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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.

Contents

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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

Table 2
Shows various techniques used to measure human trace amines and concentrations of various human trace amines in different tissues.

Human trace amines	Techniques used for measurement of human trace amines	Concentration in various tissues	References
Tyramine	High performance liquid chromatography (HPLC)	Platelet levels of tyramine in migraine patients without aura (MoA) 0.33 ± 1.31. Platelet levels of tyramine in migraine patients with aura (MA) 0.55 ± 0.89. Platelet levels of tyramine in control subjects 0.04 ± 0.07. Values are expressed as ng/10^8 platelets ± SD	[74]
Tyramine	HPLC coulometric method	Plasma levels. Mean values in controls 0.686 (ng/ml). Mean values in eating disorders patients 0.855 (ng/ml).	[13]
Tyramine	HPLC coulometric method	Plasma levels. Mean values in controls 0.686 (ng/ml). Mean values in anorexia nervosa patients 0.774 (ng/ml). Mean values in Bulimia nervosa patients 1.087 (ng/ml).	[13]
Tyramine	High-performance liquid chromatography (HPLC)	Plasma levels. Mean values in controls 0.74 (ng/ml). Mean values in chronic migraine patients 6.91 (ng/ml). Mean values in chronic tension-type headache patients 0.53 (ng/ml).	[12]
Octopamine	High-performance liquid chromatography (HPLC)	Plasma level. Mean values in controls 1.39 (ng/ml). Mean values in chronic migraine patients 1.67 (ng/ml). Mean values in chronic tension-type headache patients 2.23 (ng/ml).	[12]
Octopamine	HPLC coulometric method	Plasma levels. Mean values in controls 1.293 (ng/ml). Mean values in eating disorders patients 1.178 (ng/ml).	[13]
Octopamine	HPLC coulometric method	Plasma levels. Mean values in controls 1.293 (ng/ml). Mean values in anorexia nervosa patients 1.345 (ng/ml). Mean values in Bulimia nervosa patients 0.7082 (ng/ml).	[13]
Octopamine	Pre-column o-phthalaldehyde (OPA) derivatization and reverse phase HPLC with electrochemical detection.	Plasma levels. Mean values in controls 4.28 (ng/ml). Mean values in Parkinson's disease (PD) patients 1.80 (ng/ml). Mean values in "de novo" (DN) PD patients 0.65 (ng/ml). Mean values in non-fluctuating (NF) PD patients 2.00 (ng/ml). Mean values in fluctuating (F) PD patients 2.27 (ng/ml).	[14]
Octopamine	High performance liquid chromatography (HPLC)	Platelet levels of octopamine in migraine patients without aura (MoA) 0.69 ± 0.43. Platelet levels of octopamine in migraine patients with aura (MA) 0.39 ± 0.37. Platelet levels of octopamine in control subjects 0.22 ± 0.16. Values are expressed as ng/10^8 platelets ± SD	[74]
β-phenylethylamine	Electron-capture gas chromatography	Urinary Excretion. Mean values in controls 33.2 μg. Mean values in attention-deficit hyperactivity disorder (ADHD) children patients 10.2 μg.	[37]
Synephrine	Chemiluminescence (CL) method	Urinary Excretion. 0.052 (μg/mL)*. *Average of three measurements	[71]
Synephrine	High performance liquid chromatography (HPLC)	Plasma levels. Mean values in controls 3.47 (ng/ml). Mean values in cluster headache patients 0.96 (ng/ml).	[78]
Synephrine	High performance liquid chromatography (HPLC)	Platelet levels of synephrine in migraine patients without aura (MoA) 0.37 ± 0.29. Platelet levels of synephrine in migraine patients with aura (MA) 0.72 ± 0.44. Platelet levels of synephrine in control subjects 0.33 ± 0.25. Values are expressed as ng/10^8 platelets ± SD	[74]

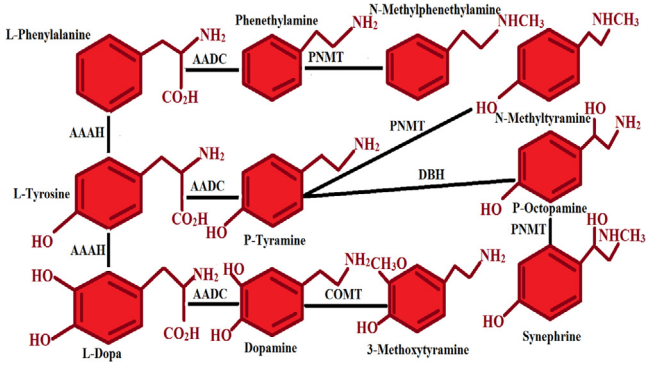

Fig. 1. Human biosynthesis pathway for trace amines. Abbreviations, AADC (Aromatic L-amino acid decarboxylase); (PNMT) Phenylethanolamine *N*-methyl-transferase; (DBH) Dopamine beta-hydroxylase; (COMT) Catechol-*O*-methyltransferase; (AAAH) Aromatic amino acid hydroxylases.

neurotoxins such as MPTP [32], rotenone [32] and 6-OHDA [33]. β-PEA-induced oxidative stress has been linked to its ability to inhibit mitochondrial complex-I [30], directly leading to the generation of cytotoxic hydroxyl radical (OH) in a dose-dependent manner [30]. In addition, β-PEA has also been reported to inhibit mitochondrial O_2 consumption, suggesting that the generation of cytotoxic (OH) is the underlying cause [31].

