Top Med Chem (2017) 23: 175–194
DOI: 10.1007/7355_2014_78

Published online: 9 December 2014

Neuronal Functions and Emerging Pharmacology of TAAR1

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Abstract Trace amine-associated receptor 1 (TAAR1) is a member of TAAR family of G protein-coupled receptors (GPCRs). The members of this class of receptors discovered in 2001 have been found in some tissues ranging from the central nervous system to the olfactory epithelium and in some peripheral organs. The best studied receptor, TAAR1, is activated by a class of compounds named trace amines (TAs) that include compounds such as β-phenylethylamine (PEA), *p*-tyramine, octopamine, and tryptamine normally present at low levels in the mammalian brain. Although TA levels have been associated with many neuropsychiatric disorders, only the discovery of TAAR1 validated their physiological role. TAAR1 can modulate monoamine neurotransmission and, in particular, dopamine systems. Several studies have demonstrated that TAAR1 knockout (TAAR1-KO) mice display a supersensitive dopaminergic system, while activation of TAAR1 can reduce dopaminergic hyperactivity obtained either with pharmacological tools or present in genetic mouse model. For these reasons, TAAR1 has been proposed as a novel therapeutic target for neuropsychiatric disorders such as schizophrenia, bipolar disorder, and addiction. Moreover, several peripheral functions of TAAR1 have been described recently indicating intriguing novel TAAR1 roles in system physiology. Here we will review brain and peripheral functions mediated by TAAR1 and other TAARs.

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Keywords Dopamine, Neuropsychiatric disorders, TAAR1, Trace amines

Contents

1 Introduction

Trace amine-associated receptors (TAARs) are a family of G protein-coupled receptors (GPCRs) that have been discovered in 2001 [1, 2]. From their first description by two independent groups, TAARs attracted an enduring interest among physiologists and pharmacologists, since they have been shown to be involved in many different physiological processes ranging from regulation of brain functions to olfaction and, more recently, to immune system [3–6]. Among them, TAAR1 has been mostly characterized with its particular role in the regulation of brain functions, although new intriguing functions of this receptor in the periphery are emerging. The initial observation from TAAR1 knockout (TAAR1-KO) mice was further strengthened by several recent studies using selective TAAR1 full and partial agonists, suggesting an important role for TAAR1 in the regulation of dopaminergic system and indicating TAAR1 as new potential target for the treatment of neuropsychiatric disorders such as schizophrenia, bipolar disorder, ADHD, and addiction [7–12]. Since the amount of literature on TAARs is increasing monthly, this review will focus on TAAR1 and particularly on recent reports that highlight TAAR1 influence on monoamine systems and its possible role in psychiatric diseases. We will also give brief introduction of the history of TAAR discovery and provide description of potential functions of TAAR1 in the periphery.

2 Trace Amines

The term "trace amines" (TAs) refers to a class of endogenous compounds that have been found at low levels in mammalian brain [3, 13–16]. These non-catecholic amines are closely related to the classic monoamines (dopamine, noradrenaline, and serotonin) in terms of structure, synthesis, metabolism, and distribution, so that for a long time they have been considered only as side products with little physiological relevance [3, 14]. With the cloning of the family of TAARs in 2001, TAs' role has been reconsidered and a growing amount of studies are now focused on more precise physiological role for these compounds [3, 4, 14, 17]. Conventionally, TAs include molecules such as β-phenylethylamine (PEA), *p*-tyramine, octopamine, synephrine, and tryptamine, but if we consider as "trace amine" an endogenous amine that is able to activate a TAAR, then we should include also other compounds such as 3-methylamine (a TAAR5 agonist), 3-metoxythyramine (a TAAR1 agonist), and others [18, 19]. Generally, most of TAs are synthetized from the decarboxylation of the L-amino acid precursors by the action of the L-amino acid decarboxylase (AADC) [14], while octopamine is formed from the hydroxylation of *p*-tyramine by the enzyme dopamine β-hydroxylase. Regarding the metabolism, the major route of degradation is mediated by the action of the monoamine oxidases (MAO), with MAO-B being the prototypical enzyme for PEA degradation [20] and both MAO-A and MAO-B responsible for the metabolism of the other TAs [21, 22]. MAO-B metabolizes also dopamine, and MAO-B inhibitors are clinically used for the treatment of Parkinson's disease and depression. Interestingly, MAO-B-deficient mice show higher PEA extracellular levels with no change in dopamine levels [23], suggesting a potential role for PEA in the therapeutic efficacy of these drugs.

