat TAAR1. Similarly, DA appears to be a partial agonist at TAAR1 from all species examined. Of note, however, the *O*-methyl metabolite of DA, 3-methoxytyramine, shows considerably greater agonistic properties at TAAR1 than does the parent amine. A similar trend is seen with normetanephrine and metanephrine, the *O*-methyl

metabolites of noradrenaline and adrenaline, respectively. The deaminated *O*-methyl metabolites such as homovanillic acid are not, however, ligands at TAAR1. The relevance of such activity of previously assumed inactive metabolites requires further investigation. Two immediate possibilities arise. First, these observations may suggest that TAARs (at least TAAR1) function physiologically to respond to the levels of monoamine neurotransmitter metabolites, and thereby regulate neurotransmission. Alternatively, however, these observations may merely represent the increased lipophilicity of *O*-methyl metabolites providing increased access to the intracellular receptor pool.

Beyond endogenous amines and their derivatives, the pharmacological profile of TAAR1 has generated considerable interest. In particular, a number of drugs of abuse, particularly amphetamine and its derivatives, show full agonist activity. This is of particular interest given the close structural relationship between 2-phenylethylamine and amphetamine (Figure 1). Both amphetamine and its *N*-methyl derivatives methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy') show low to submicromolar potency at TAAR1. Somewhat surprisingly, however, very little stereoselectivity was seen with amphetamine and methamphetamine, both R- and S- isomers being approximately equipotent although this maybe species dependent. The most potent amphetamine derivative at TAAR1 was *p*-hydroxyamphetamine, the major metabolite of amphetamine. In addition, the hallucinogenic ergoline *d*-lysergic acid diethylamide (LSD) shows submicromolar affinity as does the endogenous hallucinogen *N*,*N*-dimethyltryptamine. At present, antagonists of TAAR1 have not been identified. Indeed a number of compounds that show antagonist activity at other monoamine receptors/transporters, were found to be agonists at TAAR1. In particular, phentolamine (α-adrenergic antagonist), cyproheptadine (5-HT receptor antagonist), and nomifensine (DA transporter blocker) were effective TAAR1 agonists.

The identification of cognate ligands for TAAR family members is ongoing. A number of possibilities have been raised, including O-methyl metabolites of monoamines, thyronamine derivatives of thyroid hormone, imidazolines, and β-carbolines. Of interest in this respect is the previous identification of imidazoline-binding sites, which appeared distinct from known neurotransmitter-related receptors and enzymes. Whether these sites are synonymous with one or more TAAR requires clarification. Imidazoline ligands have been shown to be agonists at invertebrate octopamine receptors, although as discussed above, such activity may not be readily transferable to mammalian TAAR.

Physiological Responses to Trace Amines

Consistent with the distant phylogenetic relationship between invertebrate and vertebrate trace amine receptors, evidence suggests that mammalian and invertebrate trace amines may serve different physiological functions. Invertebrate trace amines, in particular, tyramine and octopamine, are well-characterized neurotransmitter substances. In mammalian species, however, this does not appear to be the case. Iontophoretic application of trace amines to neurons does not directly elicit changes in the membrane potential of the neuron under study. Rather, the trace amines appear to alter neuronal responsivity to coexisting neurotransmitters (Table 3). Specificity exists within these responses. 2-Phenylethylamine has been shown to potentiate neuronal responses to dopaminergic and noradrenergic stimuli, while having no effect on neuronal responses to acetylcholine, 5-HT, and glutamate. Earlier studies suggested that there was also no effect on γ-aminobutyric acid (GABA)-mediated transmission, although more recent evidence suggests that 2-phenylethylamine decreases inhibitory responses mediated by GABA-B receptors. Similarly, tyramines potentiate neuronal responses to DA, noradrenaline, and possibly GABA (at GABA-B receptors), while

Table 3 Interaction of trace amines with neurotransmitters

	2-Phenylethylamine	*p-Tyramine*	*Tryptamine*	*p-Octopamine*
Dopamine	+	+		−
Noradrenaline	+	+		+
5-HT	−	−	+[a]	
Acetylcholine	−		−	
GABA	−/+	−		
Glutamate	−	−		

[a]Inhibitory 5-HT responses are potentiated while excitatory responses remain unaffected or are converted to inhibitory responses in the presence of trace amine.