A common disease that an estimated 4–9% of young children suffer from is attention deficit hyperactive disorder (ADHD) [34]. ADHD is a chronic child hood disorder which is characterized by a number of behavioral symptoms, including a small attention span, increased frustration, distractibility, and often depression and anxiety [35]. PEA was recently described as a biomarker for ADHD [36]. This novel discovery will improve the confidence of the diagnostic efforts, possibly leading to reduced misdiagnosis and overmedication. Specifically, the urinary output of PEA was lower in a population of children suffering from ADHD, as compared to the healthy control population, an observation that was paralleled by reduced PEA levels in ADHD individuals [37,38]. Methylphenidate (MPD) is a central nervous system (CNS) stimulant, which belongs to the phenethylamine group and is mainly used in the treatment of attention deficit hyperactive disorder (ADHD). However, a growing number of young individuals misuse or abuse MPD to sustain attention, enhance intellectual capacity and increase memory [39]. Recently, the use of MPD as a cognitive enhancement substance has received much attention and raised concerns in the literature and academic circles worldwide.

Depression is a very common, sometimes serious disease that affects a wide range of people. It is currently the second leading cause of disability in the age group of 15–44. By the year 2030, depression is predicted to be the primary cause of disability [40]. Selective serotonin re-uptake inhibitors (SSRI) are the most

popular antidepressant prescribed worldwide [41]. SSRI function by blocking the serotonin transporter and thus inhibiting the re-uptake of serotonin [42,43]. This will result in an increase of the synaptic concentration of serotonin. However, SSRI act very slowly at the beginning of the treatment, while exhibiting a range of side effects upon long term use. These long-term side effects include insulin resistance [44], bone density loss [45]. Overall, the question has been raised where to go from here [41] and a need for the novel approaches to depression treatment is evident. The study by Xie and Miller [46], that had shown that PEA altered the serotonin transporter by interacting with TAAR1, may point towards a safer alternative to SSRI treatment of depression in the form of PEA.

2.3. Tryptamine

Tryptamine is a monoamine alkaloid. It contains an indole ring structure, and is structurally similar to the amino acid tryptophan, from which derives the name. Tryptamine is found in trace amounts in the brains of mammals and is believed to play a role as a neuromodulator or neurotransmitter [47].

It seems almost certain that the only route of synthesis for brain tryptamine is by direct decarboxylation of L-tryptophan by aromatic amino acid decarboxylase (AAD). Several authors have demonstrated a rise in brain tryptamine concentration following L-tryptophan administration, an effect enhanced by monoamine oxidase inhibitor (MAOI's) [48–51].

The subcellular localization of tryptamine has been little investigated. Snodgrass and Iversen, concluded that 3H-tryptamine formed from 3H-tryptophan in rat spinal cord slices was located in neurones since it could be released by a high potassium concentration in the buffer and also by electrical stimulation [52]. A number of studies have been aimed at determining whether tryptamine formed in brain tissue is releasable by physiological or pharmacological stimuli. Martin et al., implanted push-pull cannulae in cortex, thalamus, hypothalamus, caudate and hippocampus of anaesthetized dogs and claimed to be able to demonstrate significant release of tryptamine into the perfusate [53]. 3H-tryptamine formed from 3H-L-tryptophan in rat spinal cord slices could be released by electrical and high potassium challenges to the tissue [52]. The electrically induced release was abolished in a high magnesium, low calcium medium and also by the introduction of colchicine into the medium. The authors concluded that tryptamine was probably released by exocytosis from vesicular stores contained in neuronal elements in the slices. The effects of intraperitoneal injections of tryptamine and 5HT on body temperature in the mouse were compared by [54]. Both amines caused a dose-related hypothermia which was antagonized by the peripherally acting antagonist xylamidine suggesting a common peripheral receptor for the two amines in this case.

The effects of tryptamine on behaviour have been described for a number of species including mouse, rat, guinea pig, rabbit, cat and chicken. In general the amine appears to exert weak excitatory effects on behaviour which are profoundly enhanced by inhibition of MAO. Generalized behavioural excitation, as determined by increased locomotor activity, appears to be a feature of the effects of tryptamine on behaviour in the rat [55,56]. Marsden and Curzon, have also described similar behavioural actions of tryptamine including clonic forepaw movements [57].