While in invertebrates TAs such as tyramine and octopamine serve as major neurotransmitters [14, 24, 25], in mammals the precise physiological functions of these compounds are still not clear [3]. Before the discovery of TAARs, TAs were described as false neurotransmitters and sympathomimetic substances [26–28]. These effects are believed to be due to the nonspecific action that they have on vesicular and plasma membrane monoamine transporters and occurs at high, nonphysiological concentrations. In fact, PEA, at high doses, is able to reverse the function of dopamine transporter (DAT) and to increase locomotor activity producing an amphetamine-like effect [14]. For this reason, PEA has been considered as the "endogenous amphetamine." Interestingly, when PEA, at the same stimulating doses, is administered to mice lacking the DAT (DAT-KO mice), it produces a decrease in locomotor activity [29] revealing the specific, non-DAT-related effect that PEA has likely via TAAR1 activation. Indeed, many reports showed that the TAAR1-selective activation produces a "calming" effect on a hyperactive dopamine system obtained by either a pharmacological treatment (cocaine) or present in genetic animal models (DAT-KO mice) (see next sections) [10, 11]. TAs, as demonstrated by many studies, are present at low levels in mammalian brains, with an extracellular concentration that normally is estimated in the low nanomolar range and is tightly regulated by AADC and MAO activity [14]. As described below, TAAR1 is activated by PEA with an EC_{50} around 200–900 nmol/L, depending on the species and on the type of the assay, usually performed in heterologous cell system [1, 2, 30–36]. These discrepancies could be due to the nonphysiological cellular systems where these assays are performed and may reflect some deficiency of the transduction machinery in these artificial systems. For example, TAAR4 is also activated by PEA, with an EC_{50} obtained in COS-7 cells in the low micromolar range [1]. Conversely, when PEA was used to stimulate TAAR4 in its natural environment, the olfactory sensory neurons, it emerged that PEA started to stimulate TAAR4 in the picomolar range [37], with a strikingly higher affinity than in transfected cells. Similarly, TAAR1 sensitivity to *p*-tyramine in inducing K^+ currents through Kir3 channels was much higher, when tested in dopaminergic neurons, compared to when they were expressed in heterologous systems [34]. Finally, PEA was able to induce different effects in leukocytes in a TAAR1-dependent manner at low nanomolar concentrations [38], further suggesting that these receptors would need their natural environment to fully express their native pharmacology.

3 Trace Amine-Associated Receptors

TAAR family consists of 9 genes in human (including 3 pseudogenes) and in chimpanzee (including 6 pseudogenes), while 19 and 16 genes (including 2 and 1 pseudogenes) are present in the rat and mouse genome, respectively [4, 39]. All these genes cluster in a narrow region of approximately 100–200 kilobases on the same chromosome, reminiscent of similar chromosomal organization of some members of the olfactory receptors [18]. All these genes are encoded by a single exon, except TAAR2, and are of a length of about 1 kilobase. Interestingly, the region where TAARs are located on chromosome 6 (the locus 6q23) has been associated with schizophrenia and bipolar disorder in linkage/association studies [40]. Regarding the in vivo expression and tissue distribution, different groups carried out several studies, with sometime conflicting results, most likely due to the different techniques used to detect TAARs expression. All TAARs, with the exception of TAAR1, have been found in the olfactory epithelium as described by Lieberles and Buck [18] and believed to serve as new class of olfactory receptors. In this study, no detection of TAAR transcripts in the brain and periphery was reported; however, several other studies found that at least some members of TAAR family are expressed in many organs and in the brain [1, 2, 34, 41]. The first two groups that cloned TAAR family found that TAAR1 is expressed in many brain regions and in peripheral organs such as the liver, kidney, spleen, pancreas, and heart [1, 2]. There is also evidence that other TAARs are expressed in the brain including TAAR5, TAAR6, and TAAR9 [3]. Intriguingly, TAAR6 polymorphisms have been associated with susceptibility to schizophrenia, and mutations found in this gene have been studied in correlation with antidepressant response and suicidal behavior [40, 42]. TAAR1 and TAAR2 are also expressed in human blood leukocytes, particularly in polymorphonuclear (PMN) T and B cells, and lower expression was found for TAAR5, TAAR6, and TAAR9 [38, 43, 44]. RNA extracted from rat heart demonstrated that TAAR1, TAAR2, TAAR3, TAAR4, and TAAR8a are expressed in this organ [3, 45].

4 TAAR1

At the moment, TAAR1 is the best studied member of the TAAR family. Since its expression was found in the brain regions, most of the studies focused on TAAR1 role in brain physiology and pathology. TAAR1, alongside with TAAR4, is the only TAAR subtype that is activated by TAs, and if we consider that TAAR4 in humans is a pseudogene, TAAR1 could be considered as the primary target for these amines in humans. Several studies, using different experimental approaches, demonstrated that TAAR1 is expressed in various brain regions. While this expression was not at such high levels as for some other GPCRs, it was found to be in key regions for monoamine systems [1–3, 34, 46]. RNA transcript for TAAR1 was found in mouse and rat brain in ventral tegmental area (VTA), dorsal raphe, substantia nigra, striatum, and frontal cortex. Expression in dopaminergic areas such as the substantia nigra and striatum has been found also in rhesus monkey brain [41]. In humans, fewer studies were performed, but high expression of TAAR1 was found at least in the amygdala [1]. Using a transgenic mouse model, where LacZ gene was inserted in TAAR1 gene to have a specific expression of the LacZ driven by TAAR1 promoter, Lindemann et al. confirmed that TAAR1 was present in dopaminergic and serotonergic areas such as VTA, amygdala, dorsal raphe, subiculum, and parahippocampal region [34]. In the periphery, TAAR1 was found in several organs including liver, spleen, kidney, gastrointestinal tract, pancreas, heart, and leukocytes [2, 3]. At subcellular levels, it is still not clear whether TAAR1 in its natural environment such as neurons is expressed at the membrane as most GPCRs or in the intracellular compartments. Difficulties in reliable evaluation of cellular distribution of TAAR1 are, in part, determined by technical limitations such as the lack of specific antibodies.

