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Trace Amines and Their Relevance to Psychiatry and Neurology: A Brief Overview

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ÖZET:

Eser aminler ve psikiyatri ve nöroloji ile ilişkisi: Kısa bir gözden geçirme

Arilalkilaminler β-feniletilamin, m- ve p-tiramin, triptamin, m- ve p-oktapamin, feniletanolamin ve sinefrin klasik amin nörotransmitterler olan noradrenalin, dopamin ve 5-hidroksitriptamin (5-HT, serotonin)'e oranla santral sinir sistemindeki mutlak konsantrasyonlarının düşük olması nedeniyle eser aminler olarak adlandırılmıştır. Düşük konsantrasyonlarda bulunmalarına rağmen bu aminler bir çok psikiyatrik ve nörolojik hastalığın etyolojisi ve farmakoterapisinde yer alırlar. Eser aminlerle ilgili çalışmalar 1970'ler ve 1980'lerde kapsamlı elektrofizyolojik çalışmalar ve bazı reseptör bağlanma çalışmaları ile birlikte bu aminler için duyarlı testlerin gelişmesinden sonra artmıştır. Geçtiğimiz son on yılda bu aminlere olan ilgi, G-proteini ile çalışan reseptör ailesinin keşfi ve klonlanması ile canlanmıştır, bunlardan bazıları eser aminlerle seçici olarak aktive olması nedeniyle eser aminle ilişkili reseptörler (trace amine associated receptors (TAARs)) olarak adlandırılmıştır. Bu reseptörlerin eser aminlerin etkisi ile ve diğer birçok nörokimyasal ve psikotropik ilaçlarla ilişkisi tartışılmıştır.

Anahtar sözcükler: Eser aminle ilişkili reseptörler, β-feniletilamin, tiramin, oktapamin, triptamin, psikiyatrik ve nörolojik hastalıklar

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ABSTRACT:

Trace amines and their relevance to psychiatry and neurology: a brief overview

The arylalkylamines, β-phenylethylamine, m- and p-tyramine, tryptamine, m- and p-octopamine, phenylethanolamine and synephrine, have been termed trace amines because of their low absolute concentrations in the central nervous system relative to the classical neurotransmitter amines, noradrenaline, dopamine and 5-hydroxytryptamine (5-HT, serotonin). Despite being present at low concentrations, these amines have been implicated in the etiology and pharmacotherapy of several psychiatric and neurological disorders. Studies on trace amines flourished in the 1970s and 1980s, following the development of sensitive assays for these amines, and were accompanied by comprehensive electrophysiological studies and some receptor binding studies. There has been a resurgence of interest in these amines in the past decade with the discovery and cloning of a unique family of G-protein-coupled receptors, some of which are selectively activated by trace amines; these receptors have been termed trace amine, associated receptors (TAARs). The relevance of these receptors to the actions of the trace amines and to the actions of several other neurochemicals and psychotropic drugs is discussed.

Key words: Trace amine-associated receptors, β-phenylethylamine, tyramine, octopamine, tryptamine, psychiatric and neurological disorders

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INTRODUCTION

Since the 1960s, there has been considerable interest in the so-called trace amines in the central nervous system (CNS) because of their possible involvement in 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 [review books and articles: (1-8)]. These amines are 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), and include ß-phenylethylamine (PEA), tryptamine (T), phenylethanolamine (PEOH), m- and p-tyramine (TA), m- and p-octopamine (OA) and synephrine (SYN) [some authors include N,N-

