Encyclopedia of Psychopharmacology
DOI 10.1007/978-3-642-27772-6_211-2

Trace Amines

Sara Tomlinson[a], Darrell D. Mousseau[b], Glen B. Baker[a]* and Ashley D. Radomski[a]
[a]Neurochemical Research Unit and Bebensee Schizophrenia Research Unit, Department of Psychiatry, University of Alberta, Edmonton, AB, Canada
[b]Cell Signalling Laboratory, Department of Psychiatry, University of Saskatchewan, Saskatoon, SK, Canada

Synonyms

Arylalkylamines; Microamines

Definition

Trace amines, which include β-phenylethylamine (PEA), tryptamine (T), phenylethanolamine (PEOH), tyramines (TAs), octopamines (OAs), and synephrine (SYN) [some authors include *N*, *N*-dimethyltryptamine (DMT) in this list], are amines related structurally to, but present in the brain at much lower concentrations than, the classical neurotransmitter amines – dopamine (DA), noradrenaline (NA), and 5-hydroxytryptamine (5-HT, serotonin).

Pharmacological Properties

History

The trace amines are so named because of their low absolute concentrations in the brain compared to the classical neurotransmitter amines DA, NA, and 5-HT; they are very similar structurally to these neurotransmitter amines (often only lacking one or both hydroxyl moeities on the benzene ring: Fig. 1), but have much higher turnover rates, and in contrast to their hydroxylated analogs, PEA and T pass the blood–brain barrier readily.

From the 1960s through to the 1990s, there was a great deal of interest in the trace amines in the central nervous system (CNS) as behavioral and pharmacological studies in animals and neurochemical measurements in body fluids from human subjects suggested their involvement in the etiology and pharmacotherapy of a number of psychiatric and neurological disorders, including depression, schizophrenia, phenylketonuria (PKU), Reye's syndrome, Parkinson's disease, attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, epilepsy, and migraine headaches (Baker et al. 1993; Berry 2007). In the 1970s, there was a flurry of activity in trace amine research because of the development of a number of elegant, sensitive analytical techniques which facilitated their measurement in the brain. During the 1980s, binding studies suggested possible receptors for the trace amines, while electrophysiological and behavioral research suggested that these amines might act as neuromodulators for DA, NA, or 5-HT. There was a resurgence of interest in the trace amines in 2001, following reports of the discovery of a novel family of G protein-coupled receptors, some of which appear to be selectively activated by trace amines.