TAAR1 expression and functional studies in heterologous cell system such as HEK-293 cells have been challenging, since TAAR1 was found mainly in the intracellular compartments leading to a difficulty in its coupling to G protein to transduce the signal [2, 30, 31, 33, 36, 47]. TAAR1 is a Gαs-coupled receptor and its stimulation increases cAMP levels, but likely only with sufficient membrane expression it is possible to properly study its pharmacology. Many strategies have been used to improve TAAR1 membrane expression such as building a human/rat chimera [2] or adding a peptide from bovine rhodopsin at the N-terminus of the receptor [18]. In our lab, we fused the first nine amino acid of the β2-adrenergic receptor to the N-terminus, leading to a significant level of membrane expression sufficient to reliably study TAAR1 pharmacology [36]. TAAR1, as demonstrated by many laboratories under different experimental conditions, can be activated by PEA and *p*-tyramine, with PEA being more potent against mouse and human TAAR1 and *p*-tyramine being more potent against rat TAAR1 [1, 2, 4, 5, 30–33, 35, 36, 47]. TAAR1 has been reported also to have a weaker affinity for tryptamine and octopamine [1–3, 36]. When stimulated by an agonist, TAAR1 couples to Gαs and stimulates the production of cAMP. Using a BRET-based biosensor, it was possible to study the dynamics of cAMP fluctuations after TAAR1 stimulation, and by using this approach we observed that TAAR1 poorly desensitizes upon agonist binding [36]. While cAMP levels, produced by β2-adrenergic receptor, a prototypical GPCR, decrease after 5 min and then return to basal levels, TAAR1 agonist-stimulated cAMP decreases slightly only after 10–20 min. This evidence was confirmed by β-arrestin2 translocation studies after TAAR1 stimulation [36, 48]. PEA was able to recruit β-arrestin2-GFP but in a small proportion and at a lesser degree compared to other GPCRs such as β2-adrenergic receptor. This property of TAAR1 resembled D3 dopamine receptor that has been demonstrated to poorly recruit β-arrestin2 [49]. By using cAMP assay in rat TAAR1, Bunzow et al. performed a screening of several classes of compounds as regards to TAAR1 activity [2].

Apart from classic TAs, many other known compounds were able to activate TAAR1. Among them, amphetamines and their derivatives are of particular interest. In this assay, D-amphetamine, L-amphetamine, D-methamphetamine, and (±)-MDMA acted as TAAR1 agonists, and later reports confirmed these data on human, mouse, rat, and rhesus monkey TAAR1 expressed in different cellular systems [30, 31, 33, 35, 36, 41, 47, 50]. Interestingly, the concentrations of amphetamine found to be necessary to activate TAAR1 are in line with what was found in drug abusers [3, 51, 52]. Thus, it is likely that some of the effects produced by amphetamines could be mediated by TAAR1. Indeed, in a study in mice, MDMA effects were found to be mediated in part by TAAR1, in a sense that MDMA auto-inhibits its neurochemical and functional actions [46]. Based on this and other studies (see other section), it has been suggested that TAAR1 could play a role in reward mechanisms and that amphetamine activity on TAAR1 counteracts their known behavioral and neurochemical effects mediated via dopamine neurotransmission. On the other hand, whether TAAR1 mutations or functional deficits in humans are associated with drug addiction would be an interesting point to evaluate.

Other interesting endogenous substances that are TAAR1 agonist are thyronamines, compounds structurally related to thyroid hormones [53, 54]. 3-Iodothyronamine (T1AM) and its deiodinated relative thyronamine (T0AM) are potent full agonists of human, rat, and mouse TAAR1, and when administered to rats, they induce profound physiological effect such as hypothermia, alteration of metabolism, cardiac effects, and behavioral suppression [3, 54–56]. Similarly, metabolites of amiodarone that has a chemical structure similar to thyronamines and is used in clinic to treat arrhythmias are TAAR1 agonists [57]. It should be noted, however, that these compounds are highly nonselective and can interact, for example, with the functions of plasma membrane and vesicular monoamine transporters [58]. Bunzow et al. [2] have found also that the O-metabolites of catecholamines such as 3-methoxytyramine (3-MT), 4-methoxytyramine (4-MT), normetanephrine, and metanephrine can exert potent TAAR1 agonistic activity. Our group and others also confirmed that 3-MT and 4-MT are potent agonists against human TAAR1 [31, 36]. This observation is particularly intriguing, since 3-MT is a dopamine metabolite formed by the activity of catechol *o*-methyltransferase (COMT) and traditionally has been considered as a compound with no biological activity but only as reflection of extracellular dopamine levels [59]. Our lab studied the potential effect of 3-MT in mice and documented that