The clinical literature does provide some indications about the involvement of tryptamine in neuropsychiatric manifestations. The urinary output of tryptamine and its major metabolite Indole-3-acetic acid (IAA) has been claimed to be disturbed in schizophrenic patients [58] and in a general psychiatric population [59]. The urinary output of tryptamine seemed to be positively correlated with increasing severity of psychosis [58]. Depressed patients, on the other hand, apparently exhibit decreased urinary output of tryptamine, although there was no concurrent alteration in IAA excretion [60]. Also, tryptamine, administered intravenously failed to act as an antidepressant [60]. Parkinsonian patients also may excrete abnormal amounts of tryptamine. Smith and Kellow, have provided evidence that tryptamine levels are high in the urine of Parkinsonian patients and this was confirmed for some, but not all such patients [61].

2.4. Tyramine

Tyramine (4-hydroxyphenethylamine; para-tyramine, mydrial or uteramin) is a naturally occurring monoamine compound and trace amine derived from the amino acid tyrosine [62]. Tyramine occurs widely in plants and animals, and is metabolized by the enzyme monoamine oxidase. In foods, it is often produced by the decarboxylation of tyrosine during fermentation or decay. Foods containing considerable amounts of tyramine are chocolate; alcoholic beverages; and fermented foods, such as most cheeses; yogurt, shrimp, soybean condiments, teriyaki sauce, tempeh, miso soup, beans, green bean pods [63]. It is unable to cross the blood-brain barrier, resulting in only non-psychoactive peripheral sympathomimetic effects. Hypertension can occur, from ingestion of tyramine-rich foods in conjunction with monoamine oxidase inhibitors (MAOIs) [64]. Foods that contain tyramine may trigger headaches in migraineurs by facilitating a chain reaction which results in selective cerebral vasoconstriction followed by rebound dilation of the cranial vessels (the most common cause of the throbbing headache pain). This sequence of events is implicated in migraine headache. This complication is more common in people, when they ate foods containing tyramine while they were taking anti-depression drugs (MAOIs) [65]. However, the precise mechanism behind, how tyramine can trigger migraines is not clear. Evidence for the presence of tyramine in the human brain has been confirmed by postmortem analysis [66]. Additionally, the possibility that tyramine acts directly as a neurotransmitter was revealed by the discovery of a G protein-coupled receptor with high affinity for tyramine, called TAAR [67,68].

Szczuka et al., investigated the effect of injections of four biogenic amines (serotonin, dopamine, octopamine and tyramine) on behavior patterns displayed by workers of the red wood ant Formica polyctena during dyadic confrontations with four types of opponents: a nestmate, an alien conspecific, an allospecific ant (Formica fusca), and a potential prey, a nymph of the house cricket (Acheta domesticus). Tyramine administration exerted a suppressing effect on threatening behavior directed to F. fusca, but led to shortening of the latencies to the first open-mandible threat during the tests with cricket nymphs. Biogenic amine administration also influenced non-aggressive behavior of the tested ants [69]. However the effects of tyramine on mammals behavior including mouse, rat has not been studied.

2.5. Synephrine

Synephrine, or, more specifically, *p*-synephrine, is an alkaloid, occurring naturally in some plants and animals, and also in approved drugs products as its m-substituted analog known as neo-synephrine. Low levels of synephrine have been found in normal human urine, [70,71] as well as in other mammalian tissue [72,73]. D'Andrea et al., showed increased levels of synephrine in platelets from patients suffering from aura-associated migraine [74]. Evidence that synephrine might have some central effects comes from the research of Song and co-workers, who studied the effects of synephrine in mouse models of anti-depressant activity [75]. These researchers observed that oral doses of 0.3–10 mg/kg of racemic synephrine were effective in shortening the duration of

immobility produced in the assays, but did not cause any changes in spontaneous motor activity in separate tests.

Cluster headache (CH) is a trigeminal autonomic cephalalgia (TAC) characterized by unilateral, excruciating, severe headache attacks. Most of the patients present with episodic CH in which the painful attacks occur with a variable frequency, daily or weekly during the active periods and then subside in remission periods. The active periods last from weeks to months and occur in a periodic manner. The pathogenesis of CH is unknown; however, increasing evidence shows that profound alterations of tyrosine (Tyr) metabolism may have an intriguing role in the occurrence of this primary headache [76,77]. Tyr is the amino acid precursor for the synthesis of catecholamines and trace amines. D'Andrea et al., measured the levels of dopamine and noradrenaline together with those of trace amines, such as tyramine, octopamine and synephrine, in plasma of chronic cluster patients and control individuals. The plasma levels of dopamine, noradrenaline and tyramine were several times higher in chronic cluster headache patients compared with controls. The levels of octopamine and synephrine were significantly lower in plasma of these patients with respect to control individuals [78]. These results suggest that anomalies in tyrosine metabolism play a role in the pathogenesis of chronic cluster headache and constitute a predisposing factor for the transformation of the episodic into a chronic form of this primary headache.

