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The emerging roles of human trace amines and human trace amine-associated receptors (hTAARs) in central nervous system

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ABSTRACT

Human trace amines (TAs) are endogenous compounds, previously almost ignored in human pathology for many reasons (difficulty of their measurement in biological fluids, unknown receptors for elusive amines), are now considered to play a significant role in synaptic transmission within the central nervous system (CNS) acting as neuromodulators. The recent discovery of a novel family of G-protein-coupled receptors (GPCRs) that includes individual members that are highly specific for TAs indicates a potential role for TAs as vertebrate neurotransmitters or neuromodulators, although the majority of these GPCRs so far have not been demonstrated to be activated by TAs. Human trace amine receptors (including TAAR1 TAAR2 TAAR5 TAAR6 TAAR8 TAAR9) are expressed in the brain and play significant physiological and neuropathological roles by activation of trace amines. We herein discuss the recent findings that provide insights into the functional roles of human trace amines (including *P*-Octopamine, β phenylethylamine, Tryptamine, Tyramine, Synephrine, 3-Iodothyronamine, 3-Methoxytyramine, *N*-Methyltyramine, *N*-Methylphenethylamine) in brain. Furthermore, we discuss the known functions of human trace amine receptors in brain.

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1. Introduction

Trace-amines (TAs) are primary amines that are natural side products of synthesis or metabolism of monoamine precursors. As their name suggests, TAs are found at low levels within the mammalian/vertebrate brain at concentrations approximately 100 times lower than traditional monoamines such as dopamine, serotonin or norepinephrine [1,2]. Common TAs found within the brain include para-/meta-tyramine, tryptamine, β-phenylethylamine (β-PEA), synephrine, para-/meta-octopamine, 3-iodothyronamine [1,2] and potentially, 3-methoxytyramine [3]. Although trace amines have been known to exist in mammalian brain for decades, little evidence supported their independent role in the brain, and hence they were generally considered to be by-products or false neurotransmitters. Recently, altered brain TAs levels have been reported in several neuropsychiatric disorders, including schizophrenia, attention deficit hyperactivity disorder (ADHD), depression, and Parkinson's disease (PD), suggesting the involvement of these amines in pathophysiology of monoaminergic systems [4,5] Tables 1 and 2 and Fig. 1.

Over 50 trace amine associated receptors (TAAR) genes have been identified in mammals by genome scanning efforts, which include 9 genes in humans (TAAR1, TAAR2, TAAR5, TAAR6, TAAR8, TAAR9 including 3 pseudogenes), 9 in chimpanzees (including 6 pseudogenes), 19 in rats (including 2 pseudogenes), and 16 in mice (including 1 pseudogene). Each subtype can include more genes (paralogues). Genes that are paralogues, generated through a gene duplication event within the lineage of one species and distinguished by a letter suffix [6]. The discovery of this receptor family has rekindled an interest to investigate trace amines as neuromodulators or neurotransmitters in the brain, although most of these receptors still remain orphans. The role of the TAAR1 receptor is most understood in the central nervous system, where it is believed to modulate monoaminergic neurotransmission, thus affecting a number of neural networks and processes. Human homologs of *TAAR3*, TAAR4, and TAAR7 are thought to be pseudogenes but TAAR5 does have an apparently functional human ortholog and the results suggest that functional members of the family more generally respond to trace amines. Recently some responses were reported for the gene products of other human orthologs TAAR2, TAAR6, TAAR8, and TAAR9, although role in humans for these TAARs is not yet clear.

Table 1
List of human trace amines.

1. Phenethylamines
• *N*-Methylphenethylamine
• Phenylethanolamine
• *m*-Tyramine
• *p*-Tyramine
• *N*-Methyltyramine
• *m*-Octopamine
• *p*-Octopamine
• Synephrine
• 3-Methoxytyramine
2. Thyronamine compounds
• 3-Iodothyronamine
3. Tryptamine

2. Human trace amines

2.1. p-Octopamine

p-Octopamine is a hydroxylated phenylethylamine that naturally occurs in plants, insects, mollusks and other invertebrates, and animals. It was first isolated from the salivary glands of octopus [7,8]. *p*-Octopamine is believed to be biosynthesized in these systems from tyramine which in turn is a metabolite of the amino acid L-tyrosine [9,10], with brain and nerve tissues constituting the primary sites of synthesis in mammals. As a consequence, measurable levels of *p*-octopamine occur in plasma.

A growing body of information indicates that trace amines including *p*-octopamine may exert significant roles in biogenic amine-based neurosynaptic physiology [5]. *p*-Octopamine may function as a neuromodulator. A pathophysiological role for trace amines including *p*-octopamine has been advocated in association with depression, Parkinson's disease, migraine and other neurological disorders [11]. Controversy exists regarding the precise role and function of *p*-octopamine. It is believed that a metabolic shift occurs in L-tyrosine metabolism in association with various neurological disorders.

In migraine, an increased synthesis of *p*-octopamine and tyramine occurs [12]. Plasma levels of *p*-octopamine were shown to be lower in bulimic subjects as compared to controls [13]. Low circulating levels of *p*-octopamine occur in the early stages of Parkinson's disease, possibly due to abnormalities of tyrosine decarboxylase activity. It has been suggested that plasma levels of *p*-octopamine may serve as a biomarker of early Parkinson's disease [14].

Deficit productions of *p*-octopamine and tyramine have been reported in cases of depression [15]. Significant decreases in the urinary excretion of *p*-hydroxymandelic acid, the primary metabolite of *p*-octopamine, occur in depressed patients as compared to control subjects. Conversely, increases in plasma concentrations of *p*-octopamine have been reported to occur at least in some cases of chronic liver disease and hepatic coma [16] and hepatic encephalopathy [17].

2.2. β-Phenylethylamine (β-PEA)

β-PEA is a naturally-occurring plant-derived biogenic amine found in cocoa beans[18] and its products [19], and is also an endogenous amine produced by decarboxylation of phenylalanine in the mammalian brain [20,21]. β-PEA is present in trace amounts in various food items such as chocolate [19,22,23] cheese [24] and wine [25,26], with the highest being reported in chocolate [22,23]. Although β-PEA is distributed throughout the mammalian brain, its concentration in dopaminergic areas such as the caudate-putamen is relatively high [1,27].

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopamine-containing neurons in the substantia nigra pars compacta (SNc), resulting in four cardinal behavioral abnormalities: tremor, rigidity, akinesia and postural instability [28,29]. It has been reported recently that long term administration of β-PEA to rodents causes oxidative stress [30,31], similar to that produced by parkinsonian