3-MT can induce a behavioral activation in a dopamine-independent manner [19]. Central infusion of 3-MT produced mild hyperactivity and a complex set of abnormal movements that were less pronounced in TAAR1-KO mice. Moreover, 3-MT could induce the phosphorylation of ERK and CREB in striatum in a TAAR1-dependent manner [19]. This study indicates that COMT is not simply a metabolizing enzyme, but it may also serve as the rate-limiting step for the production of this novel neuromodulator active at TAAR1. It would be interesting to evaluate the role of 3-MT in behavioral manifestations under conditions where its concentrations are particularly high such as in Parkinson's disease patients with dyskinesia after a long-term treatment with L-DOPA [60].

A recent intriguing study also suggested that food additive ractopamine used to feed livestock in the USA is a full agonist of TAAR1 [61]. It should be underlined that since TAs and most compounds with TAAR1 agonistic activity are not selective and bind also other receptors and transporters [2], it is difficult to study TAAR1 physiology in vivo by analyzing physiological effects of these compounds in normal mice [29]. Until recently, the use of TAAR1-KO mouse line was the only possibility to evaluate TAAR1 contribution in CNS physiology. However, in the last 4 years, several selective full and partial TAAR1 agonists were synthesized and characterized [9–11]. The studies performed with these compounds in various preclinical models supported the idea that TAAR1 could be a novel target for managing psychiatric disorders such as schizophrenia, bipolar disorder, and addiction (see below). Despite the large number of agonists available at the moment, only one antagonist was described. However, poor solubility and brain-blood barrier penetration of this compound gives the possibility to investigate only in vitro effects of TAAR antagonism [8]. To advance pharmacological innovation, two groups attempted to discover the molecular determinants responsible for ligand-receptor interaction for TAAR1 [62–64]. For this purpose, our group developed a theoretical model of the human TAAR1 developed by homology modeling and made docking studies with known TAAR1 agonists finding important amino acid residues for the activity of these ligands [63]. By comparing the derived hTAAR1 model with known models such as of the β2-adrenergic receptor and the 5-HT1a serotonergic receptor, we identified two residues (D103 and N286) as potential anchor points for the ligand recognition process. Also Grandy's laboratory, with mutagenesis studies, described the structural determinants responsible for TAAR1 ligand-binding pockets with respect to amphetamine and methamphetamine and identified a residue responsible for the species stereoselectivity toward D- and L-amphetamine [64]. These studies, along with the screening of new chemical entities, could help in the drug discovery process to find new TAAR1 ligands such as agonists and systemically available antagonists that would improve the comprehension of TAAR1 physiology.

5 TAAR1 as a Novel Drug Target for Psychiatric Disorders

The idea that TAAR1 could be involved in the pathophysiology of psychiatric disorders was initially suggested by the fact that TAs could activate TAAR1. Historically, dysregulated TAs levels have been linked to many human disorders such as schizophrenia, ADHD, Parkinson's disease, migraine, and depression [14, 16, 65, 66]. Clinical studies found elevated PEA plasma levels in schizophrenic patients and increased urinary excretion in paranoid schizophrenics [67, 68]. By looking to its expression pattern in the brain, TAAR1 is well positioned to modulate monoamine systems, and monoamines play a pivotal role in the pathophysiology of many psychiatric disorders [4, 34]. First evidence about the TAAR1 role in brain functions came from the study of the mouse line lacking this receptor. Up to now, three different TAAR1-KO mouse lines have been generated, and substantially similar phenotype has been reported as regards to a supersensitive dopaminergic system and other monoamine-related dysregulations [30, 34, 46]. TAAR1-KO mice do not demonstrate overt phenotype, breed normally, and do not show striking differences in most neurological and behavioral tests versus their wild-type (WT) littermates. However, these mice were found to be more sensitive to the amphetamine-induced behavioral and neurochemical effects. Amphetamine was able to produce an enhanced response in terms of locomotion as well as in terms of dopamine released in the striatum as measured in microdialysis experiments [30, 34, 46]. Another amphetamine compound, MDMA, has been shown to increase dopamine release in the frontal cortex, striatum, and nucleus accumbens at a greater extent in TAAR1-KO mice compared to WT mice [46]. Similar results were obtained for serotonin, with an enhanced release in the striatum and the nucleus accumbens, but not in the frontal cortex. Furthermore, TAAR1-KO mice showed a significant deficit in prepulse inhibition (PPI), indicating an impairment of sensorimotor gating that is known to be deficient in schizophrenic patients [30].