2.6. 3-Iodothyronamine

3-Iodothyronamine (T1AM) is an endogenous thyronamine. T1AM was detected by mass spectrometry, coupled to an appropriate separation technique, usually HPLC in brain [79], heart [80], and blood [81]. Tissue concentrations were found to be on the order of 1–90 pmol/g, and the highest values were detected in liver, brain, and muscle [82].The presence of T1AM in human blood was confirmed with a chemiluminescence immunoassay [83], and its concentration was estimated to be much higher, namely 66 nM.

T1AM is not a ligand for nuclear thyroid hormone receptors, but it was found to stimulate with high affinity trace-amine associated receptor 1 (TAAR1), a G protein-coupled membrane receptor [79]. Using cell cultures expressing heterologous TAAR1, T1AM was found to activate rat and mouse TAAR1, inducing cAMP production with EC50 of 14 and 112 nM, respectively [79]. In these models T1AM was more potent than all other trace amines. Preliminary evidence that T1AM interacts with TAAR5 has been reported [84], and TAAR8 has also been suggested as a potential target, on the basis of the pharmacological effects produced in the isolated rat heart [85].

Current studies suggest neurological roles of T1AM. Electrophysiological recordings performed in Locus Coeruleus (LC) showed that the rate of discharge of adrenergic neurons was modified by local application of T1AM (10 μM) [86]. There is reason to believe that TAAR1, now considered as a specific T1AM receptor, can interact with the adrenergic system.

Microinjections of T1AM in the preoptic region produced a considerable reduction in non-REM sleep (at doses of 1 and 3 μg = 2.5 and 7.5 nmoles) and an increase in low and theta frequencies in the power spectrum of EEG defined wakefulness (at a dose of 3 μg = 7.5 nmoles) [87,88]. Consistent with these findings, i.c.v. injection of T1AM in a mouse model (at doses of 1.32 and 4 μg/Kg = 3.3–10.2 nmol/Kg) produced an important increase in exploratory activity evaluated through the hole-board test [89]. Furthermore, T1AM (1.32–4 μg/Kg = 3.3–10.2 nmol/Kg) produced pro-learning and anti-amnestic responses when administered i.c.v. [89]. Musilli et al., has suggested that T1AM main oxidative metabolite, 3-iodothyroacetic acid (TA1), may also play a significant role in the stimulation of memory acquisition [90].

T1AM has also important effects on the regulation of food intake. Intracerebral T1AM injection induced significant alteration in feeding behavior in fasting mice and in mice fed *ad libitum*. In the latter group, when T1AM was administered either in the arcuate nucleus (at doses of 0.12–1.2 nmol/Kg) or in cerebral ventricles (at the dose of 1.2 nmol/kg), an orexigenic effect was induced [91]. However, the mechanism of feeding modulation by T1AM is not clear.

2.7. 3-Methoxytyramine

3-Methoxytyramine (3-MT) is a metabolite of the neurotransmitter dopamine formed by the introduction of a methyl group to dopamine by the enzyme catechol-*O*-methyl transferase (COMT). 3-MT can be further metabolized by the enzyme monoamine oxidase (MAO) to form homovanillic acid (HVA), which is then typically excreted in the urine.

Dopamine, the main neurotransmitter involved in motor control and Parkinsons disease, is metabolized both intra-, and extraneuronally. The extraneuronal dopamine metabolite,3-methoxytyramine (3-MT), which is present in the synaptic cleft at relatively low concentrations, comparable to those of the neurotransmitter itself, is considered to be a marker of dopamine release [92]. It was reported that given intraventricularly at high concentrations 3-MT produced stimulatory behavioral effects [93], however, at lower concentrations (from 0.05 to 2 μmol/rat), it dose-dependently reduced movement time in rats [94]. Antkiewicz-Michaluk et al., have shown that 3-MT binds to the rat noradrenergic cortical α_1 and striatal dopamine D_1 and D_2 receptors in nanomolar concentration range, and to cortical α_2 adrenoceptor at low micromolar concentration. Bilateral intrastriatal injections of 3-MT (0.25 μmol in 0.5 μl) did not affect significantly locomotor activity in naive rats but strongly antagonized amphetamine-induced (1 mg/kg s.c.) hypermotility [95]. To explore if trace amines or other endogenous compounds active on TAAR1 could be involved in movement control in mammals, Sotnikova et al., performed an unbiased screen of several compounds that activate TAAR1 for their potential effects on locomotor activity in akinetic DDD (dopamine-deficient DAT-KO) mice [96]. They observed potent behavioral and biochemical effects of the dopamine metabolite 3-MT that were partially dependent on TAAR1 [97]. These observations indicate that 3-MT is not just an inactive metabolite of dopamine but a neuromodulator that may play a role of its own in motor control.

Cocaine is one of the most dangerous compounds because it produces a very strong and long-lasting dependence. It was reported that even a single cocaine administration induces profound and persistent neurochemical changes [98]. Cocaine, being a potent inhibitor of monoamine transporters [99], blocks dopamine, noradrenaline and serotonin reuptake with approximately equal potency [100,101]. Recently Wąsik et al., examined the role of extracellular concentrations of both dopamine and its metabolite, 3-MT, in cocaine-induced locomotor sensitization in rat using an *in vivo* microdialysis study. Their results suggest that locomotor hyperactivity is dependent not only on dopamine concentration in the extracellular space, but also on the ratio of [DA/3-MT]. The extraneuronal metabolite of dopamine, 3-MT, may play a crucial role in its anti-craving effects [102].