Blank cells indicate that interactions between the individual neurotransmitter and trace amine have not been investigated.

+ = neurotransmitter response potentiated by trace amine; − = no effect on neurotransmitter response of trace amine.

leaving 5-HT and glutamate responsivity unaffected. Octopamines also potentiate neuronal responses to noradrenaline; however, in this instance, no effect is observed on DA-mediated responses, nor on those of 5-HT. Finally, tryptamines have been shown to potentiate 5-HT responses, while leaving cholinergic responses unaffected. However, this effect of tryptamines appears to be somewhat more complex than that observed with other trace amines. Specifically, inhibitory 5-HT responses have been shown to be potentiated, while excitatory responses remain either unaffected or are reversed to inhibitory responses in the presence of tryptamine.

Although the above-described responses require the presence of coexisting neurotransmitter, endogenous stores of neurotransmitter are not required. This is important, since at higher concentrations, trace amines will act as false transmitters, displacing monoamine neurotransmitters from synaptic vesicles. Such false transmitter responses, however, require concentrations at least two orders of magnitude above basal trace amine concentrations. Further, the modulatory responses of trace amines appear to be mediated at the level of postsynaptic receptors, since responses to synthetic agonists are also potentiated. However, a direct binding of trace amines to neurotransmitter receptors does not occur. The role of TAAR in these modulatory responses of trace amines, while intuitively attractive, has yet to be investigated. Heterodimerization, following trace amine binding, of intracellular TAAR with membrane-inserted neurotransmitter receptors has been hypothesized, but as yet not investigated.

Since the function of trace amines appears to be to modulate the efficacy of coexisting neurotransmitter substances at postsynaptic receptors, and the synthesis of trace amines (AADC activity) is inversely related to stimulation of neurotransmitter receptors, it has been suggested that trace amines may function as a fine-tune mechanism, keeping basal neuronal tone within defined physiological limits. Such a proposal appears consistent with the suggestions that trace amine receptors are involved in adaptive responses, which may vary from species to species. Further, such a function is also consistent with the very high turnover rate of trace amines, allowing a regulation of neurotransmission on a second-by-second basis.

Relevance to Human Pathology

Historically, alterations in trace amine metabolism have been reported in a number of psychiatric disorders, in particular schizophrenia and depression. Although the reported changes in trace amine and/or metabolite levels in various body fluids are indicative of altered trace amine functioning, such studies are difficult to interpret further with respect to any underlying pathology. Although there is currently no definitive link between trace amines and any pathologic condition, evidence is accumulating that trace amines may play a role. The following paragraphs will briefly outline those CNS disorders in which alterations in trace amine functioning is most strongly linked.

Trace amines have often been suggested as a possible etiological factor in schizophrenia. Initially, this was largely based on the close structural relationship between 2-phenylethylamine and amphetamine (**Figure 1**), combined with the well-documented similarity between symptoms of paranoid schizophrenia and amphetamine overdose. Further, in very high, supraphysiological doses, 2-phenylethylamine shows a pharmacological profile similar to that of amphetamine. This link is seemingly strengthened by the observed pharmacological profile of TAAR1, numerous psychoactive/hallucinogenic agents having been shown to be agonists at this receptor. Differences have however been observed in the behavioral phenotypes induced by amphetamine and 2-phenylethylamine. Possibly of greater relevance is the observed chromosomal location of the trace amine receptors, at chromosome 6q23.1. This location coincides with one of the most robustly replicated susceptibility factors identified for schizophrenia, the SCZD5 locus. Specifically this locus appears to correlate with the TAAR6 gene. Conformation of a role of TAAR mutations as a susceptibility factor for schizophrenia will, however, be difficult. The heterogeneity of the disorder is a major complicating factor, since a single cause is unlikely to be the root cause of all schizophrenic disorders. A further genetic link is seen with the observation that a variant form of COMT shows an increased transmission in patients with schizophrenia. As discussed previously, *O*-methyl metabolites of central monoamines appear to be particularly good agonists at TAAR.

Of possible relevance with respect to schizophrenia is the observed similarity between some of the cognitive associated symptoms associated with phenylketonuria and schizophrenia. Phenylketonuria, a classical inborn error of metabolism, is due to a deficiency in the ability to convert L-phenylalanine to L-tyrosine. In addition to the marked changes in amino acid metabolism that such a deficit causes, it would also be expected to cause a pronounced elevation in 2-phenylethylamine levels.