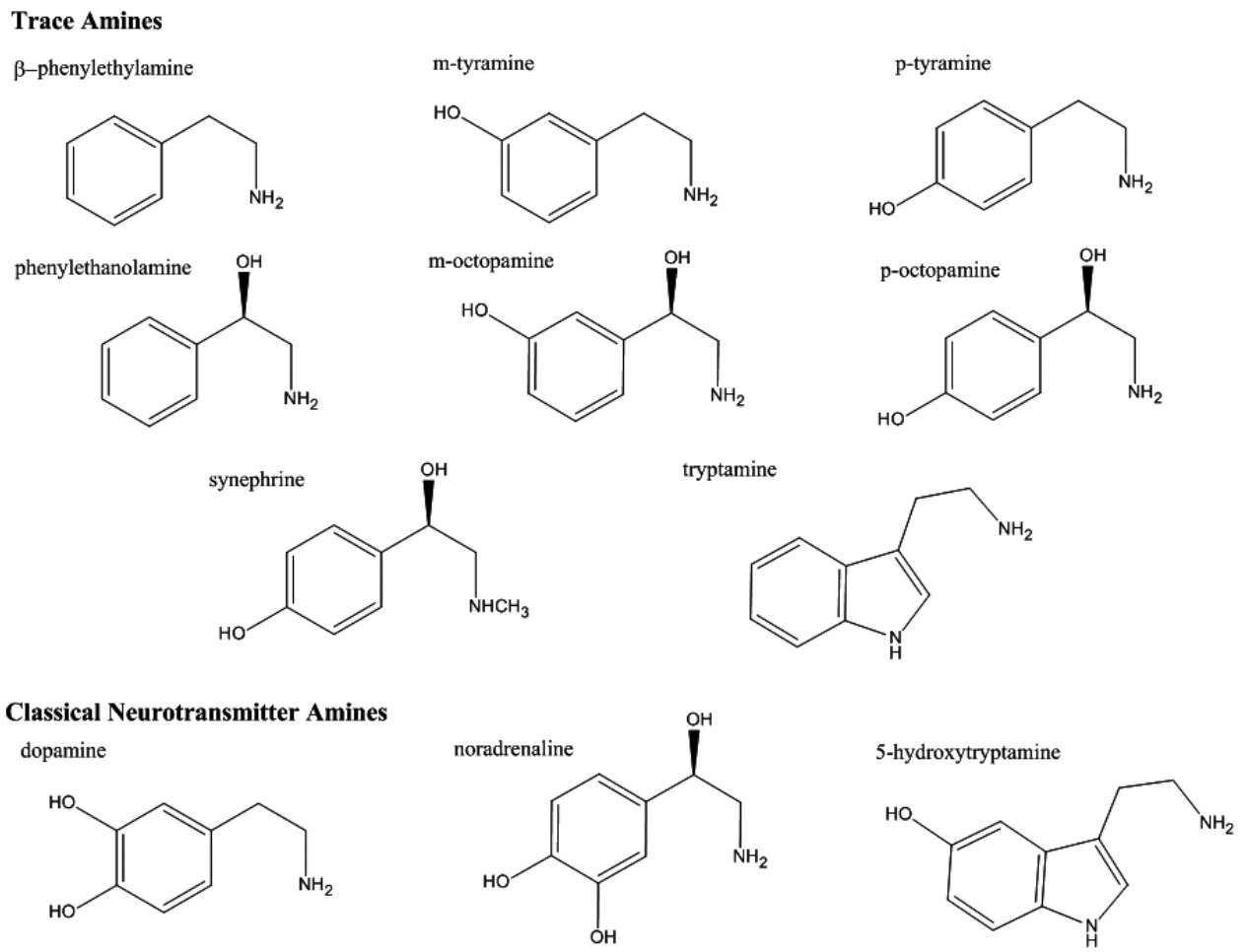

Figure 1: Chemical structures of trace amines and classical neurotransmitter amines.

dimethyltryptamine (DMT) in this list]. See Figure 1 for structures of these trace amines. This brief review will focus on PEA, TA, OA and T.

During the 1970s and 1980s, the development of a number of sensitive analytical techniques which facilitated the measurement of trace amines in the brain and body fluids (1) resulted in extensive research on the bioavailability, distribution and function of trace amines. Comprehensive electrophysiological and behavioral research was also conducted (1,3,5-7), and the findings suggested that these amines might act as neuromodulators for DA, NA and/or 5-HT [although there is strong evidence for OA being a neurotransmitter in invertebrates (3,6,9)]; however, not all of the results ascribed to trace amines could be accounted for by simple neuromodulatory mechanism(s) and this conclusion was subsequently supported by binding studies that suggested the existence of specific receptors for some of the trace amines (10-14). Although research on the trace amines decreased in the 1990s, there has been a resurgence of interest in these amines following reports in 2001 of the discovery of a novel family of G protein-coupled receptors, some of which appeared to be selectively activated by trace amines (15,16).

