The trace amine-associated receptor 1 agonists – non-dopaminergic antipsychotics or covert modulators of D2 receptors?

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Critique/Commentary

The trace amine-associated receptor 1 agonists – non-dopaminergic antipsychotics or covert modulators of D2 receptors?

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Abstract

A major effort of the pharmaceutical industry has been to identify and market drug treatments that are effective in ameliorating the symptoms of psychotic illness but without the limitations of the current treatments acting at dopamine D2 receptors. These limitations include the induction of a range of adverse effects, the inadequate treatment response of a substantial proportion of people with schizophrenia, and the generally poor response to negative and cognitive features of the disease. Recently introduced drug treatments have gone some way to avoiding the first of these, with a reduced propensity for weight gain, cardiovascular risk and extrapyramidal motor effects. Despite claims of some small improvements in negative symptoms, these drugs have not demonstrated substantial increases in efficacy. Of the drugs currently in development as antipsychotic agents, several are misleadingly described as having novel 'non-dopaminergic' mechanisms that may offer improvements in addressing the limitations of adverse effects and efficacy. It will be argued, using the trace amine-associated receptor 1 agonist as an example, that several of these new drugs still act primarily through modulation of dopaminergic neurotransmission and, in not addressing the primary pathology of schizophrenia, are therefore unlikely to have the much-needed improvements in efficacy required to address the unmet need associated with resistance to current treatments.

Keywords

Schizophrenia, psychosis, antipsychotic agents, ulotaront, trace amine-associated receptor 1, dopamine, D2 receptor

Introduction

Schizophrenia is a relatively common severe mental illness that, for many people, is inadequately treated. The currently available antipsychotics provide relief of positive psychotic symptoms in many cases, although the negative and depressive symptoms of the disease remain poorly responsive, as do the cognitive deficits that are apparent in many people with schizophrenia (Jauhar et al., 2022). Current drug treatments, comprising the first-generation dopamine D2 receptor antagonists, the second-generation drugs which are primarily 5-HT2/D2 antagonists and the D2 partial agonists all have antipsychotic effects mediated by action at the D2 receptor; in a study of two second-generation drugs, it is the occupancy of this receptor in the striatum which predicts response in positive psychotic symptoms (Agid et al., 2007). This action ameliorates the hyperactivity of dopamine function which, in one useful paradigm, is thought to result in the misattribution of salience underlying the positive symptoms of the disease (Kapur et al., 2005).

It is this pharmacology, along with actions at a variety of other receptor sites, that is also responsible for the unwanted and often limiting side effects of many of these drugs (Reynolds, 2004). These adverse effects, including extrapyramidal motor symptoms, excessive sedation, hyperprolactinaemia, QT interval prolongation, weight gain and other metabolic disturbances, are to some extent avoided by more recently introduced treatments, including lurasidone and the D2 partial agonists aripiprazole and cariprazine (Huhn et al., 2019). However, all the available treatments have limited efficacy against the cognitive, negative and depressive symptoms of schizophrenia (Huhn et al., 2019). It is these features of the disease that are particularly disabling in limiting normal social function (Addington and Addington, 1993).

These concerns have driven the search for more effective pharmacotherapies for schizophrenia, particularly those that address cognitive deficits and negative symptoms. The approaches used in this search have included, among others, the design of highly specific mechanism-based molecules to target the GABAergic or glutamatergic pathology of schizophrenia, as well as more target-free assessment of compound libraries by behavioural screening. The former approach continues to generate good candidates although so far these have not progressed successfully beyond phase 3 trials, while in development are a variety of other candidates with mechanisms that are not considered to be directly influencing GABA/glutamate neuronal pathology or the D2 receptor. These include compounds acting at muscarinic cholinergic receptors or inhibiting phosphodiesterase 10A, for example. The common feature of all these potential antipsychotic agents is that they are generally considered 'non-dopaminergic' (Citrome and Meyer, 2023) and avoid the adverse

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effects associated with D2 receptor ligands or with actions at other monoamine receptors.

The TAAR1 agonists

One novel molecule with potential antipsychotic efficacy is ulotaront, a trace amine-associated receptor 1 (TAAR1) agonist. This and several other TAAR1 agonists at earlier stages of development have been investigated for efficacy in ameliorating the symptoms of schizophrenia (Liu et al., 2023). The TAARs are the sites of action of a series of naturally occurring monoamines which are structurally related to the catecholamine transmitters but were originally considered to be present in far lower concentrations in the brain (Boulton et al., 1980). We know now that this distinction, based on a brain concentration typically below 100 ng/g, is arbitrary and inconsistent – for example, concentrations of dopamine in the human frontal cortex are much lower, although cortical dopamine neurotransmission is nevertheless considered to have an important role in normal brain function (Puig et al., 2014).