Another feature that links TAAR1 to schizophrenia is the D2 dopamine receptor supersensitivity. In particular, it has been found that TAAR1-KO mice have a greater proportion of D2 dopamine receptors in the high-affinity state compared to WT [30]. As for increased amphetamine responsiveness and PPI deficits, also an increase in D2 dopamine receptor-mediated striatal functions has been traditionally associated with schizophrenia [69]. A direct functional interaction between TAAR1 and D2 dopamine receptor is one of possible mechanisms that might be responsible for the modulation of dopaminergic system by TAAR1. In VTA dopaminergic neurons, stimulation of TAAR1 modulates D2 dopamine autoreceptor activity to decrease D2 receptor activity and promote D2 receptor desensitization [8, 9]. By studying the outward current mediated by D2 receptors, it has been demonstrated that in VTA slices from TAAR1-KO mice or in slices from WT mice treated with the selective TAAR1 antagonist EPPTB, quinpirole desensitization was prevented, and the quinpirole potency was increased by fourfold [8]. On the contrary, the application of *p*-tyramine decreased quinpirole potency. Interestingly, the same type of modulation was found between TAAR1 and 5-HT1A autoreceptors in the dorsal raphe, where TAAR1 is expressed and modulates 5-HT1A activity [9]. Both D2 dopamine and 5-HT1A serotonin autoreceptors are important for the regulation of mood, cognition, and motor behavior and for the response to antidepressant and antipsychotic drugs [70–72]. In the VTA and dorsal raphe, TAAR1 can also modulate the firing rate of dopaminergic and serotonergic neurons, with higher firing frequency in TAAR1-KO animals or in WT mice treated with the antagonist EPPTB being observed [8]. This modulation is independent on cAMP levels and D2 dopamine receptors but mediated by the $G_{\beta\gamma}$ subunits of the activated G protein and resulted in the modulation of the K^+ current mediated by the Kir3-type K^+ channel. D2 dopamine autoreceptor functions are also altered in the nucleus accumbens of TAAR1-KO mice [73]. In fact, in vivo microdialysis and fast-scan cyclic voltammetry (FSCV) studies have revealed that in the nucleus accumbens but not in the dorsal striatum, the basal dopamine release was increased and activation or blockade of TAAR1 could modulate this release. Moreover, with a FSCV paired-pulse approach, it was possible to directly demonstrate that D2 dopamine autoreceptor activity was reduced in TAAR1-KO animals, leading to higher level of second pulse-induced stimulated dopamine release [73]. There is also significant amount of evidence that TAAR1 could have an influence also on postsynaptic D2 dopamine receptors. In an in vitro study, by using a bioluminescence energy transfer (BRET)-based assay, it has been demonstrated that TAAR1 could form a heterodimer with the long isoform of the D2 dopamine receptor [74] that it is known to be mostly expressed at the postsynaptic sites. This heterodimer was sensitive to D2 receptor conformation, and haloperidol, a D2 antagonist, was able to decrease the complex formation. Similarly, haloperidol treatment increased the TAAR1 responses mediated by PEA. This functional interaction of the D2 postsynaptic receptors was also evident in vivo, since haloperidol-induced catalepsy and c-Fos expression in dorsal striatum were reduced in TAAR1-KO animals [74]. Another line of research also focused on a possible influence of TAAR1 on dopamine transporters [5, 33, 41]. Co-expression studies revealed the presence of TAAR1 and DAT in a subset of neurons in the substantia nigra, and experiments done in synaptosomal preparations and cells revealed that TAAR1 can modulate DAT functions [50, 75–77]. It is notably, however, that TAAR1 agonists can effectively block hyperactivity in mice lacking the DAT and no alterations in DA uptake kinetics were found after application of TAAR1 agonists or antagonist in FSCV studies in striatal and accumbal slices [73].

