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Pharmacology of human trace amine-associated receptors: Therapeutic opportunities and challenges☆

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ABSTRACT

The discovery in 2001 of a G protein-coupled receptor family, subsequently termed trace amine-associated receptors (TAAR), triggered a resurgence of interest in so-called trace amines. Initial optimism quickly faded, however, as the TAAR family presented a series of challenges preventing the use of standard medicinal chemistry and pharmacology technologies. Consequently the development of basic tools for probing TAAR and translating findings from model systems to humans has been problematic. Despite these challenges the last 5 years have seen considerable advances, in particular with respect to TAAR1, which appears to function as an endogenous rheostat, maintaining central neurotransmission within defined physiological limits, in part through receptor heterodimerization yielding biased signaling outputs. Regulation of the dopaminergic system is particularly well understood and clinical testing of TAAR1 directed ligands for schizophrenia and psychiatric disorders have begun. In addition, pre-clinical animal models have identified TAAR1 as a novel target for drug addiction and metabolic disorders. Growing evidence also suggests a role for TAARs in regulating immune function. This review critically discusses the current state of TAAR research, highlighting recent developments and focussing on human TAARs, their functions, and clinical implications. Current gaps in knowledge are identified, along with the research reagents and translational tools still required for continued advancement of the field. Through this, a picture emerges of an exciting field on the cusp of significant developments, with the potential to identify new therapeutic leads for some of the major unmet medical needs in the areas of neuropsychiatry and metabolic disorders.

Contents

Abbreviations: 2-AI, 2-aminoindane; 2C-B, 2,5-dimethoxy-4-bromophenethylamine; 5-IAI, 5-iodo-2-aminoindane; COMT, catechol-O-methyl transferase; CPP, conditioned place preference; DAT, dopamine transporter; DIO, diet-induced obese; DMT, *N*,*N*-dimethyltryptamine; EAAT2, excitatory amino acid transporter 2; EPPTB, *N*-(3-ethoxyphenyl)-4-pyrrolidin-1-yl-3-trifluoromethylbenzamide (RO5212773); FMO3, flavin-containing monooxygenase 3; GirK, G protein-coupled inwardly-rectifying potassium; GLP-1, glucagon like peptide 1; GPCR, G protein-coupled receptor; IUPHAR, International Union of Basic and Clinical Pharmacology; LSD, lysergic acid diethylamide; m-CPP, *m*-chlorophenylpiperazine; MDMA, 3,4-methylenedioxymethamphetamine; NC-IUPHAR, International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification; PANSS, positive and negative symptom scale; phMRI, pharmacological magnetic resonance imaging; SNpc, substantia nigra pars compacta; TAAR, trace amine-associated receptor; VTA, ventral tegmental area.

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1. Introduction

Interest in the therapeutic potential of trace amines has spanned over 50 years. The term trace amine was originally coined to represent any endogenous (mono)amine with physiological levels below 100 ng/g tissue (Boulton, 1974), approximately two orders of magnitude lower than the aminergic neurotransmitters dopamine, noradrenaline, and serotonin (Berry, 2004; Grandy, 2007). As initial trace amine research focussed largely on *p*-tyramine, 2-phenylethylamine, and to a lesser extent tryptamine and *p*-octopamine, the term subsequently became synonymous with these compounds. These initial research efforts stalled, however, through a combination of a focus on the "false neurotransmitter", amphetamine-like, indirect sympathomimetic action of *p*-tyramine and 2-phenylethylamine at plasma membrane monoamine transporters, and the lack of a receptor target for other effects. Consequently, by the early-1990s virtually all trace amine research had ceased. This changed 15 years ago when two groups independently identified a family of G protein-coupled receptors (GPCRs), a sub-set of which were selectively activated by *p*-tyramine and 2-phenylethylamine, with tryptamine and *p*-octopamine also showing agonistic activity (Borowsky et al., 2001; Bunzow et al., 2001). As will be discussed in subsequent sections, current research suggests, however, that a return to the original intent of the term trace amine is warranted, as additional receptor family members are activated by endogenous amines outside of the more narrow definition of trace amines that has come into general use.