A phase 2 trial, with an open-label extension, demonstrated an antipsychotic efficacy of ulotaront (Achtyes et al., 2023). However, two phase 3 trials of ulotaront in acutely psychotic people with schizophrenia have recently been completed with an initial news release indicating that the trials 'did not meet their primary endpoint' of an improvement, relative to placebo, in PANSS score at 6 weeks (Otsuka press release, 2023). From the limited information available at present, the improvements seen with various doses of the drug were not significantly differentiated from a relatively large placebo response, although in each of the trials, there was an indication of some dose dependence in the response to ulotaront. The many further questions that these findings generate must await the peer-reviewed publication of this and other ongoing studies while other neuropsychiatric indications still remain as potential targets (Liu et al., 2023).

This apparent clinical failure for ulotaront follows closely from the termination of phase 2 trials of another TAAR1 agonist, ralmitaront, in schizophrenia. While these results may be a disappointment to those interested, or invested, in TAAR1 agonism as an antipsychotic mechanism, they are unlikely to completely dampen the enthusiasm for this receptor as a therapeutic target.

Trace amines and TAAR1

Interestingly, 50 years ago, there was a burgeoning interest in the role that trace amines might have in the aetiology of major psychiatric disorders. Thus, 2-phenylethylamine (PE), p-tyramine and octopamine were being enthusiastically investigated in psychiatric diseases, particularly schizophrenia and depression, and generating interesting, if ultimately mistaken, hypotheses (Boulton, 1980; Reynolds, 1979). That their mechanisms of action might involve more than an amphetamine-like disruption of monoamine neurotransmitter transport and storage had long been suspected; octopamine was known to be a neurotransmitter in the insect nervous system and specific G-protein-linked tyramine/octopamine receptors were subsequently identified (Hiripi et al., 1994). Subsequently, the first mammalian TAAR was identified and cloned (Borowsky et al., 2001). Compared with other monoamine transmitter receptors, TAAR1 is relatively unspecific in having a sub-micromolar affinity for a range of monoamines based on the PE structure which, as well as several trace amines, includes both amphetamine and dopamine.

TAAR1 and D2

The likely function of the TAAR1 receptors is slowly being clarified. They are primarily intracellular proteins but will translocate to the plasma membrane when interacting, through dimerization for example, with other receptors. They stimulate the production of cAMP via Gs-protein coupling and also recruit a second signalling pathway, the β-arrestin2 cascade; second messenger systems that also mediate dopamine D2 receptor activity (Espinoza et al., 2013). Early observations indicated that TAAR1 influenced dopaminergic neurotransmission (Lindemann et al., 2008); it was subsequently reported to have effects through the modulation of presynaptic D2 receptors (Leo et al., 2014). Notable in the current context is that this modulation appears to be through TAAR1 agonist-induced attenuation of the function of the dopamine D2 receptor: the two receptors act in opposing ways on second messenger systems as TAAR1 has excitatory effects via stimulation of cAMP formation, while D2 receptor activity inhibits this process. So a TAAR1 agonist may act similarly to a D2 antagonist in its effects on dopaminergic neurotransmission.

Such a functional interaction may reflect the ability of the TAAR1 protein to dimerize with the D2 receptor (Espinoza et al., 2011). Thus, where such heterodimers are present, TAAR1 ligands could be considered to act as allosteric regulators of D2 receptor function (Misganaw, 2021). That TAAR1/D2 heterodimers are observed in experimental systems does not prove their presence and functionality in the organism, although there is evidence from co-immunoprecipitation experiments that they may occur in brain tissue (Harmeier et al., 2015).

Such mechanisms involving interaction with the D2 receptor may therefore underlie the preclinical evidence of the antipsychotic efficacy of the TAAR1 agonists. That ulotaront may act through effects on dopamine function is not surprising, given how it was identified. It emerged from a behavioural screen aimed at identifying compounds with potential antipsychotic action, the behavioural phenotype being 'established and validated with marketed CNS drugs' (Dedic et al., 2019). Thus, the technique searches for behavioural similarities with, in this case, established antipsychotic agents. Given that all currently available antipsychotic drugs are antagonists or partial agonists at dopamine D2 receptors, this 'target agnostic' approach is still likely to identify compounds that modulate dopamine function with the same downstream effects, even if those with a direct dopamine D2 activity are excluded.

The TAAR1 agonists are not unique in modulating dopaminergic activity independent of direct action at the D2 receptor. Other drugs in development as antipsychotic agents but with very different pharmacology may still exhibit their main effects through interaction with dopaminergic systems. One example is that of xanomeline, a muscarinic M1/M4 agonist which, in combination with a peripherally acting M1 antagonist, has very recently been shown to be effective in phase 3 trials (Kaul et al., 2023). Xanomeline has been transparently described as having an antidopaminergic action (McKinzie and Bymaster, 2012),

acknowledging the reciprocal activity of acetylcholine and dopamine in striatal function. Nevertheless, recent reviews have described it as being non-dopaminergic (Citrome and Meyer, 2023; Granger et al., 2023).