The recent development of TAAR1-selective ligands, particularly full and partial agonists, has been of extremely importance for a better understanding of TAAR1 physiology. Since all the other known TAAR1 ligands possess other important activities (e.g., on DAT), these new selective ligands provided the first opportunity to understand the consequence of TAAR1 activation in experimental animal models. As the absence of TAAR1 results in a supersensitive dopaminergic system, TAAR1 activation negatively regulates dopamine system, decreasing an excess of dopaminergic activation, either obtained with pharmacological treatment or present in genetic animal models [9–11]. Moreover, TAAR1 agonists influence also the serotonergic system, and for these reasons, they have been proposed as possible treatment for diseases such as schizophrenia, bipolar disorder, depression, and drug abuse [6, 10]. Two full agonists and two partial agonists have been tested in various studies, and although a substantially similar profile was found between these compounds, there are also some important differences between full and partial agonists. TAAR1 activation reduces hyperlocomotion induced by pharmacological treatment with the DAT inhibitor cocaine or with the NMDA receptor antagonists L-687,414 and PCP as well as spontaneous hyperlocomotion present in DAT-KO mice or in NR1 knockdown mice [9–11]. Both hyperdopaminergia and hypoglutamatergia are considered to model schizophrenia endophenotypes and represent the two main hypotheses for the etiology of schizophrenia. Thus, these data indicate that TAAR1 activation can reduce what are considered as the positive symptoms in different pharmacological and genetic model of schizophrenia [11]. Interestingly, both full and partial agonists can potentiate the effect of two atypical antipsychotics olanzapine and risperidone in these behavioral paradigms suggesting also that TAAR1 agonists are potential add-on treatment to current antipsychotics [11]. TAAR1 treatment seems not to produce extrapyramidal side effects, and partial TAAR1 agonist can in fact reduce haloperidol-induced catalepsy, suggesting that under certain conditions such as deficient dopamine transmission caused by D2 dopamine receptors blockade, TAAR1 partial agonist might behave as an antagonist [11]. In contrast to olanzapine and other atypical antipsychotics that lead to weight gain, these compounds do not possess this side effect, but rather they can reduce the weight gain induced by a chronic treatment with olanzapine.

Furthermore, pharmacological magnetic resonance imaging (phMRI) study has revealed that, while differences exists, both full and partial TAAR1 agonists share a similar pattern with olanzapine in terms of brain region activation pattern including the prefrontal area, suggesting a potential role of TAAR1 in prefrontal cortical-related functions such as cognition. In fact, TAAR1 agonists can improve cognitive performance in the object retrieval paradigm in monkeys increasing the percentage of correct responses [11]. Similarly, in rats, TAAR1 agonist can revert the deficit induced by PCP in the attentional set-shifting test. Since TAAR1 is known to influence serotonin system, potential antidepressant and anxiolytic properties of these compounds have been also explored [9]. While only the partial agonists were effective in the forced swim test in rats, both the partial and full agonists showed antidepressant effect in monkeys in the differential reinforcement of low-rate behavior paradigm [10, 11]. Moreover, TAAR1 activation induced anxiolytic-like behaviors in the stress-induced hyperthermia test further indicating that TAAR1 modulation of serotonergic system could be of importance in mood disorders [10]. These data strongly support the idea that TAAR1 could be considered as a new multifaceted target to treat neuropsychiatric diseases such as schizophrenia and mood disorders. Intriguingly, the partial TAAR1 agonist, while showing a similar profile to the full agonist, has at the same time some peculiar differences such as the ability to reduce the haloperidol-induced catalepsy. It also can increase the firing activity in VTA dopaminergic neurons like the selective TAAR1 antagonist EPPTB [8]. This suggests that under certain conditions a basal TAAR1 activation by natural ligands is present and that TAAR1 partial agonist could decrease or increase dopamine-related behavior depending on the rate of dopaminergic activity.

Moreover, partial TAAR1 agonist at high doses was able to promote wakefulness, like caffeine, as a stimulating compound further indicating this putative "stabilizing" property [10, 11]. Whether TAAR1 partial activation might be more useful for the treatment of mood and anxiety disorders and the full TAAR1 agonist in others such as schizophrenia remains to be tested, but it would be very interesting to further understand in detail the differences between these compounds.

A recent study explored the possibility that apomorphine, a prototypical D1 and D2 dopamine receptor nonselective agonist, might exert its behavioral actions in part via TAAR1 activation [78]. Following an initial observation by Bunzow et al., this study confirmed that apomorphine is a partial agonist at rat and mouse TAAR1 with little activity at human and cynomolgus monkey TAAR1. While the lack of TAAR1 did not influence the locomotor behavior induced by apomorphine at low doses, apomorphine-induced climbing behavior and stereotypies were reduced in TAAR1-KO mice. Interestingly, when WT mice were injected with a TAAR1 agonist in combination with a D1 and D2 dopamine receptor selective agonists, they could reproduce a level of climbing behavior similar to what was obtained with apomorphine. Since apomorphine-induced climbing has been used for decades as the screening test for new antipsychotics [79], this study suggests that not only dopamine receptors but also TAAR1 could be in part responsible for this apomorphine effect, and compounds with putative antipsychotic activity identified by using this test could have also TAAR1 activity.