2.8. N-*Methyltyramine (NMT)*

N-Methyltyramine (NMT), also known as 4-hydroxy-*N*-methylphenethylamine, is a human trace amine [103] and natural-phenethylamine alkaloid found in a variety of plants [63]. As the name implies, it is the *N*-methyl analog or derivative of the well-known biogenic amine, tyramine, with which it shares many

pharmacological properties. Biosynthetically, NMT is produced by the *N*-methylation of tyramine *via* the action of the enzyme tyramine *N*-methyltransferase [63]. NMT has been shown to be an agonist of the TAAR1, similarly to its parent compound tyramine. The EC_{50} of NMT on the human TAAR1 receptor was ~2 μM, compared to ~1 μM for tyramine [104]. However the functional roles of NMT in mammalian brain is not clear Table 3.

2.9. N-*Methylphenethylamine (NMPEA)*

N-Methylphenethylamine (NMPEA) is a naturally occurring trace amine neuromodulator in humans that is derived from the trace amine, phenethylamine (PEA) [103,105]. It has been detected in human urine and is produced by phenylethanolamine *N*-methyltransferase with phenethylamine as a substrate [106]. PEA and NMPEA are both alkaloids that are found in a number of different plant species as well [63]. Like its parent compound, PEA, NMPEA is a potent agonist of human TAAR1 [103,104]. However the functional roles of NMPEA in mammalian brain is not clear.

3. Human trace amine associated receptors (TAARs)

Trace amine-associated receptors (TAAR) belong to family A of G protein-coupled receptors (GPCR) [107]. GPCRs are currently considered as key targets for drug development [108–111]. TAARs are evolutionarily conserved throughout diverse vertebrates, including humans (six TAARs, three pseudogenes) [112,113]. So far as is known, the predominant signaling pathway for TAARs utilizes G_s activation [114,115]. TAARs are ubiquitously expressed in humans and rodents, with expression in various brain regions, as well as in kidney, stomach, liver, pancreas, small intestine, pituitary, and leukocytes [116–118] Tables 4 and 5. TAARs possesses several structural hallmarks characteristic of the rhodopsin/b-adrenergic receptor superfamily with 7 transmembrane domains, and the positions of its transmembrane domains reveal short N- and C-terminals. However, TAARs members displays different degrees of divergence in the amino acid sequence and the structural similarity of various members of TAARs is still not clear. Fig. 2

3.1. TAAR1

The human TAAR1 receptor is a member of the rhodopsin-type superfamily (*i.e.* a class A GPCR), with 339 amino acids. It has a predicted seven transmembrane spanning domain structure with short N- and C-terminal domains of 23–49 and 27–33 amino acids respectively [6]. Cichero et al., have derived a homology model for the human TAAR1 and together with docking studies using RO5166017, β-phenylethylamine and 3-iodothyronamine used these data to propose key residues, D103 and N286, involved in ligand recognition [119]. Using RT-PCR, Borowsky et al. showed expression of TAAR1 mRNA in several mouse brain regions including the amygdala, cerebellum, hypothalamus, dorsal root ganglia and hippocampus [120]. They further identified the presence of TAAR1 mRNA in several monoaminergic cell regions including substantia nigra (SN), ventral tegmental area (VTA), locus coeruleus (LC) and dorsal raphe (DR) using in situ hybridization [120]. These results were subsequently confirmed in a TAAR1-knock out (TAAR1-KO) transgenic mouse strain where the coding region of the TAAR1 gene was replaced with a LacZ reporter that could be used to assess TAAR1 expression pattern. Using the LacZ reporter, specific labeling was observed in dopaminergic and serotonergic nuclei, including the hypothalamus, SN/VTA, amygdala and DR [121]. Xie et al., used rhesus monkey brain tissue to assess expression of TAAR1 mRNA. They were able to detect TAAR1 mRNA in monoaminergic regions including the SN/VTA, LC, DR, amygdala, caudate nucleus, putamen and nucleus accumbens [122]. All together, these studies clearly show that TAAR1 is expressed in brain monoaminergic systems and may therefore be implicated in the modulation of dopamine, serotonin and

Table 3
The neuropathlogical and neurophysiological functions of trace amines.

