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## **Commentary**

# A Decade of Pharma Discovery Delivers New Tools Targeting Trace Amine-Associated Receptor I

## Katie R Tallman and David K Grandy\*,1

Department of Physiology & Pharmacology, School of Medicine, Oregon Health & Science University, Portland, OR, USA

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In this issue of *Neuropsychopharmacology*, scientists from the F. Hoffmann-La Roche pharmaceutical company report results of studies involving a new line of transgenic mice overexpressing trace amine-associated receptor 1 (TAAR1) in neurons and a new selective TAAR1 partial agonist, RO5073012. Both were developed and characterized as part of a human TAAR1 medication development program.

TAAR1 made its debut in 2001 as the trace amine receptor almost a century after the first experiments involving the prototypic trace amine,  $\beta$ -phenylethylamine (PEA), were reported (Barger and Walpole, 1909). Since then, the discovery of a specific receptor for PEA is unquestionably the most significant development in the field because it fundamentally transformed our understanding of how this so-called 'false transmitter' and other TAAR1 agonists, including amphetamine, methamphetamine, methylene-dioxymethamphetamine (ecstasy), and 3-iodothyronamine, influence metabolism, physiology, and behavior at the molecular level (Grandy, 2007).

It has long been known that brain levels of PEA are altered in a number of disorders involving monoaminergic systems, including depression, schizophrenia, Parkinson's disease, and attention deficit hyperactivity disorder. However, a compelling mechanism for PEA's effects was lacking (Grandy, 2007). TAAR1's discovery and the few studies documenting its expression suggest it is well positioned to influence cognition, mood, motivated behaviors, and movement (Grandy, 2007). From this perspective, it is perhaps not surprising that Hoffmann-La Roche has invested significant resources in an effort to exploit TAAR1 as a promising target for the development of novel medications to treat a range of psychiatric disorders.

While still an orphan receptor, alignment of its amino acid sequence with other G protein-coupled receptors revealed TAAR1 shares considerable identity with the  $G\alpha_s$ -coupled  $\beta_2$  adrenergic receptor (Grandy, 2007). Subsequent *in vitro* studies confirmed TAAR1's coupling to

mediated signaling at the cellular level influences physiology and ultimately the behavior of wild-type animals has proven more challenging (Ledonne *et al*, 2011; MJ Beckstead, personal communication). Similarly, some report TAAR1 expression in dopamine- and serotonin-producing brain areas (Revel *et al*, 2012a; Revel *et al*, 2011; Xie *et al*, 2007), whereas others have had difficulty replicating these observations (Ledonne *et al*, 2011; Liberles and Buck, 2006). To fully understand the role(s) of TAAR1-mediated signaling in health and disease, these disparate experimental findings must be reconciled. Enlightenment will likely depend on the development and widespread availability of TAAR1-selective small molecules, antibodies, and lines of TAAR1-overexpressing and knockout mice.

Gα<sub>s</sub>. However, reaching a consensus as to how TAAR1-

In the course of their TAAR1 medication development effort, Hoffmann-La Roche has publically disclosed the first and so far only TAAR1-selective antagonist, EPPTB; the first TAAR1-selective agonist (RO5166017; Revel et al, 2011); and the partial agonists RO5203648 (Revel et al, 2011) and RO5073012 (Revel et al, 2012a). They have also reported the development of two lines of genetically engineered mice, one lacking TAAR1 and the other overexpressing TAAR1 in neurons (this issue of NPP). Their studies involving TAAR1 knockout mice reveal an elevated spontaneous firing frequency of midbrain dopamine neurons and a hypersensitivity to amphetamine (Revel et al, 2011). At face value, these data suggest TAAR1-mediated signaling normally exerts an inhibitory tone on dopamine neuron activity. Wolinsky et al (2007) independently reached a similar conclusion.

To further test the effect of TAAR1-mediated signaling on dopamine neuron activity, Revel et al explored TAAR1-mediated hyper-signaling with mice overexpressing TAAR1, and report their findings in this issue of Neuropsychophar-macology. Contrary to what was expected, TAAR1 transgenic mice do not display behavioral abnormalities under baseline conditions. Despite higher-than-normal extracellular levels of dopamine, noradrenaline, and serotonin compared with their wild-type littermates, they also do not show significant aberrations in monoamine synthesis or the number of dopamine receptors or transporters. Although they attribute the altered monoamine levels to increased firing rate of neurons expressing TAAR1, it is important to

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remember developmental compensation can occur in genetically altered animals, potentially confounding a straightforward interpretation of the data.

