# News & views

Structural biology

## Amphetamine-binding receptor visualized

Harald H. Sitte

High-resolution structures of TAAR1 — the receptor bound by amphetamines and molecules called trace amines — reveal detailed interactions with ligand molecules that will inform efforts to design antipsychotic drugs. **See p.663 & p.672**

Small molecules known as trace amines have been reported in biological materials for nearly 150 years[1]. They are present in the nervous systems of mammals at low levels — about 100 times lower than the concentrations of the structurally related 'monoamine' neurotransmitter compounds, such as dopamine and serotonin[2] — and bind to proteins known as trace amine-associated receptors (TAARs). One of these receptors, TAAR1, has a potential role in a range of neuropsychiatric conditions, and is associated with diabetes, obesity and immune disorders. On pages 672 and 663, respectively, Xu *et al.*[3] and Liu *et al.*[4] present an astonishing 12 cryo-electron microscopy structures of human and mouse TAAR1 in complex with an array of ligand molecules. The findings will aid the development of therapeutics that bind to TAAR1.

TAARs belong to the superfamily of membrane-bound proteins known as G-protein-coupled receptors (GPCRs). Unlike most GPCRs, however, TAARs do not extensively decorate the cell membrane, but are instead expressed in low amounts inside cells[5–7]. Most TAARs are found in the olfactory system, but TAAR1 is expressed in both the central and peripheral nervous systems[5], and has garnered particular attention since its discovery[6,7] in 2001. In the mammalian brain, TAAR1 activation regulates the activity of several neurotransmitter signalling pathways by decreasing the basal firing rates of the neurons involved, and by lowering the sensitivity of receptors to neurotransmitters[5].

Crucially, mammalian TAAR1 binds not only trace amines (and their monoamine metabolic products), but also a large number of compounds that are not found naturally in mammals — particularly many psychoactive analogues of the drug amphetamine[1,8]. Moreover, the human *TAAR1* gene is found in a region of the genome that is associated with a susceptibility for schizophrenia, substance-use disorders and various other mood disorders[5,6].

Currently available antipsychotic drugs used to treat schizophrenia and similar conditions work either by blocking the activity of the D2 receptor[9], or by blocking both D2 and the 5-$HT_{2A}$ receptor (a subtype of the serotonin receptor). However, these drugs can cause severe side effects, such as motor impairment and metabolic problems. There is therefore a need for antipsychotic medications that have different mechanisms of action.

In drug development, targeting TAAR1 with small molecules has already yielded some interesting compounds. These include Ralmitaront (RO-6889450), which is a partial agonist of TAAR1 (it binds to TAAR1 but does not elicit the maximum possible efficacy); and Ulotaront (SEP-363856), which is a full agonist of both TAAR1 and the 5-$HT_{1A}$ receptor (another subtype of the serotonin receptor, and a target of certain therapies for anxiety). Ulotaront also advantageously binds with low affinity at the D2 and 5-$HT_{2A}$ receptors, suggesting it might not have the severe side effects of current antipsychotics. Both compounds are under clinical investigation as antipsychotic medications.

The US Food and Drug Administration has expedited the development of Ulotaront, which could become the first non-D2-targeting antipsychotic to be approved since reserpine in 1955 (the use of reserpine has, however, largely been discontinued because of its debilitating side effects[8]). But would a full agonist that targets TAAR1 alone, or which acts only at TAAR1 and 5-$HT_{1A}$, be better for therapeutic applications?

The structures of drug targets can help to direct the search for new medicines, but until now, the only available structures of TAAR1 were 'homology' models derived by comparing the amino-acid sequence of this receptor with that of the β2-adrenergic receptor[10] (another GPCR). However, the sequence similarity of TAAR1 and the β2-adrenergic receptor is relatively low (about 41% overall, increasing to about 60% in the proteins' transmembrane domains[10,11]).

Xu *et al.* and Liu *et al.* now present an array of TAAR1 structures (mouse and human) at around 3-ångström resolution, which were obtained using single-particle cryo-electron microscopy. These reveal how ligand

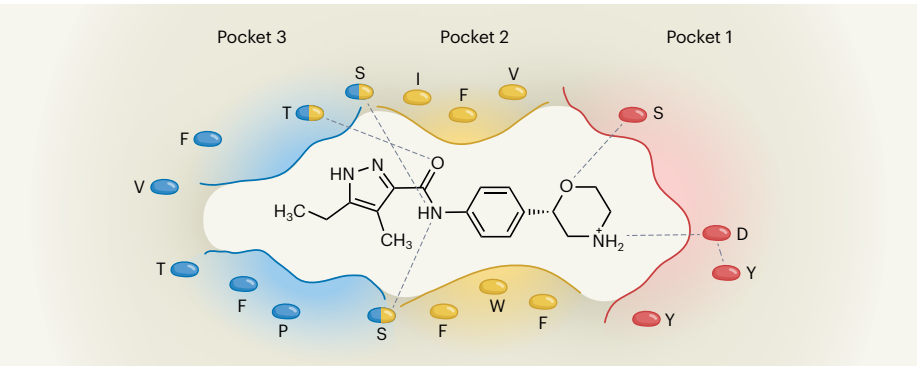


**Figure 1 | Binding pockets in the TAAR1 protein.** The TAAR1 receptor protein has a potential role in various neuropsychiatric conditions, and is bound by natural and synthetic ligand molecules, including amphetamines. Two papers[3,4] report cryo-electron microscopy structures of the TAAR1 protein in complex with a range of ligand molecules, revealing several pockets in the TAAR1 binding site that can be accessed by different ligands. One ligand is the potential therapeutic compound Ralmitaront (RO-6889450; shown as a 2D representation in the binding site), which is a partial activator of TAAR1. This shows that the ligand interacts with TAAR1 amino-acid residues (represented by single-letter codes) in three of the pockets. Dashed lines indicate hydrogen-bonding interactions. (Adapted from Ext. Data Fig. 6a in ref. 3.)

molecules such as trace amines, TAAR1 agonists (including Ulotaront and Ralmitaront) and psychoactive substances (*S*-amphetamine and methamphetamine) interact with and activate TAAR1. Both research groups also report the structure of the human 5-$HT_{1A}$ receptor in complex with Ulotaront, to examine this compound's dual-agonist activity.