Considerable circumstantial evidence also exists linking an alteration in trace amine metabolism to affective disorders. In particular, depression has been hypothesized to be associated with a decrease in 2-phenylethylamine functioning. Decreases in

2-phenylethylamine and its main metabolite phenylacetic acid have been reported in various body fluids. Similarly, decreases in other trace amines and their primary metabolites have been sporadically reported. In agreement with a proposed 2-phenylethylamine deficiency, the combined administration of (–)deprenyl with L-phenylalanine has been suggested to be an effective therapy in up to 60% of patients. Such a regimen would be expected to elevate endogenous 2-phenylethylamine (PE) levels; (–)deprenyl is a selective inhibitor of MAO-B, thereby inhibiting PE metabolism, while L-phenylalanine is the precursor amino acid of PE, and is expected to simultaneously elevate PE synthesis. Somewhat surprisingly, however, replication of this study does not appear to have been attempted. In further support of an antidepressant role for 2-phenylethylamine, MAO-B knockout mice show a behavioural phenotype consistent with that seen following administration of known antidepressant compounds. The only change in neuroactive amines seen in these animals is a pronounced elevation of endogenous PE levels. Finally, the mood-elevating effects of exercise may be due to an exercise-induced increase in PE levels, although the molecular basis of such an elevation is unclear.

At the receptor and gene level, there is also circumstantial evidence to support a role for PE in mood elevation. As detailed above, the available evidence suggests that TAARs are particularly associated with the amygdala, a brain region particularly implicated in the control of emotion and affect. Polymorphisms in the trace amine synthetic enzyme AADC have been suggested to be a susceptibility factor for both unipolar and bipolar disorder, although such associations require replication. Further, bipolar disorder has been linked to chromosome 6q. As seen above, this is the site of all TAAR genes. In this aspect, a similar confounding factor applies, as was detailed with schizophrenia. Affective disorders represent a spectrum of disorders, with a single causative agent unlikely to be present. A number of known antidepressants result in a downregulation of β-adrenergic receptors. Of interest in this regard is evidence that chronic elevation of endogenous PE results in a similar downregulation. Finally, the antidepressant agent phenelzine has been shown to be metabolized to PE.

The link between trace amines and disorders of higher cognitive functioning such as schizophrenia and affective disorders is appealing. As detailed, TAARs have been suggested to be involved in adaptive responses. Further, the observed physiological effects of trace amines acting to modulate the efficacy of neurotransmitter amines, possibly functioning to keep neuronal tone within physiological limits, are an attractive site for therapeutics for disorders of higher cognitive functioning involving multiple neurotransmitter systems. In this respect, trace amines have been implicated in other disorders associated with higher cognitive functioning, in particular attention-deficit/hyperactivity disorder, and also eating disorders and drug abuse/dependence.

Though not psychiatric in nature, one final disorder which warrants consideration with respect to the trace amines is migraine. This neurovascular disorder has often been linked to the trace amines largely on the basis of the elevated levels of trace amines found in foodstuffs known to precipitate migraine attacks in susceptible individuals. In particular, chocolate contains high levels of 2-phenylethylamine, while red wine and aged cheeses contain high levels of tyramine.

Thus, although many questions remain unanswered with respect to the endogenous ligand and physiological functioning of TAAR, they have attracted considerable interest with respect to being a viable target for development of novel therapeutic agents. Of note, many of the diseases in which trace amines are being actively investigated are of unknown etiology and likely involve multiple neurotransmitter systems. The apparent role of trace amines in modulating the responsivity of a variety of neurotransmitter systems makes them an attractive area of investigation in various neurological and psychiatric disorders.

See also: Amphetamines; Attention Deficit Hyperactivity Disorder; Attention Deficit Hyperactivity Disorder (ADHD): Methylphenidate (Ritalin) and Dopamine; Dopamine – CNS Pathways and Neurophysiology; Drugs Addiction: Actions; Monoamine Transporters: Focus on the Regulation of Serotonin Transporter by Cytokines; Monoamines; Octopamine and Other Monoamines in Invertebrates; Schizophrenia: Epidemiology, Clinical Features, Course and Outcome; Serotonin (5-Hydroxytryptamine; 5-HT): CNS Pathways and Neurophysiology.

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