6 Role of TAAR1 in Addiction

Since TAAR1 has a strong connection to the dopaminergic system, it has been suggested that TAAR1 could have a role in addiction. Moreover, the evidence that several amphetamines, known to be addictive substances, were able to activate TAAR1, led the speculation that at least some of their effects could be mediated via TAAR1. Addictive drugs modulate brain functions in several ways, but all of them seem to have a unifying property that is to enhance mesolimbic dopamine neurotransmission [80]. The major ways to modulate synaptic dopamine levels are either influence on neuronal firing, interference with the reuptake of dopamine through DAT, or alterations in the presynaptic regulation at the level of terminals [80]. As described above, there is evidence that TAAR1 can potentially influence all of these processes. Particularly, TAAR1 has been reported to influence the firing of VTA dopaminergic neurons [34] and alter the function of presynaptic D2 dopamine receptors in nucleus accumbens [73], the brain region particularly important for addiction. TAAR1-KO mice that generally have a supersensitive dopaminergic system seem more incline to addictive properties of substances of abuse. In a study by Achat-Mendes et al. [81], the psychomotor and rewarding properties of methamphetamine were evaluated in WT and TAAR1-KO mice. Both single and repeated treatment with methamphetamine was able to produce an enhanced locomotor response in TAAR1-KO mice. Moreover, in conditioned place preference

(CPP) experiments, TAAR1-KO mice acquired the methamphetamine-induced CPP earlier than WT and retained CPP longer as evaluated by extinction training [81]. Interestingly, no difference between WT and KO for CPP induced with morphine was observed.

Another study evaluated the potential involvement of TAAR1 in alcohol abuse [82]. Using a two-bottle choice paradigm, this study showed that TAAR1-KO mice have a greater preference and consume more ethanol than WT counterparts, without difference in consumption of sucrose solution. Similarly, the sedative-like effects after ethanol consumptions were enhanced and lasted longer. These data suggest a potential role for TAAR1 in alcohol abuse disorder indicating the necessity of further studies to evaluate effects of TAAR1-selective drugs in alcohol-induced behaviors.

More evidence exists regarding potential utility of TAAR1-based drugs in cocaine addiction. The first study that was performed few years ago focused on evaluation of effects of TAAR1 agonist on cocaine self-administration in rats [10]. Using this well-validated experimental model of drug addiction, Revel et al. [10] demonstrated that partial TAAR1 agonist, dose-dependently, reduced cocaine intake in rats with a history of cocaine self-administration. Importantly, TAAR1 partial agonist did not influence lever pressing behavior in control subjects. Recently, two articles have been published regarding cocaine abuse-related effects in rats. In the first study, both partial and full agonists were studied in connection with models of cocaine relapse [7]. Context-induced renewal of drug seeking is considered close to real-life situations, since addicts often go under relapse, because they re-experienced the same context associated to past drug intake [83]. Rats with a history of cocaine self-administration went into abstinence without extinction and then put back into the same context, where they had cocaine self-administration. While saline control animals showed robust relapse to drug seeking, the treatment with both partial and full agonists dose-dependently reduces drug seeking. Importantly, at the doses used, TAAR1 agonists had no influence on a lever pressing task maintained by food. In another model of cocaine-primed reinstatement, where after extinction rats were injected by single dose of cocaine to induce relapse, TAAR1 partial agonist was able to completely block the cocaine-primed reinstatement of cocaine seeking [7]. Regarding the mechanism of action, it is shown that TAAR1 activation reduces the dopamine release induced by cocaine, as measured by FCSV in the nucleus accumbens, without altering the DAT functions, suggesting an involvement of other mechanisms than direct interference with dopamine uptake such as the alteration of D2 receptors activity [7]. In another study, TAAR1 partial agonist has been used to reduce several cocaine-mediated behaviors [12, 84]. First, TAAR1 agonist administration reduced the expression of cocaine behavioral sensitization. Moreover, in a CPP paradigm, TAAR1 agonist was able to reduce the expression but not the development of the CPP. Thus, while when administered prior to cocaine conditioning, TAAR1 agonist did not modify the development of the CPP, it could reduce the expression of the already established CPP when administered prior to the test session. Also in a model of cocaine relapse, the cocaine-primed reinstatement of cocaine seeking, TAAR1 activation reduced the relapse of the cocaine-seeking behavior [12]. Altogether, these data indicate that TAAR1 activation reduces the sensitizing, rewarding, and reinforcing effects of cocaine and TAAR1 should be explored further as a potential target for the treatment of cocaine addiction.

7 Role of TAARs in Periphery

As described above, TAARs and in particular TAAR1 are expressed in many peripheral organs. TAs effects on cardiovascular system and their pressor action have been known for many years [14], but it is evident that these actions most likely have to be attributed to their "false transmitter" properties. However, the fact that TAAR1, as well as other TAAR members, is expressed in the heart raised many questions about its putative role in this organ. T1AM and T0AM are endogenous compounds found in brain extracts and also in periphery [45, 54]. They can activate potently TAAR1 in vitro and produce important physiological responses when injected to animals. As described in several studies, thyronamines induce a behavioral suppression with locomotor inhibition, ptosis, reduced metabolic rate, hypotension, and hypothermia [45, 54, 56, 85]. All these effects were dose-dependent and reversible in few hours after the administration of these compounds. Of particular importance, the cardiac effects produced by thyronamines T1AM and T0AM, when injected in mice, induced a drop in the heart rate and a similar response in isolated heart preparation [45, 54]. T1AM, in ex vivo experiments and in cardiomyocytes from rats, produced a dose-dependent negative chronotropic and inotropic effects further confirming thyronamine action on heart physiology [45]. Whether TAAR1 is solely responsible for these actions or other mechanisms are involved has still to be established, since thyronamines have also activity at the monoamine membrane transporter and vesicular monoamine transporter 2 [58]. Regarding temperature control, one study showed that the hypothermic response obtained by the administration of thyronamines and other TAAR1 ligands such as amphetamines was similar in WT and in TAAR1-KO mice, suggesting that the mechanism other than involving TAAR1 was responsible for this effect [86]. On the other hand, Millan group monitored the effect of MDMA at different time points in WT and TAAR1-KO animals [46]. In WT mice, MDMA induced a biphasic thermoregulatory response, with an initial hypothermia followed by a gradual hyperthermia. In contrast, TAAR1-KO mice experienced only a hyperthermic response, suggesting that TAAR1 could have a role in thermoregulation, although more studies are necessary to understand the precise mechanism of this effect.