Another unexpected finding is TAAR1-overexpressing mice display an apparent hyposensitivity to acute amphetamine exposure, reported as a lack of enhanced locomotor activity and unaltered monoamine release in the nucleus accumbens. Interestingly, when a single dose (10 mg/kg, p.o.) of the TAAR1-selective partial agonist RO5073012 is administered to the TAAR1 overexpressors, their sensitivity to the locomotor stimulatory effects of amphetamine is restored. What is not discernable from the behavioral data presented is whether the apparent lack of amphetamineinduced activity in the overexpressors could be owing to stereotypic behaviors suppressed by RO5073012 treatment. It would also be of interest to know whether another TAAR1 partial agonist (RO5203648; Revel et al, 2012b) has the same effect in this animal model. It seems unlikely such accomplished scientists would not have compared both partial agonists in each study; so if such data exist, would there be any reason not to report them?

These days, pharmaceutical companies are investing their resources more cautiously than ever. Consequently, Hoffmann-La Roche and their team of creative scientists are to be commended for developing the first TAAR1-selective small molecules and lines of genetically engineered mice as they pursue TAAR1 as a medication target. However, drug companies are in business to make a profit, and so the research they conduct—and report—must support this primary goal. In contrast, academic research is rarely motivated by profit, so studies can be conceived of, experiments conducted, and data publically reported in the spirit of discovery, with full disclosure and without a financial conflict of interest.

In the past, emerging areas of neuroscience benefitted from contributions made by researchers in industry and academia. Unfortunately, this has not been true for TAAR1 over the past decade. In fact, TAAR1-related research is nearly at a standstill because of limited funding from the National Institutes of Health and other nonprofit entities. In the future, this will hopefully improve, in part due to Revel et al's two most recent publications, which will draw

the attention of grant reviewers, funding agencies, and health policy makers to this exciting and important area of neuroscience research.

### **DISCLOSURE**

The authors declare no conflict of interest.

#### REFERENCES

Barger G, Walpole GS (1909). Isolation of the pressor principles of putrid meat. *J Physiol* **38**: 343–352.

Grandy DK (2007). Trace amine-associated receptor 1—family achetype or iconoclast? *Pharmacol Ther* 116: 355–390.

Ledonne A, Berretta N, Davoli A, Rizzo GR, Bernardi G, Mercuri NB (2011). Electrophysiological effects of trace amines on mesence-phalic dopaminergic neurons. *Front Syst Neyrosci* 5: 1–5.

Liberles SD, Buck LB (2006). A second class of chemosensory receptors in the olfactory epithelium. *Nature* 442: 645–650.

Revel FG, Meyer CA, Bradaia A, Jeanneau K, Calcagno E, André CB et al (2012a). Brain-specific overexpression of trace amine-associated receptor 1 alters monoaminergic neurotransmission and decreases sensitivity to amphetamine. Neuropsychopharmacology 37: 2580–2592.

Revel FG, Moreau JL, Gainetdinov RR, Bradaia A, Sotnikova TD, Mory R et al (2011). TAAR1 activation modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypogluatmatergic activity. Proc Natl Acad Sci USA 108: 8485–8490.

Revel FG, Moreau JL, Gainetdinov RR, Ferragud A, Velázquez-Sánchez C, Sotnikova TD *et al* (2012b). Trace amine-associated receptor 1 partial agonism reveals novel paradigm for neuropsychiatric therapeutics. *Biol Psychiatry*; e-pub ahead of print 15 June 2012 (in press).

Wolinsky TD, Śwanson CJ, Smith KE, Zhong H, Borowsky B, Seeman P *et al* (2007). The trace amine 1 receptor knockout mouse: an animal model with relevance to schizophrenia. *Genes Brain Behav* **6**: 628–639.

Xie Z, Westmoreland S, Bahn ME, Chen GL, Yang H, Vallender EV et al (2007). Rhesus monkey trace amine-associated receptor 1 signaling: enhancement by monoamine transporters and attenuation bt the D2 autoreceptor in vitro. J Pharmacol Exp Ther 321: 116–127.