The two studies report similar architectures for TAAR1, with the seven transmembrane α-helices characteristic of GPCRs, and an additional extracellular helix (called ECL2) folded over as a 'cap' for the ligand-binding site — a feature often observed in receptors for classical biologically active amines, such as serotonin and adrenaline. Both studies also find that amphetamines occupy the ligand-binding site, which prominently features an aspartate amino-acid side chain that forms hydrogen bonds with a tyrosine and a histidine residue. Some differences do emerge, however: Liu *et al*. present pharmacological data showing that TAAR1 generally interacts with a particular G protein (one that triggers signalling from the receptor), whereas Xu *et al*. observe coupling to other G proteins, depending on the ligand that is bound — a point that certainly warrants further clarification.

Xu *et al*. find that the methyl group of *S*-amphetamine extends into a shallow groove formed by two residues from the sixth and seventh transmembrane helices. By contrast, Liu *et al*. find that the trace amine β-phenethylamine (β-PEA) adopts a slightly different arrangement in the binding site owing to its smaller size. This might explain why β-PEA is a particularly potent activator of TAAR1 (more than ten times more potent than methamphetamine, for example). Xu *et al*. also identify a particular pocket in the binding site that is accessed by another mammalian trace amine, 3-iodothyronamine (T1AM).

When Xu *et al*. compare the structures of human and mouse TAAR1 in complex with T1AM, they find that T1AM assumes an almost identical binding pose in both cases. There is, however, one notable difference attributable to human TAAR1 having a different amino-acid residue than the mouse receptor has at a particular position in the binding site. This could mean that the affinities of molecules for this binding site differ between species — crucial knowledge for medicinal chemists targeting TAAR1, given that mice are often used as a model species for drug development.

Perhaps the most exciting aspect of these studies is how they might advance the development of therapeutic TAAR1 agonists. For example, the comparisons of how Ulotaront binds to TAAR1 and to 5-$HT_{1A}$ reveal similarities that explain why it is an agonist of both of these receptors. Liu *et al*. also report the structure of TAAR1 bound to a particularly selective and potent TAAR1 agonist, RO5256390. This reveals that RO5256390 forms intimate interactions with residues that other compounds do not make, and which probably explain its potency. Overall, the structures presented in the two studies indicate that TAAR1 ligands have a 'core' binding mode, complemented by two extended binding modes that can be used by certain compounds — and which Xu *et al*. attribute to interactions formed with several binding pockets (Fig. 1).

One point to consider when developing TAAR1-targeting therapeutics is that the compounds must either be lipophilic enough to cross the cell membrane to reach TAAR1, or be substrates of a transporter protein at the cell surface. TAAR1-targeting drugs that are misused, such as methamphetamine and *S*-amphetamine, are typically carried into cells by dopamine transporters[9]. Care must therefore be taken to ensure that new TAAR1 agonists do not exert strong psychostimulant effects as a result of them being substrates for these transporters, to avoid the risk of people developing addiction[8,9].

Intriguingly, the amphetamine-type stimulant MDMA has been proposed as a potential 'breakthrough therapy' for treatment of post-traumatic stress disorder[12]. MDMA is also a TAAR1 agonist, albeit a weaker and less-potent activator than *S*-amphetamine[13] — suggesting that TAAR1 affinity might be an important feature to include in the pharmacological profiles of drugs under development for treating neuropsychiatric conditions.

Taken together, the reported structures of TAAR1 from two species will accelerate scientists' understanding of ligand interactions with this receptor, and stimulate the development of drugs that bind selectively to it — thereby avoiding side effects caused by binding to off-target proteins. Studies with truly selective TAAR1 agonists will help to paint a clearer picture of how monoamine synaptic function regulates neurotransmitter storage, secretion and reuptake in health and disease.

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Chemoinformatics

# Chemistry automated by large language models

**Ana Laura Dias & Tiago Rodrigues**

Automation of chemistry research has focused on developing robots to execute jobs. Artificial-intelligence technology has now been used not only to control robots, but also to plan their tasks on the basis of simple human prompts. **See p.570**

Chemistry research is grounded on iterative cycles in which experiments are designed, executed and then refined to achieve a particular goal. The experience and intuition of researchers has a crucial role in working out the initial design, and in the subsequent optimization process — something that could not previously have been replicated in autonomous systems that carry out chemistry research. On page 570, Boiko *et al*.[1] report an artificial intelligence (AI) agent named Coscientist that can plan and orchestrate multiple tasks in the chemistry-research cycle without detailed human input, bringing the vision of self-driving laboratories a step closer to reality.

Work done by chemists is multipronged — it requires not only technical skills to execute chemical reactions, but also knowledge to plan them. For example, designing an organic synthesis might involve carrying out retrosynthetic analyses (working backwards from the target molecule to identify simpler precursor molecules), searching databases for suitable reaction conditions and selecting the reactions that are most likely to achieve a pre-established research goal, such