Trace amines	Neuropathlogical and neurophysiological functions	References
P-Octopamine	In migraine, an increased synthesis of *p*-octopamine occur.	[10]
	Low circulating levels of *p*-octopamine occur in the early stages of Parkinson's disease.	[14]
	Deficit productions of *p*-octopamine have been reported in cases of depression.	[78]
	The level of octopamine was significantly lower in plasma of cluster headache patients with respect to control individuals.	[15]
β phenylethylamine (β-PEA)	Long term administration of β-PEA to rodents causes oxidative stress.	[30,31]
	PEA was recently described as a biomarker for attention deficit hyperactive disorder (ADHD).	[36]
	Urinary output of PEA was lower in a population of children suffering from ADHD, as compared to the healthy control population.	[37,38]
	PEA altered the serotonin transporter by interacting with TAAR, may point towards a safer alternative to SSRI treatment of depression in the form of PEA.	[46]
Tryptamine	Increased locomotor activity, appears to be a feature of the effects of tryptamine on behaviour in the rat.	[55–57,60]
	Depressed patients apparently exhibit decreased urinary output of tryptamine, although there was no concurrent alteration in IAA excretion.	[61]
	Parkinsonian patients also excrete abnormal amounts of tryptamine.	
Tyramine	Foods that contain tyramine may trigger headaches in migraineurs.	[65]
	In migraine, an increased synthesis of tyramine occur.	[10,12]
	Deficit productions of tyramine have been reported in cases of depression .	[15]
Synephrine	Oral doses of 0.3–10 mg/kg of racemic syephrine were effective in shortening the duration of immobility produced in the mice depression model.	[75]
	The level of synephrine was significantly lower in plasma of cluster headache patients with respect to control individuals.	[78]
3-Iodothyronamine	Electrophysiological effects on the Locus Coeruleus: Increased neuronal firing.	[86]
	EEG patterns (microinjection in the preoptic region): Reduction in nREM sleep.	[87]
	Behavior (i.c.v. administration): Increase in exploratory activity.	[89]
	Memory (i.c.v. administration): Prolearning and antiamnestic effect.	[90]
	Food intake (acute central administration): In ad libitum fed mice: orexigenic effect.	[91]
	In fasting mice: biphasic effect, with anorexic properties at low doses and orexigenic effects at higher doses.	
3-Methoxytyramine (3-MT)	3-MT is not just an inactive metabolite of dopamine but a neuromodulator that may play a role of its own in motor control.	[97,95]
	The extraneuronal metabolite of dopamine, 3-MT, may play a crucial role in its anti-craving effects .	[102]

Table 4
Pharmacology of human trace amine associated receptors.

Human Trace amines	human TAAR1 EC50	human TAAR2 EC50	human TAAR5 EC50	human TAAR6 EC50	human TAAR8 EC50	human TAAR9 EC50
β−Phenylethylamine	0.3 μM [6] 0.3 μM [120]	0.43 ± 0.05 nM [118]	Not. Determined	Not. Determined	Not. Determined	Not. Determined
p-Tyramine	1.1 μM [6], 0.2 μM [120]	0.52 ± 0.05 nM [118]	Not. Determined	Not. Determined	Not. Determined	Not. Determined
Octopamine	10.3 μM [6] 4.0 μM [120]	Not. Determined	Not. Determined	Not. Determined	Not. Determined	Not. Determined
Tryptamine	46.9 μM [6], 6.0 μM [120]	Not. Determined	Not. Determined	Not. Determined	Not. Determined	Not. Determined
3-Iodothyronamine	1.5 μM [154]	0.25 ± 0.04 nM [118]	1.9 ± 0.9 μM [140]	Not. Determined	Not. Determined	Not. Determined
Trimethylamine	Not. Determined	Not. Determined	116 μM [136]	Not. Determined	Not. Determined	Not. Determined

Table 5
Expression and functions of human trace amine associated receptors in brain.

Human Trace amine associated receptors	Other names	Expression in brain	Functions in brain
TAAR1	TA1	(TAAR1) is expressed in mammalian brain in major monoaminergic regions, such as ventral tegmental area (VTA) and dorsal raphe, and their projections, including striatum, amygdala, hypothalamus and frontal cortex [120,123,121,129].	TAAR1 exerts a negative control on dopaminergic activity [121,123,124,125–127]. Several reports have indicated that TAAR1 is able to influence striatum-dependent behaviors, such as amphetamine-induced locomotor hyperactivity and haloperidol-induced catalepsy [129]. TAAR1 plays an important role in the modulation of NMDA receptor-mediated glutamate transmission in the PFC and related functions. These data suggest that development of TAAR1-based drugs could provide a novel therapeutic approach for the treatment of disorders related to aberrant cortical functions [129].
TAAR2	GPR58	TAAR2 was found to be expressed in the human cerebellum [133].	A SNP nonsense mutation (G368A resulting in W123STOP) was detected in TAAR2 in schizophrenia patients [134].
TAAR5	PNR	TAAR5 expression has been demonstrated in the olfactory epithelium [68,135]. Dinter et al., analyzed the expression of TAAR5 in distinct hypothalamic regions. They performed *in situ* hybridization with double DIG-labeled LNA probes on mouse brain sections to achieve high specificity and sensitivity with minimal risk for genomic DNA contamination. Signals specific for TAAR5 were detected in the arcuate nucleus (ARC), the ventromedial hypothalamus (VMH), and the amygdala [140].	Not determined
TAAR6	–	Xie et al., showed that TAAR6 protein is detectable by Western blotting in the selected rhesus monkey brain areas [122]. Real time RT-PCR studies revealed that TAAR6 mRNA is not detectable in selected rhesus monkey brain regions, including monoaminergic nuclei [46].	Some significant associations have been reported between TAAR6 and bipolar and schizophrenic disorders [142–144]. A wide genome scan in a large sample of schizophrenic patients and their families (270 families, 1408 individuals) found an association between a genetic locus which encloses the TAAR6 and depressive symptomatology [145]. TAAR6 is coded in position 6q23.2 and it spans about 1 kb. This locus has been associated with schizophrenia [142]. Study of Pae et al., suggest a possible role of TAAR6 in antidepressant response and suicide behavior in patients with depressive disorder [144].
TAAR8	TA5, TRAR5, TAR5, GPR102	Study of D'Andrea et al., showed expression of TAAR8 in astrocytes [10].	Recent findings by D'Andrea et al., showed that TAAR8 transcripts in astroglial cells are up-regulated following stimulation with lipo-polysaccharides strengthened the assumption of a TAAR8 distinct role in the brain [10]. Mühlhaus et al., confirmed basal $G_{i/o}$ signaling activity for TAAR8, however the physiological function of TAAR8 in brain tissues remains to be elucidated [153].
TAAR9	TA3, TRAR3, TAR3	Not determined	Not determined