Another area of contention relates to the multiple terminologies that have been used to describe these receptors. Following their initial discovery different groups employed different nomenclature systems, with the receptor family variously referred to as TA (Borowsky et al., 2001), TAR (Bunzow et al., 2001), and TRAR (Duan et al., 2004), and little consistency in the numbering of individual subtypes. This was resolved in 2005, when a unifying nomenclature, trace amine-associated receptors (TAARs), was proposed (Lindemann et al., 2005). The TAAR classification was supported by a strong rationale based on genomic organization, gene sequences, and phylogenetic relationships between different family members, which has subsequently been independently verified by multiple groups (Azzouzi, Barloy-Hubler, & Galibert, 2015; Eyun, Moriyama, Hoffmann, & Moriyama, 2016; Gao et al., 2016; Hashiguchi & Nishida, 2007; Hussain, Saraiva, & Korsching, 2009; Libants et al., 2009; Tessarolo, Tabesh, Nesbitt, & Davidson, 2014; Vallender, Xie, Westmoreland, & Miller, 2010). Further, the proposed nomenclature recognized the important confound that not all family members responded to the classical, limited group of trace amines. It is thus not surprising that the TAAR nomenclature proposed by Lindemann and colleagues has been widely accepted, and is now more or less the default nomenclature used within the literature. Despite the uniform use of the TAAR system for over a decade by those active in the field, currently the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) has adopted TA_1 as the name of the only family member that has been de-orphanized (Alexander et al., 2015; Maguire et al., 2009). This is based partly on the argument and adherence to convention that the names of receptor proteins be based on the name of the endogenous ligand. Unfortunately this is prone to confusion with the original TA designation (Borowsky et al., 2001), whose numbering of individual family members was not based on a full phylogenetic analysis. For example TA_2 and TA_4 of Borowsky *et al.* corresponds to TAAR4 and TAAR6 respectively of Lindemann and colleagues. For consistency and clarity it is necessary to resolve this discrepancy through renewed dialogue between the leading researchers in the trace amine field and IUPHAR. Consistent with the current practices in the trace amine field we have used the nomenclature proposed by Lindemann *et al.* (2005) throughout this review.

Even with a family of receptors identified initial progress in the field was slow. Researchers struggled to come to grips with many unique and challenging aspects of TAARs including low expression levels (Babusyte, Kotthoff, Fiedler, & Krautwurst, 2013; Borowsky et al., 2001; Dinter, Muhlhaus, Wienchol et al., 2015; Ito et al., 2009; Raab et al., 2016; Revel et al., 2013), high species variability in the functional TAAR complement (Eyun et al., 2016; Gloriam, Bjarnadottir, Schioth, & Fredriksson, 2005; Hashiguchi & Nishida, 2007), preferential intracellular location of the receptors (Bunzow et al., 2001; Miller et al., 2005; Raab et al., 2016), broad ligand tuning of the receptors (Bunzow et al., 2001; Ferrero et al., 2012; Pacifico, Dewan, Cawley, Guo, & Bozza, 2012; Saraiva et al., 2016; Zhang, Pacifico, Cawley, Feinstein, & Bozza, 2013), and the lack of a single consensus ligand that defines the family as a whole (Ferrero et al., 2012; Lindemann et al., 2005). These, and other factors, have conspired to make TAARs resistant to traditional medicinal chemistry approaches, frustrating and confounding researchers, and leading to the receptors being referred to in such colourful terms as 'iconoclast' (Grandy, 2007) and 'protean' (Burchett & Hicks, 2006). Despite these challenges being identified as long ago as 2005 (Lindemann & Hoener, 2005), the development of high quality, commercially available, selective reagents to further probe the system has been slow, further hindering progress. Through the dedicated work of a small number of groups these limitations have now begun to be overcome. This entire group was brought together for the first time at the 23rd International Stress & Behaviour Conference (St. Petersburg, Russia) in May 2016. From this meeting genuine optimism emerged that the TAAR field is on the cusp of significant breakthroughs, including identifying new therapeutic targets for some of the largest unmet medical needs. Such developments are the focus of the current article. While a brief background to the field is provided, we will focus on the recent developments that have occurred since 2010, while also identifying the challenges that still remain to be addressed. For a more thorough discussion of the history and background to the trace amine field the reader is referred to earlier excellent and thorough review articles that link the earlier trace amine work to the initial characterization of TAARs (Berry, 2004; Grandy, 2007). Since this review focuses on the therapeutic potential of TAAR we will primarily restrict discussion to those TAARs for which there is a functional human isoform.

2. The Human TAAR Family

TAARs are a family of vertebrate, rhodopsin-like, type A, GPCR (Borowsky et al., 2001; Bunzow et al., 2001). Although up to 26 subtypes of TAAR have been identified in mammalian species (Eyun et al., 2016; Hashiguchi & Nishida, 2007; Hussain et al., 2009), they all belong to nine sub-families (TAAR1-9) (Gloriam et al., 2005; Hashiguchi & Nishida, 2007; Lindemann et al., 2005). Within these nine sub-families repeated species specific expansions and pseudogenization events have occurred giving rise to species-specific isoforms and a large variation in the functional TAAR complement present between species (Eyun et al., 2016; Shi et al., 2016; Vallender et al., 2010). Humans express a single functional variant of 6 of the TAAR family members (TAAR1, 2, 5, 6, 8 and 9) (Table 1), with TAAR3, 4 and 7 subtypes appearing to be pseudogenes (Lindemann et al., 2005). Consequently, while there is a body of literature concerning the physiology and pharmacology of TAAR3, 4, and 7 in typical laboratory species, this will not be discussed in the current review. The key features of the human TAAR family that are expanded upon throughout this manuscript are summarized in Table 1.

2.1. Human TAAR genes

In mammals, TAAR genes are arranged as a single cluster on an individual chromosome, with the human cluster mapping to chromosome 6q23.2 (Borowsky et al., 2001; Bunzow et al., 2001). This position may have therapeutic relevance as it coincides with a putative susceptibility locus for schizophrenia (Cao et al., 1997; Kaufmann et al., 1998; Levinson et al., 2000) and affective disorders (Venken et al., 2005).