*Email: glen.baker@ualberta.ca

Encyclopedia of Psychopharmacology
DOI 10.1007/978-3-642-27772-6_211-2

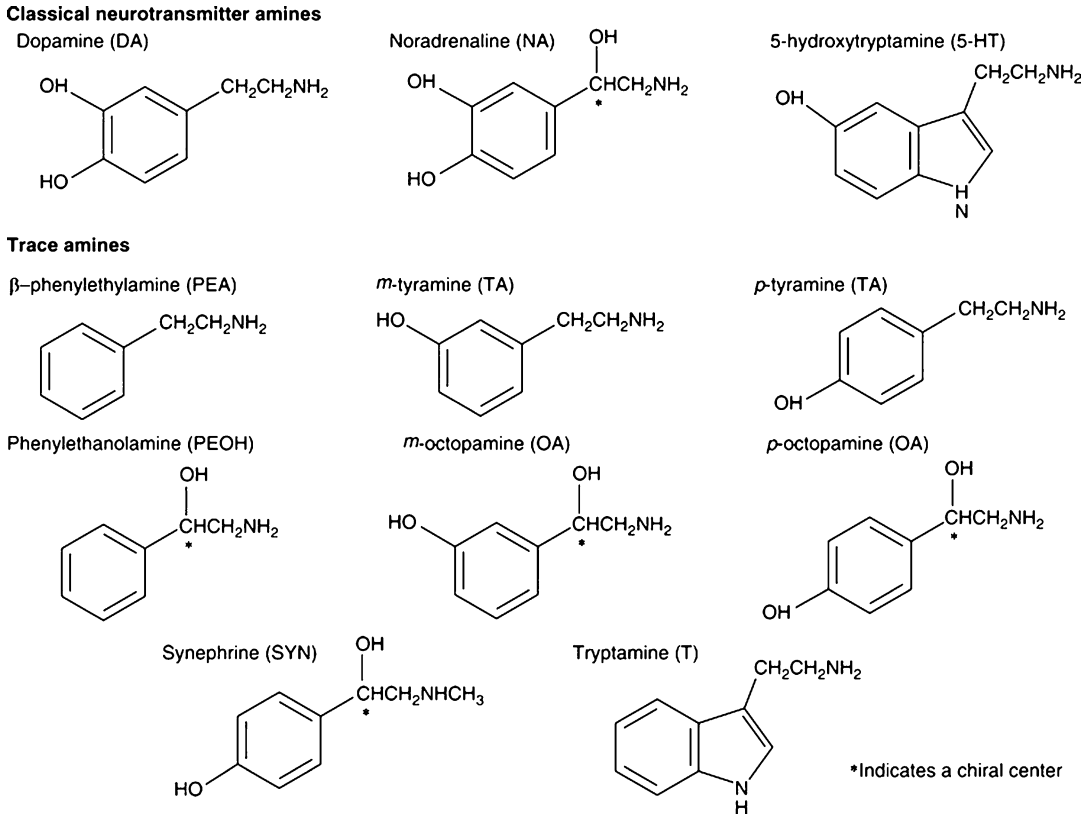

Fig. 1 Structures of some classical neurotransmitter amines and trace amines

Synthesis, Catabolism, and Localization

The trace amines PEA, T, and TA are synthesized in neuron terminals by decarboxylation of precursor amino acids (phenylalanine, tryptophan, and tyrosine, respectively), catalyzed by the enzyme aromatic L-amino acid decarboxylase (AADC), which is also involved in the decarboxylation of L-3,4-dihyroxyphenylalanine (L-DOPA) and 5-hydroxytrytophan (5-HTP) in the synthesis of the catecholamines (DA, NA) and 5-HT, respectively. However, tyrosine hydroxylase and tryptophan hydroxylase are the rate-limiting enzymes in the synthesis of the catecholamines and 5-HT, while AADC is the major enzyme involved in the synthesis of PEA, T, and TA. Thus, alterations of AADC activity would be expected to have little effect on the levels of DA, NA, and 5-HT in the brain while possibly markedly affecting the levels of trace amines (Berry 2007).

Tyramine is further metabolized to OA and PEA to PEOH by dopamine β-hydroxylase (DBH). Tyramine and OA have been proposed to function as neurotransmitters rather than neuromodulators in invertebrates. Octopamine can be further metabolized to synephrine by phenylethanolamine *N*-methyltransferase (PMNT) or related methyltransferases. The trace amines are all substrates for monoamine oxidase (MAO). Abnormal levels of the resultant acid metabolites of the trace amines have also been reported in several psychiatric and neurological disorders (Berry 2007; Boulton et al. 1985).

The trace amines are distributed heterogeneously throughout the brain, with the highest concentrations generally reported in the striatum or hypothalamus. Burchett and Hicks (2006) have provided a comprehensive review of their regional brain distribution and localization relative to catecholaminergic and serotoninergic neuronal systems in the brain. Although PEA, T, and TA have been shown to be present in synaptosomes, studies with reserpine and neurotoxins suggest that *m*-

DOI 10.1007/978-3-642-27772-6_211-2

and *p*-TA may be stored in vesicles, while PEA and T are not (Boulton et al. 1985). PEA and T appear to cross cell membranes passively, but there is some evidence for activity-dependent veratridine (a neurotoxin causing persistent activation of sodium ion channels)-induced release of *m*- and *p*-TA from striatal slices.

What Is the Function of the Trace Amines in the CNS?