The trace amines can alter the release and/or reuptake of NA, DA and/or 5-HT (17,18), not only by regulating the active transport of these neurotransmitters across the plasma membrane, but also by involving mechanisms of action targeting the neurotransmitter vesicles themselves. Electrophysiological studies have revealed that several trace amines can also potentiate the actions of these classical monoamine neurotransmitters by altering the sensitivity of their receptors; such findings have led some researchers to propose that one role of trace amines is to maintain the activity of NA, DA and/or 5-HT within

defined physiological limits (1,4,5,19,20). Interestingly, PEA can also stimulate acetylcholine release through activation of glutamatergic signaling pathways (21), and PEA and p-TA have been reported to depress GABAB receptor-mediated responses in dopaminergic neurons (22,23). Although PEA, T and p-TA have been reported to be present in synaptosomes (nerve ending preparations isolated during homogenization and centrifugation of brain tissue) (24), research with reserpine and neurotoxins suggests that m- and p-TA may be stored in vesicles while PEA and T are not (25-27). In a comprehensive review paper, Burchett and Hicks (28) have provided a review of the regional brain distribution of the trace amines and their localization relative to catecholaminergic and serotonergic neuronal systems in the brain and have suggested four kinds of trace amine activity in the CNS: co-transmitters released with the catecholamines or 5-HT; transmitters with their own receptors; false transmitters at catecholamine receptors; and neuromodulators.

INVOLVEMENT OF TRACE AMINES IN THE ETIOLOGY OF PSYCHIATRIC AND NEUROLOGICAL DISORDERS

There is an extensive literature on the levels of trace amines and/or their acid metabolites in body fluids (and in some cases postmortem brain tissue) of patients with psychiatric or neurological disorders. Although abnormal levels have been reported in affective disorders (29-35), schizophrenia (29,36-38), Reye's syndrome (39,40), ADHD (41-44), Tourette's syndrome (7), PKU (45-47), and migraine and cluster headaches (48,49), these studies are not without controversy [for comprehensive reviews see (5) and (18)]. Interestingly, the gene for aromatic amino acid decarboxylase (AADC), the major enzyme involved in the synthesis of the trace amines, is located in the same region of chromosome 7 that has been proposed as a susceptibility locus for ADHD (50). Elevated PEA levels may be associated with increased stress and anxiety in laboratory animals and humans (51,52), and high doses of PEA have been reported to induce seizures in mice. This latter effect can be antagonized by benzodiazepines, suggesting an interaction with the GABAergic system (53). Other studies have proposed that PEA can modulate both glutamatergic and GABAergic systems (5).

Brain levels of trace amines have been reported to be altered by several drugs used to treat neuropsychiatric disorders. Administration of monoamine oxidase (MAO) inhibitor antidepressants such as phenelzine and tranylcypromine results in a greater increase in brain levels of trace amines than of classical neurotransmitter amines (1, 54). In addition, chronic administration of PEA to rats produces a ß-adrenoceptor down-regulation similar to that observed with some antidepressants (56), while reserpine depletes central levels of some trace amines (54), and the antidepressant effects of exercise have been suggested to be due to an elevation of PEA (57). l-Deprenyl (selegiline), a selective inhibitor of MAO-B, is used in the treatment of Parkinson's disease and produces a marked increase in brain levels of PEA relative to other amines (20,58). In rodents, acute administration of the antipsychotics chlorpromazine, fluphenazine and haloperidol has been shown to decrease striatal p-TA levels, and similar studies with PEA have shown that these antipsychotics increase the rate of accumulation of this trace amine in the striatum (59,60).

TRACE AMINE-ASSOCIATED RECEPTORS (TAARs)

In 2001, the discovery and cloning of a unique family of G protein-coupled receptors, some of which are selectively activated by trace amines (15,16), stimulated a resurgence of interest in the trace amines. The mechanisms by which the trace amines activate these receptors are not yet entirely clear (43). However, there has been a flurry of research on these receptors, and endogenous ligands other than the trace amines have been proposed including: dopamine, O-methyl metabolites of catecholamines, thyronamine metabolites of thyroid hormones and imidazoline ligands including ß-carbolines (4,5,16-17).

The TAAR family comprises three subgroups (TAAR1-4, TAAR5 and TAAR6-9) which are phylogenetically and functionally distinct from other G protein-coupled receptor families and from OA and TA receptors in invertebrates (43). Genes for TAARs have been discovered in several species, including humans, chimpanzees, rats and mice (61-63), and it is interesting that there are marked inter-species differences in the distribution of these receptors. Findings to date indicate

there are as many as 19 TAAR genes in the rat genome, 16 in the mouse genome, and 9 in the human and chimpanzee genomes (43,64). Such variability has led to speculation that these receptors are linked in an intimate way to species-specific functioning (5). In humans, TAARs are located in various areas in brain, with highest levels of TAAR1 mRNA in the amygdala region (15). The genes for TAARs are located in a narrow region on a locus on chromosome 6 which has also been linked to schizophrenia and bipolar disorder (65,66). Indeed, a TAAR1 knockout (KO) mouse has been proposed as an animal model for schizophrenia (67). TAAR6 has also been proposed to be associated with bipolar disorder and schizophrenia (68-70), but this remains a matter of controversy (71,72).