potentially norepinephrine neurotransmission. Many studies have focused on the role of TAAR1 in the modulation of dopaminergic system, and it is evident that generally TAAR1 exerts a negative control on dopaminergic activity [121,123,124,125–127]. TAAR1 knock out (TAAR1-KO) mice are more sensitive to the neurochemical and behavioral effect of several amphetamine derivatives [123,121,128,129].

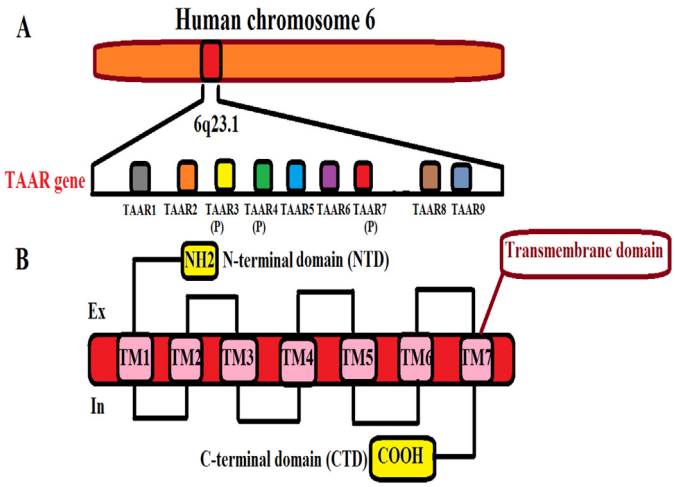

Fig. 2. (**A**) Chromosomal localization of TAAR genes in human. So far, more than 50 TAAR genes have been identified in mammals by genome scanning efforts, which include 9 genes in humans (including 3 pseudogenes). The TAAR1 gene along with the genes for other TAAR members is located on the chromosomal region of 6q23.1. (**B**) A common modular domain structure of TAARs. N-terminal domain (NTD), 7 transmembrane domains and C-terminal domain (CTD) assemble to form functional receptor. TAARs members displays different degrees of divergence in the amino acid sequence, which is largely unknown for various members of TAARs.

3.2. TAAR2

TAAR2, also known as GPR58, is G protein coupled receptor. This gene contains one exon and predicts a protein of 306 amino acids. The predicted secondary structure contains 7 putative transmembrane domains [130]. The receptor shares identities with the putative neurotransmitter receptor (PNR) (42%) and the 5-hydroxytryptamine (serotonin) receptor 4 (HTR4) (34%) receptors [6]. Though ligands are currently unknown [130,6], phenylethylamine (PEA) has been suggested [130]. This suggestion is interesting since PEA has been found to be elevated in the urine [131] and blood [132] of schizophrenics. TAAR2 was found to be expressed in the human cerebellum [133]. Bly, have identified an interesting single nucleotide polymorphism (SNP) that may be associated with schizophrenia. A SNP nonsense mutation (G368A resulting in W123STOP) was detected. The nonsense mutation terminates the protein after three of its predicted 7 transmembrane domains. Comparison with other trace amine receptors [130] seems to indicate that this mutation would eliminate the ligand binding domain of the protein [134].