It has long been known that trace amines such as PEA exert amphetamine-like effects on the CNS when administered to rats or mice. However, the levels required for such effects are well above normal concentrations in brain, and it is thought that other roles for trace amines at their endogenous, physiological concentrations must exist. Researchers found mounting evidence that trace amines may play a neuromodulatory role in the CNS. The trace amines are known to inhibit reuptake of and stimulate release of NA, DA, and/or 5-HT; and in electrophysiological studies, several trace amines have been shown to potentiate the actions of the classical monoamine neurotransmitter amines DA, NA, and/or 5-HT by altering the receptor sensitivity to these neurotransmitter amines, suggesting that the trace amines serve to maintain the activity of the classical monoamine neurotransmitters within defined physiological limits (Berry 2007). PEA has also been reported to stimulate acetylcholine release by activating glutamatergic signaling pathways, and PEA and *p*-TA have been demonstrated to depress $GABA_B$ receptor-mediated responses in dopaminergic neurons. In the 1980s, specific and saturable binding sites for radiolabeled PEA, T, and *p*-TA were reported, suggesting that these amines might have a role independent of the classical neurotransmitter amines. Burchett and Hicks (2006) have suggested four kinds of trace amine activity in the CNS: cotransmitters released with the catecholamines or 5-HT, transmitters with their own receptors, false transmitters at catecholamine receptors, and neuromodulators.

Receptors

A resurgence of interest in trace amines in the past few years followed the publication of papers in 2001 on the discovery and cloning of a unique family of G protein-coupled receptors, some of which are selectively activated by trace amines (Borowsky et al. 2001; Bunzow et al. 2001). The mechanisms by which the trace amines activate these receptors are not yet fully defined (Lindemann and Hoener 2005). To date only two members of the family of receptors have been demonstrated to be responsive to trace amines, and endogenous ligands for these receptors other than the trace amines have been proposed; these include O-methyl metabolites of catecholamines, thyronamine metabolites of thyroid hormones, and imidazoline ligands including β-carbolines (Berry 2007; Bunzow et al. 2001; Ianculescu and Scanlan 2010).

The trace amine-associated receptor (TAAR) family consists of three subgroups (TAAR1-4, TAAR5, and TAAR6-9) which are phylogenetically and functionally distinct from other G protein-coupled receptor families and from invertebrate OA and TA receptors (Lindemann and Hoener 2005). Genes for TAARs have been discovered in humans, chimpanzees, rats, and mice. There are marked interspecies differences in the distribution of the TAARs, with more TAARs in rodents than in humans. This variability has led some researchers to suggest that these receptors are linked in an intricate way to species-specific functioning (Berry 2007). In humans, all TAAR genes are located in a narrow region in the locus 6q23.1, which has also been linked to schizophrenia and bipolar disorder. Recent studies on TAAR1 knockout (KO) mice suggest that the TAAR1 is a regulator of dopaminergic neurotransmission and that such mice may represent a useful model for development of drugs for treatment of some positive symptoms of schizophrenia. Studies by Sotnikova et al. (2008) in TAAR1-KO mice, DA transporter (DAT)-KO/TAAR1-KO mice, and TAAR1-deficient/DA-deficient mice suggested that the TAAR1 is involved in tonic inhibitory actions on

locomotor activity. Based on these same observations, the authors proposed that blockade of the TAAR1 by antagonists may represent a novel way to enhance the anti-Parkinson effects of L-DOPA. Studies in recent years using volatile amines such as trimethylamine and isoamylamine have shown that these amines are ligands for TAARs, which suggests that some TAARs are olfactory receptors distinct from classical olfactory receptors (Ferrero et al. 2012).

Several amphetamines [amphetamine, MDMA (Ecstasy), DOI, 4-hydroxyamphetamine] are relatively potent agonists at the TAAR1 receptor, as are ergometrine, dihydroergotamine, LSD, so-called hallucinogens [N,N-dimethyltryptamine (DMT), 5-hydroxy-N,N-dimethyltryptamine, and 5-methoxy-N,N-dimethyltryptamine], the anti-Parkinsonian agents bromocriptine and lisuride, and inhibitors of the DA transporter. Interestingly, the trace amine *p*-TA has been demonstrated to be necessary for sensitization to cocaine in *Drosophila*. These findings are of interest because it is possible that the TAAR1 may be a mediator of at least some of the effects of these drugs, providing a possible future target for treatment of drug abuse. It is also of interest that several biogenic amine antagonists, including phentolamine, tolazoline, cyproheptadine, metergoline, and chlorpromazine, as well as nomifensine and MPTP, act as agonists at the TAAR1.