Findings with TAAR1 KO mice suggest that TAAR1 is a regulator of dopaminergic neurotransmission (73), and as such, these mice could be a useful model for development of drugs for treatment of some symptoms of schizophrenia. Sotnikova et al. (74) conducted studies using TAAR1-KO mice, DA transporter (DAT)/TAAR1-KO mice and TAAR1-deficient/DA-deficient mice and proposed that TAAR1 is involved in tonic inhibitory actions on locomotor activity. These authors suggested that blockade of TAAR1 by specific antagonists may enhance the antiparkinsonian effects of L-DOPA.

Thyronamines are structurally similar to the thyroid hormones, and 3-iodothyronamine (T1AM) is a naturally occurring derivative of thyroid hormone which is reported to be a potent agonist at TAAR1 in rodents (75-77). Administration of exogenous T1AM modulates lipid and carbohydrate metabolism, heart rate and insulin secretion, and causes hypothermia, increased food intake, bradycardia and behavioral changes (75-79). However, a recent study showed that T1AM and trace amines do not mediate thermoregulatory changes by their actions on TAARs (80). Amiodarone, a drug which is structurally similar to the iodothyronamines, is used to treat cardiac arrhythmias and its desethyl metabolite also has antiarrythmic properties (81). Snead et al. (81) studied the effects of amiodarone and several potential metabolites on TAAR1 and found that several of these compounds were specific agonists at the TAAR1 receptor in rats and mice, but were devoid of activity in a chimeric rat-human TAAR1 system.

Other agonists at the TAAR1 receptor include several amphetamines [amphetamine, MDMA (Ecstasy), 4-iodo-2,5-dimethoxyamphetamine (DOI), 4-hydroxyamphetamine] as well as ergometrine, dihydroergotamine, LSD and anti-Parkinson agents (e.g. bromocriptine, lisuride) and inhibitors of the DA transporter (5,15,16,82). Xie and Miller (83-85) have reported that PEA and methamphetamine may affect regulation of classical amine neurotransmitter transport across the neuronal plasma membrane through their effects on TAAR1. Such regulation may be particularly important for chronic amphetamine or methamphetamine abusers with high plasma concentrations of these drugs (86). It has been reported that the presence of the trace amine p-TA is a requirement for the occurrence of sensitization to cocaine in Drosophila (87). The above findings are of considerable interest because it is possible that TAAR1 may be a mediator of at least some of the effects of drugs of abuse, providing a much-needed possible future target for treatment of drug addiction. In addition, several biogenic amine antagonists, including phentolamine, tolazoline, cyproheptadine, dihydroergotamine and metergoline, as well as nomifensine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and chlorpromazine act as agonists at the TAAR1 (5,17). Therefore, it is possible that trace amines acting via TAARs in the brain play an important role in psychiatric and neurological disease conditions which previously were thought to be directly and strictly associated with classical neurotransmitter amine activity.

SUMMARY

An extensive literature over many years on behavioral, pharmacological and neurochemical studies in animals and investigations in body fluids of humans has suggested strongly that trace amines such as PEA, T, TA and OA may be involved in the causation and/or pharmacotherapy of several psychiatric and neurological disorders. Although there is evidence that OA may be a neurotransmitter in invertebrates, electrophysiological and neurochemical research seems to favor a role for OA and other trace amines as neuromodulators rather than neurotransmitters in human and rodent brain, with their activity related closely to the classical neurotransmitters amines DA, NA and 5-HT. In the past decade there has been a marked increase of interest in the trace amines and their possible roles in the central nervous system since the cloning of a unique family of G protein-coupled receptors, some of which are selectively

activated by trace amines. Functional studies on theses TAARs may shed further light on the possible role of the trace amines in the CNS, the action of other neurochemicals which may be endogenous ligands at these receptors, and the mechanisms of action of a number of drugs of abuse. Thus, the TAARs may prove to be very useful in the ongoing search for more selective drugs for the treatment of neuropsychiatric disorders, including addictions.

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