The first evidence that certain TAARs are expressed in leukocytes comes from the study by Nelson et al. [87]. Further studies confirmed the presence of several TAAR members in human, mouse, and rhesus monkey leukocytes [38, 43, 44]. The fact that compounds that target monoamine receptors and transporters such as ecstasy (MDMA) could influence the functions of leukocytes and affect immune response [88, 89] led to the idea that TAARs might be involved in this process. By

Western blot technique, it has been shown that TAAR1 is expressed in normal and malignant B cells derived from patients with several diseases [43]. TAAR1 was more expressed in activated B cells compared to resting ones confirming already published data [87]. Moreover, several TAAR1 agonists induced cytotoxicity in these cells suggesting a potential use for these compounds in the treatment of blood diseases such as leukemias and lymphomas. Also in rhesus monkey lymphocytes, TAAR1 expression was increased after immune activation, and methamphetamine induced a TAAR1-dependent signaling through PKA and PKC phosphorylation [44]. A recent interesting study focused on human blood leukocytes and TAAR1-/TAAR2-mediated functions [38]. Krautwurst et al. found that TAAR1, TAAR2, TAAR5, TAAR6, and TAAR9 were expressed in different leukocyte types including PMN, T cells, B cells, NK cells, and monocytes [38]. Among them, TAAR1 and TAAR2 were the most abundant receptors, with a similar expression profile, and while all TAAR1-expressing cells co-expressed also TAAR2, there was some percentage (16%) of cells that expressed only TAAR2. Interestingly, PEA, tyramine, and T1AM were able to induce several activities at very low concentration, in the low nanomolar range, which reflects the endogenous levels of these TAs [38]. TAAR1/TAAR2 activation triggered chemotactic migration of PMN cells in a concentration-dependent manner. Importantly, when TAAR1 and TAAR2 were downregulated with siRNA, this response was largely abolished. PEA was also able to induce, in a TAAR1-/TAAR2-dependent way, the IL-4 secretion in T cells and to modulate the expression of several genes, with chemotactic chemokine CCL5 being the highest expressed gene, which plays a role in allergy. Finally, TAAR1/2 activation mediated the secretion of IgE from B cells. These data suggest that TAs could play a previously unappreciated important role in immune-mediated functions (through cells migration, cytokine, and IgE productions) at concentrations found normally in the blood that could be easily increased simply by the ingestions of some type of food. Thus, these observations suggest a role of TAARs in mechanisms involved in food-related allergy.

Conclusions

Since the discovery of TAARs and particularly TAAR1, many studies have been performed to understand their physiology. It is now evident that TAAR1 has a primary role in the modulation of monoaminergic systems, in particular dopamine. Both the studies on TAAR1-KO mice and the recent development of selective ligands demonstrate that TAAR1 generally behaves as a “brake” for dopamine neurotransmission decreasing a hyperactive dopaminergic system. It is interesting to note that partial TAAR1 agonists can act also as antagonists, depending on the context, and in these cases, as for haloperidol-induced catalepsy, they seem to counteract a hypofunctional dopamine signaling. Thus, it might be expected that TAAR1 partial agonists could behave as dopamine system stabilizer, although more studies are necessary to

(continued)

uncover the mechanisms of this phenomenon. This panel of actions on dopamine physiology indicates that TAAR1 could be a novel target to treat dopamine-related disorder such as schizophrenia and addiction. On the other hand, TAAR1 activity on serotonergic system suggests that TAAR1 is able to modulate also phenotypes related to mood disorders such as depression and bipolar disorder. While there is now strong evidence of TAAR1 role in several experimental models either in mouse, rat, or nonhuman primates, to fully validate TAAR1 role in brain physiology, it will be of great importance to have a proof of concept in humans. Another interesting point would be to extend this line of research to other aspects related to brain physiology, such as cognition, since it is likely that TAAR1 could be involved also in cognition-related brain functions. Finally, important TAAR functions in periphery are emerging, and detailed descriptions of these mechanisms will be necessary to uncover these intriguing new roles of TAARs.

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