Involvement in Psychiatric and Neurological Disorders: Neurochemical Studies

Several studies looking at the levels of trace amines and/or their acid metabolites in body fluids of patients with psychiatric or neurological disorders found potential associations with depression, bipolar disorder, schizophrenia, Reye's syndrome, ADHD, Tourette's syndrome, and PKU (Baker et al. 1993; Berry 2007; Boulton et al. 1985), although these studies are not without controversy. It has been reported that excess DMT in body fluids is related to production of psychoses, these yet findings have been controversial, and more recently it has been suggested that DMT acts on TAARs and that at low levels it is anxiolytic and suppresses the symptoms of psychoses (Jacob and Presti 2005). Increased PEA levels have been reported in mania, while depressed states have been found to be associated with deficits in PEA and the acid metabolites of OA and TA. Associations between paranoid schizophrenia and increased PEA excretion have been proposed as well. Decreased body fluid levels of PEA have been reported in Parkinson's disease. Urine levels of Tryptamine have also been reported to be increased in schizophrenics and to correlate with disease severity, and plasma levels of the *p*-TA metabolite p-hydroxyphenylacetic acid have been reported to be decreased in schizophrenia. Increased PEA levels in the brain have been reported in PKU. Evidence to date from several research groups suggests decreased urinary PEA in ADHD and Tourette's syndrome; there is also evidence for decreased PEA levels in brain and plasma in ADHD and for decreased urinary levels of *m*- and *p*-TA and indole-3-acetic acid (the major metabolite of T) in Tourette's syndrome. Animal studies and limited data in humans suggest that elevated PEA may be associated with an increase in stress and anxiety. High doses of PEA can induce seizures in mice, and this effect can be antagonized by benzodiazepines, suggesting an interaction with the GABA system. Other studies have suggested that PEA modulates glutamatergic and GABAergic systems. It is of interest that the gene for AADC, the rate-limiting enzyme involved in the synthesis of the trace amines, is located in the same region of chromosome 7p that has been suggested as a susceptibility locus for ADHD; 7p has also been linked to nicotine dependence. Elevations of TA and OA have been reported in hepatic encephalopathy and Reye's syndrome.

The effects of drugs used to treat psychiatric illnesses provide further support for the importance of trace amines in physiological and pathological brain function. It is known that monoamine oxidase inhibitor antidepressants such as phenelzine and tranylcypromine cause a much greater increase in levels of trace amines than of classical neurotransmitters such as 5-HT and NA in the brain, and increases in brain levels of PEA have been reported with tricyclic antidepressants and

DOI 10.1007/978-3-642-27772-6_211-2

ECT. L-Deprenyl (selegiline) and rasagiline are used in the treatment of Parkinson's disease, and because they are selective inhibitors of MAO-B, they cause a marked increase in PEA levels in the brain relative to other amines. The antipsychotics chlorpromazine, fluphenazine, and haloperidol have been shown in acute studies in rodents to decrease striatal *p*-TA levels other studies have found that antipsychotics increase the rate of PEA accumulation in the striatum (see Boulton et al. 1985 for studies on these drug effects). Studies with R05166017, a selective TAAR1 agonist, suggest that the TAAR1 is involved in control of several dopamine- and 5-HT-driven behaviors, indicating possible antipsychotic and anxiolytic properties for such agonists (Revel et al. 2011).

Summary

Behavioral, pharmacological, and neurochemical studies in animals as well as investigations in body fluids of humans have long suggested that trace amines such as PEA, T, TA, and OA may be involved in the etiology and/or pharmacotherapy of a number of psychiatric and neurological disorders. There has always been debate about whether the trace amines have a neurotransmitter role. Although there is good evidence that OA may be a neurotransmitter in invertebrates, electrophysiological research has suggested that trace amines act as neuromodulators in the human brain, with their activity related closely to the classical neurotransmitters amines DA, NA, and 5-HT.