Other receptor mechanisms

But does ulotaront have other actions that might contribute to its possible clinical effects? Few so-called 'selective' drugs are truly selective for action at a single site, even at clinically used doses. There are certainly other pharmacological properties of ulotaront that deserve consideration. Its binding affinity to the 5-HT7 receptor is the highest reported of all receptors studied (Dedic et al., 2019), although its functional activity as a partial agonist determined by cAMP assay was found to be 200-fold weaker. Such a discrepancy between displacement of radioligand binding and agonist efficacy is not uncommon, since the latter is very dependent on the experimental conditions. Further investigation of this action at the 5-HT7 receptor would be valuable in understanding the clinical effects of ulotaront; 5-HT7 ligands have been proposed to be valuable as potential treatments for a wide range of neuropsychiatric indications (Nikiforuk, 2015). These include cognitive dysfunction (Gasbarri and Pompili, 2014) – 5-HT7 antagonism has been proposed to underlie a relatively greater procognitive effect of lurasidone (Olivola et al., 2023) – and affective disorders (Gottlieb et al., 2023), albeit without any selective ligands currently licensed.

Another pharmacological property of ulotaront is its reported partial agonist activity at the 5-HT1A receptor (Dedic et al., 2019). This site may be a valuable adjunctive target for antipsychotic agents by reducing extrapyramidal effects and potentially improving mood and negative symptoms (Newman-Tancredi, 2010). The interest in this possible contributory mechanism is such that recent publications have referred to ulotaront as a combined TAAR1/5-HT1A agonist (Xiao et al., 2022). Its functional activity at the 5-HT1A receptor is almost 20-fold lower than at the TAAR1 site, which would indicate a relative selectivity for the latter. Nevertheless, preclinical evidence suggests that the 5-HT1A receptor contributes to the effect of ulotaront (Dedic et al., 2019).

Additional effects at the 5-HT7 and 5-HT1A receptors are not unique to ulotaront; several currently available antipsychotic agents, including both clozapine and lurasidone, have affinities at these sites that are likely to translate into effects at clinical doses. 5-HT1A partial agonism present in several second-generation and D2 partial agonist antipsychotics may also be valuable in ameliorating certain side effects and improving some symptoms. However, there is little to indicate that 5-HT7 and 5-HT1A receptor mechanisms, either for ulotaront or for the available antipsychotic agents, make a substantial contribution to the primary antipsychotic response.

Conclusion

So, returning to the question in the title, we might ask: does it matter? Whether or not a drug that acts indirectly to modulate dopamine receptor function can be described as non-dopaminergic is, perhaps, a semantic question. However, other aspects are important. A drug labelled as non-dopaminergic suggests it has two general properties of relevance to its use in the clinic. One is that it should be devoid of dopaminergic side effects; certainly, there is no indication that ulotaront produces hyperprolactinemia, and there is minimal evidence for dopaminergic motor effects (Achtyes et al., 2023). The other implication is that the antipsychotic action addresses mechanisms independent of dopamine neurotransmission and thus may avoid some of the other limitations of currently available treatments – which include their inadequate efficacy in many patients and poor response to negative and cognitive features of the disease. Whether this might be true of ulotaront seems unlikely given the failure of this drug in phase 3 trials in schizophrenia.

Therefore, on current theoretical, pharmacological and clinical evidence, it is difficult to differentiate the action and efficacy of TAAR1 agonists from the established D2 receptor antagonists and partial agonists currently available. While we cannot rule out a direct effect of TAAR1 agonists on glutamate or other transmitter systems (Dedic et al., 2021), on current evidence a dopaminergic mechanism appears both necessary and sufficient to explain their potential antipsychotic effects. Thus, it would be best to presume that the main action they have is primarily a modulatory one on dopamine neurotransmission through effects at dopaminergic synapses in the dorsal striatum.

As mentioned above, this limitation is not unique to ulotaront; while an in-depth discussion is beyond the scope of the current article, the mechanisms of some other drugs in development for schizophrenia also involve effects on dopaminergic systems. As well as those acting at muscarinic receptors this includes inhibitors of phosphodiesterase 10A (Świerczek et al., 2019). These pharmacologies are, therefore, unlikely to help those who do not respond to drugs acting at the D2 receptor, in whom that treatment resistance can be considered a subtype of psychosis without dopaminergic hyperactivity (Jauhar et al., 2019). Only treatments addressing the dysfunctional glutamate/GABA neuropathology, its causal mechanisms or its (non-dopaminergic) downstream consequences – yet to be clearly identified – are likely to be effective for this substantial proportion of people with schizophrenia.

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