TAAR1 transforms thinking about a plant alkaloid that transformed the practice of medicine

David K. Grandy
Department of Physiology & Pharmacology, School of Medicine and the Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA

Received 1 May 2014; Reviewed 2 May 2014; Revised 1 May 2014; Accepted 2 May 2014;
First published online 5 June 2014

Key words: Apomorphine, dopamine, Parkinson’s Disease, mouse, trace amine.

In this issue of the Journal Sukhanov et al., report their experimental results in support of the hypothesis: trace amine-associated receptor 1 (TAAR1) mediates apomorphine’s effects in mice – in particular, climbing activity.

For many familiar with this alkaloid the conclusions reached by these authors come as a surprise. After all, apomorphine is one of the oldest and most studied dopamine receptors, in particular those of the D2 subtype (Bonuccelli and Pavese, 2007).

However, this relatively simple scenario became more complicated in 2001 when Bunzow et al. (2001) reported that at 1 µM R(−)- but not S(+) - apomorphine is nearly a full agonist of an orphan rat Gαs-coupled receptor that is also activated by the non-catecholic biogenic trace amines β-phenylethylamine and p-tyramine as well as amphetamine and 3-iodothyronamine and now referred to as trace amine-associated receptor 1 (TAAR1; Grandy, 2007). Six years later Wainscott et al. (2007) evaluated more than 70 biogenic amines with respect to their ability to stimulate cAMP production by activating human and rat species of TAAR1 heterologously expressed in vitro. Included in their Table 5 is the surprising result: R(−)-apomorphine is not an agonist of human TAAR1. Neither this unexpected species difference nor the question of whether apomorphine even binds to the human receptor were discussed by the authors.

To be fair, at the time the radiolabelled ligands needed to assess apomorphine binding to human and rat species of TAAR1 did not exist. It was not until 2009 when scientists working for Hoffmann-La Roche reported the characterization of the first TAAR1-selective antagonist, EPPTB (Bradaia et al., 2009). With the company’s considerable resources behind the effort their drug discovery team mapped out the chemical space around the receptor’s putative ligand binding pocket and identified agonists and partial agonists selective for rodent and primate species of TAAR1 (Galley et al., 2012). It is the recent availability of these ligands in labelled form, together with a line of mice genetically engineered to lack the taar1 gene (Wolinsky et al., 2007) that enabled Sukhanov et al. (2014) to conduct their study.

Using tritiated forms of Hoffmann-La Roche’s selective agonists for rodent (3H-R05166017) and primate (3H-R05192022) species of TAAR1, Sukhanov et al. (1) show R(−)-apomorphine binds to mouse, rat, human
and monkey species of TAAR1 expressed in HEK 293 cells with Ki’s of 0.373±0.04 μM, 0.369±0.03 μM, 0.698 μM, and 3.639±0.33 μM, respectively. They then go on to show apomorphine fails to functionally activate human TAAR1 expressed in vitro, confirming the finding of Wainscott et al., while acting as a partial agonist, with respect to β-phenylethylamine, of the mouse (59%) and rat (79%) species of the receptor with EC50’s of 2.493±0.3 μM and 0.985±0.07 μM, respectively, in agreement with Bunzow et al. (2001) and Wainscott et al. (2007).

Having convincingly demonstrated apomorphine is a partial agonist of mouse TAAR1 Sukhanov et al., next explored the contribution of apomorphine-activated TAAR1-mediated signalling to its behavioural effects in wild type and taar1−/− C57Bl/6 mice. As the authors point out apomorphine-induced climbing in the mouse has been used for decades to screen for compounds with potential as antipsychotic medications. Since dopamine D2 receptor antagonists block apomorphine-induced climbing in mice it is significant that apomorphine’s effect on this behaviour was less pronounced in TAAR1-deficient mice compared to intact animals. Mice lacking both taar1 genes also displayed significantly less apomorphine-induced licking than wild type mice while its effects on sniffing and gnawing were the same in both genotypes. In their final study Sukhanov et al., address the possibility that the developmental lack of TAAR1-mediated signalling could result in multiple compensatory changes, one of which that manifests as an impaired climbing phenotype in response to apomorphine. Using a combination of dopamine D1 (SKF38393) and D2 (quinpirole) receptor agonists alone and in combination with the rodent-selective TAAR1 agonist R05166017 they find all three ligands produce significantly more climbing activity in wild type mice than is produced by any of the three drugs alone or in pairwise combination. This result is consistent with the interpretation that TAAR1-mediated signalling contributes to apomorphine-induced climbing in mice.

In summary, the results reported by Sukhanov et al., are important for several reasons. First, they confirm there are significant differences between rodent and human species of TAAR1 with respect to whether apomorphine is an agonist. Rather than disqualifying TAAR1 from further investigation as a target of human medication development this knowledge provides behavioural pharmacologists with information critical to the design and interpretation of their drug screening experiments – past and present. Second is their finding apomorphine competes with [3H] R05192022 for binding to heterologously expressed human TAAR1 but does not stimulate human TAAR-mediated signalling in vitro. The authors do not address this possibility but the simplest interpretation of these results is that apomorphine is an antagonist of human TAAR1-mediated signalling. Of course additional studies would be necessary to rule it out as an inverse agonist or allosteric modulator, however, assuming apomorphine is a human TAAR1 antagonist it will be important to determine if its mechanism of action is orthosteric or allosteric. Ultimately knowing how and where apomorphine physically interacts with crystalized human TAAR1 will help guide the rational design of the next generation of TAAR1-selective therapeutics. The findings of Sukhanov et al., also encourage the speculation that at least some of the benefit apomorphine provides individuals with Parkinson’s Disease is the consequence of its activating dopamine D2-mediated signalling and blocking TAAR1-mediated signalling. Could apomorphine’s influence on dopamine and TAAR1 receptor signalling also account for its complex effects on pancreatic (Joost et al., 1983; Pinter et al., 1998; Bunzow et al., 2001; Regard et al., 2007), immune (Amerić et al., 1984; Nelson et al., 2007; Dadban et al., 2010; Panas et al., 2012) and cardiac (Finch and Haeusler, 1973; Merello et al., 1992; Khaliulin et al., 2006; Zucchi et al., 2010) function? Moreover, since dopamine is a human TAAR1 agonist in vitro is it also an agonist in vivo? And if so, how important is dopamine-activated TAAR1-mediated signalling in terms of normal and/or abnormal physiology given the receptor’s many other putative endogenous ligands, a list that currently includes: β-phenylethylamine, p-taramine and 3-iodothyronamine (Grandy, 2007)? Finally, the report by Sukhanov et al., is important because its publication will raise awareness of this receptor and by extension the eight other members of the human TAAR gene family, five of which are intact genes and three that are putative pseudo genes, for which the most fundamental aspects of their biology – the identity of their true endogenous ligands and actual physiologic roles in health and disease – are essentially unknown.

Acknowledgments

The author would like to thank Dr J.G. Nutt for sharing his perspectives on the side effects and current issues associated with the medical use of apomorphine in the United States and Europe and OHSU’s Department of Physiology & Pharmacology and the Knight Cardiovascular Institute for financial support. The author has no conflicts of interest to declare.

References


Apomorphine is a TAAR1 ligand