There has been a marked resurgence of interest in the trace amines since reports in 2001 of a unique family of G protein-coupled receptors, some of which are selectively activated by trace amines. These receptors, termed TAARs, are helping to explain the possible role of trace amines in the CNS (including their interactions with classical neurotransmitters), the effects of other compounds which may be endogenous ligands at these receptors, and the actions of a number of drugs of abuse, and may prove to be very useful in developing more selective drugs for the treatment of psychiatric and neurological disorders.

Acknowledgments

Funding from the following sources is gratefully acknowledged: Canadian Institutes of Health Research [CIHR; MOP86712 (GBB)], Canada Research Chair and Canada Foundation for Innovation programs, the University of Alberta Distinguished University Professor Program (GBB), the Alzheimer Society of Saskatchewan and the Saskatchewan Health Research Foundation (DDM), the Davey Endowment, the Abraham and Freda Berger Memorial Fund, and Donald R. and Nancy Romanow Cranston.

Cross-References

- ► Antidepressants
- ► Anti-Parkinson Drugs
- ► Antipsychotic Drugs
- ► Attention Deficit and Disruptive Behaviour Disorders
- ► Bipolar Disorder
- ► Monoamine Oxidase Inhibitors
- ► Schizophrenia

DOI 10.1007/978-3-642-27772-6_211-2

References

Baker GB, Bornstein RA, Yeragani VK (1993) Trace amines and Tourette's syndrome. Neurochem Res 18:951–956

Berry MD (2007) The potential of trace amines and their receptors for treating neurological and psychiatric diseases. Rev Recent Clin Trials 2:3–19

Borowsky B, Adham N, Jones KA, Raddatz R, Artymyshyn R, Ogozalek KL et al (2001) Trace amines: identification of a family of mammalian G protein-coupled receptors. Proc Natl Acad Sci U S A 98:8966–8971

Boulton AA, Bieck PR, Maitre L, Riederer P (eds) (1985) Neuropsychopharmacology of the trace amines: experimental and clinical aspects. Humana Press, Clifton

Bunzow JR, Sonders MS, Arttamangkul S, Harrison LM, Zhang G, Quigley DI et al (2001) Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. Mol Pharmacol 60:1181–1188

Burchett SA, Hicks TP (2006) The mysterious trace amines: protean neuromodulators of synaptic transmission in mammalian brain. Prog Neurobiol 79:223–246

Ferrero DM, Wacker D, Roque MA, Baldwin MW, Stevens RC, Liberles SD (2012) Agonists for 13 trace amine-associated receptors provide insight into the molecular basis of odor selectivity. ACS Chem Biol 7:1184–1189

Ianculescu AG, Scanlan TS (2010) 3-lodothyronamine (T(1)AM): a new chapter of thyroid hormone endocrinology? Mol Biosyst 6:1338–1344

Jacob MS, Presti DE (2005) Endogenous psychoactive tryptamines reconsidered: an anxiolytic role for dimethyltryptamine. Med Hypotheses 64:930–970

Lindemann L, Hoener MC (2005) A renaissance in trace amines inspired by a novel GPCR family. Trends Pharmacol Sci 26:274–281

Revel FG, Moreau JL, Gainetdinov RR, Bradaia A, Sotnikova TD, Mory R, Durkin S, Zbinden KG, Norcross R, Meyer CA, Metzler V, Chaboz S, Ozmen L, Trube G, Pouzet B, Bettler B, Caron MG, Wettstein JG, Hoener MC (2011) TAAR1 activation modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypoglutamatergic activity. Proc Natl Acad Sci U S A 108:8485–8490

Sotnikova TD, Zorina OI, Ghisi V, Caron MG, Gainetdinov RR (2008) Trace amine associated receptor 1 and movement control. Parkinsonism Relat Disord 14:S99–S102