3.3. TAAR5

TAAR5 is the most highly conserved TAAR subtype among all characterized mammalian species investigated so far. TAAR5 expression has been demonstrated in the olfactory epithelium [135–139]. Dinter et al., analyzed the expression of mouse TAAR1 and mouse TAAR5 in distinct hypothalamic regions, which are important for temperature and body weight regulation [140]. They performed *in situ* hybridization with double DIG-labeled LNA probes on mouse brain sections to achieve high specificity and sensitivity with minimal risk for genomic DNA contamination. Signals specific for mouse TAAR5 were detected in the arcuate nucleus (ARC), the ventromedial hypothalamus (VMH), and the amygdala. No mouse TAAR5 expression was observed in any other hypothalamic region. Furthermore, they examined the distinct G_s-, $G_{i/o}$-, $G_{12/13}$-, $G_{q/11}$- and MAP kinase-mediated signaling pathways of mouse and human TAAR5 under ligand-independent conditions and after application of 3-iodothyronamine (3-T_1AM). The murine and human TAAR5 display significant basal activity in the $G_{q/11}$ pathway but show differences in the basal activity in G_s and MAP kinase signaling. In contrast to mouse TAAR5, 3-T_1AM application at human TAAR5 resulted in significant reduction in basal IP_3 formation and MAP kinase signaling [140]. This data suggest that the human TAAR5 is a target for 3-T_1AM, exhibiting inhibitory effects on IP_3 formation and MAP kinase signaling pathways, but does not mediate G_s signaling effects as observed for TAAR1.

3.4. TAAR6

TAAR6 is an orphan GPCR, probably associated with trace amines. Trace amines are putative regulatory elements in the brain whose activity may be relevant to the pathophysiology of depressive episodes [141].

Some significant associations have been reported between one putative trace amine receptor (TAAR6, trace amine associated receptor 6, also called TRAR4) and bipolar and schizophrenic disorders [142–144]. Moreover, a wide genome scan in a large sample of schizophrenic patients and their families (270 families, 1408 individuals) found an association between a genetic locus which encloses the TAAR6 and depressive symptomatology [145]. Negative association findings have been reported as well for schizophrenia and bipolar disorder [146–148]. TAAR6 is coded in position 6q23.2 and it spans about 1 kb. This locus has been associated with schizophrenia [142], even though conflicting findings can be retrieved as well [149–152], and with depressive symptoms within a large psychotic sample [145]. Pae et al., investigated the possible association between a set of TAAR6 genetic variations (rs7452939; rs4305745; rs6903874; rs6937506; and rs8192625) with clinical features of depression including antidepressant treatment response in a sample of 187 depressive patients all of Korean origins [141]. Their results suggest a possible role of TAAR6 in antidepressant response and suicide behavior in patients with depressive disorder.

3.5. TAAR8 and TAAR9

TAAR8 (TA5, TRAR5,TAR5, GPR102) is an orphan GPCR. Recent findings by D'Andrea et al., showed that TAAR8 transcripts in astroglial cells are up-regulated following stimulation with lipopolysaccharides strengthened the assumption of a TAAR8 distinct role in the brain [10]. Mühlhaus et al., confirmed basal $G_{i/o}$ signaling activity for TAAR8, however the physiological function of TAAR8 in brain tissues remains to be elucidated [153]. TAAR9 (TA3, TRAR3, TAR3) is an orphan GPCR. Until now, no single study exists concerning the evaluation of the TAAR9 role in the brain. This emphasizes the need to evaluate its role in the brain by using KO mice models and to develop new pharmacological tools to ascertain the functional role of TAAR9 in physiological and pathological conditions.

4. Concluding remarks

Human trace amines (hTAs) synthesis and storage, in addition to their degradation and reuptake after release, are tightly regulated, and an imbalance in the levels is known to be responsible for altered brain function in many pathological conditions. Their dysregulation has been linked to various psychiatric diseases such as schizophrenia and depression, and potential roles for TAs in other conditions such as attention deficit hyperactivity disorder, migraine headache, Parkinson's disease, substance abuse and eating disorders have been suggested [155]. However, detailed understanding of (hTAs) physiology on a molecular level, (neurotransmitters or neuromodulators) is not clear. Future studies investigating the functional roles of (hTAs) on

a molecular level will be extremely useful for understanding the pathophysiology of psychiatric diseases.

Human trace amine associated receptors (hTAARs) are attractive targets for drug development because of the good chemical tractability inherent to GPCRs, which currently account for 50% of all drugs on the market [156]. The tight link of hTAARs to several psychiatric diseases, including schizophrenia, bipolar disorder, depression, make them exceptionally promising molecules. However, for a full understanding of the physiological relevance of TAs and the TAAR family, numerous vital issues need to be resolved. Overall, the available data on the brain tissue distribution of TAARs are few, and detailed expression studies will be needed for a meaningful interpretation of the receptor pharmacology on a brain level. Future Studies examining receptor expression by *in situ* hybridization and studies investigating the phenotypic characterization of targeted knockdown/knockout (KD/KO) of hTAARs will prove extremely useful in elucidating their biological functions, and in suggesting their role as potential drug targets. The process of functional ligands identification is very slow. Identification of functional TAAR ligands will support attempts to target these receptors in drug development for neurodegenerative disease and psychiatric diseases including depression and schizophrenia.

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