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Dopamine receptor heteromers: biasing antipsychotics

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“the development of purely allosteric ligands, which could bias dopamine signaling without competing for binding to the orthosteric site, might be a preferential strategy over the recently developed orthosteric ligands”

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The term antipsychotic drug (APD), also called a neuroleptic, refers to medications currently prescribed for the treatment of neuropsychiatric diseases that display psychotic features (e.g., schizophrenia) [1]. Classification of APDs is mainly based on the profile of their adverse effects; in particular, liability to produce extrapyramidal symptoms (EPS). Accordingly, typical (or first generation) and atypical (or second generation) drugs have been differentiated. Typical APDs are effective at controlling the so-called positive symptoms of schizophrenia; hallucinations and delusions, but they are more likely to produce undesired motor effects than atypical APDs [2]. However, this kind of classification has been questioned and, in fact, each APD may be considered as having a unique set of properties [3]. Meanwhile, it is important to note that a substantial number of patients do not respond adequately to existing APDs, and in particular, the negative symptoms of schizophrenia, which include cognitive deficits, social withdrawal, anhedonia and avolition, are hardly ameliorated by current treatments. Thus, there exists a clinical need for the development of mechanistically novel and more efficacious APDs.

The dopaminergic hypothesis of schizophrenia

It is well accepted that dysregulation of dopaminergic neurotransmission is central to most psychotic processes, including schizophrenia. The dopaminergic hypothesis concerning schizophrenia states that hyperactivity in the mesolimbic dopamine pathway concurs with hypofunction in the mesocortical dopamine pathway [4]. Accordingly, reducing signaling via mesolimbic dopamine D₂ receptors (D₂Rs) is probably the main mechanism through which antipsychotic therapeutics function. Indeed, APDs are either antagonists or partial agonists for D₂Rs. Importantly, the level of antipsychotic occupancy of striatal D₂Rs is related to the appearance of adverse motor effects such as EPS; neuroimaging studies have revealed that a D₂R occupancy of above 80% is associated with the appearance of EPS [5]. Interestingly, while typical APDs such as haloperidol may result in this degree of occupancy at therapeutic doses, atypical ones such as clozapine achieve antipsychotic efficacy at lower occupancy levels, which may explain why they are less likely to produce EPS [5].

D₂R-mediated β -arrestin2 signaling & antipsychotic-like activity

D₂Rs are G-protein-coupled receptors that signal via Gi/o and β -arrestin2 proteins [6]. It has been suggested that the therapeutic benefits of APDs may be specifically related to the inhibition of D₂R-mediated β -arrestin activation [7]; a mechanistic feature shared by both typical and atypical APDs. Furthermore, it was hypothesized that induction of EPS may result from an excessive reduction of G-protein-dependent signaling downstream of

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D₂R. Interestingly, expression of β -arrestin2 and also of G protein receptor kinase-2 (GRK2), which phosphorylates D₂R and enhances β -arrestin2 recruitment has been shown to be lower in striatum than in cortex [8]. These data are consistent with functional magnetic resonance imaging studies in mice, showing that dopaminergic stimulation elicits an arrestin-dependent response in cortex, but not in striatum [9]. These regional differences may support the use of weak partial D₂R agonists, which preferentially signal via the β -arrestin2, as opposed to the G protein, pathway such as β -arrestin2-biased agonists to induce D₂R-mediated β -arrestin2 signaling in cortex selectively, counteracting the hypodopaminergia which is believed to underlie negative symptoms, while antagonizing elevated dopamine signaling in the striatum thought to provoke positive symptoms [10]. In addition, it would be beneficial not to interfere with G protein signaling since this could potentially avoid EPS.

Recent studies [10,11] reported antipsychotic-like activity (i.e., reduction of PCP- and amphetamine-induced hyperlocomotion) of β -arrestin2-biased aripiprazole analogs in mice. These D₂R ligands showed a low propensity to induce catalepsy (used as an indicator of EPS liability). In addition, the antipsychotic-like activity was abolished in β -arrestin2 deficient animals, supporting the notion that β -arrestin2 plays a key role in the effects elicited by the aripiprazole derivatives. In the same work [10], one of the biased ligands, UNC9994, was reportedly unable to interact as either an agonist or an antagonist with G-protein-dependent signaling downstream of D₂Rs. This kind of behavior suggests that UNC9994 is unable to compete with dopamine at receptors coupled to G protein. However, such a mechanism appears unlikely, since, based on its aripiprazole-like structure, this ligand is expected to interact with the orthosteric binding site of D₂R. Indeed, recent data indicates that UNC9994 is a weak partial agonist at G protein-dependent potassium channel activation downstream of D₂Rs and, as expected for a weak partial agonist, antagonizes the response to a near-maximally effective concentration of dopamine [12].

Impact of D₂R heteromerization in antipsychotic drug efficacy

Apart from the differential expression of β -arrestin2 and GRK2 in cortical and striatal brain areas, the biased effects of D₂R ligands may depend on other interacting proteins, such as G-protein-coupled receptors. D₂R functioning in the striatum has been reported to be finely modulated by adenosine A_{2A} receptors (A_{2A}Rs). Indeed, the existence of direct receptor–receptor interactions (in other words, heteromerization) between D₂Rs and A_{2A}Rs, in which the protomers display reciprocal negative allosteric modulation, has been well established [13]. Conversely, the expression of A_{2A}Rs in cortex is very low compared to that observed in striatum [14]; accordingly, it seems unlikely that D₂Rs participate in D₂R/A_{2A}R heteromers in this brain region, in spite of what was recently demonstrated [15]. Within this context, the antipsychotic-like efficacy of UNC9994 was recently assessed in A_{2A}R-deficient (A_{2A}R^{-/-}) mice, in order to study its possible dependence on A_{2A}R expression [16]. Interestingly, UNC9994 exerted robust antipsychotic-like effects in wild-type, but not in A_{2A}R^{-/-} animals; thus, the compound failed to abolish PCP-induced hyperlocomotion in A_{2A}R^{-/-} mice, and reduced amphetamine-induced hyperlocomotion to a lesser extent in these animals, than in wild-type mice [16]. Taken altogether, and since UNC9994 mainly activates the β -arrestin2 signaling pathway, it was concluded that A_{2A}R expression might determine the biased nature of the ligand, by driving the formation of a striatal D₂R/A_{2A}R/ β -arrestin2 complex. However, we cannot rule out an effect on G protein signaling, especially since A_{2A}R^{-/-} mice are less sensitive to the suppressing effects of antipsychotics on basal locomotion [17].

In summary, biased antipsychotic ligands represent an interesting avenue for future research. However, the development of purely allosteric ligands, which could bias dopamine signaling without competing for binding to the orthosteric site, might be a preferential strategy over the recently developed orthosteric ligands. Indeed, a series of negative allosteric D₂R modulators, which do not interact with the orthosteric site, but modulate dopamine efficacy, has recently been reported [18]. Such ligands may serve as lead compounds for the development of biased allosteric modulators, which could potentially evolve into more efficacious APDs. In addition, understanding the impact of D₂R/A_{2A}R heteromer formation on D₂R downstream signaling will certainly contribute to the development of such novel APDs.

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