Harnessing allosterism as a novel approach to target the D2-like dopamine receptors

Rob Lane^{1,2}

¹*Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Australia,* ²*Dept of Psychiatry, Columbia University, New York, USA*

The dopamine D2-like receptors (D2-likeR) are targets for the treatment of Parkinson's disease, schizophrenia and drug abuse. To date, drug discovery efforts have focused on targeting the orthosteric site of the D2-likeR that binds dopamine. Orthosteric D2R agonists are employed for the treatment of PD but display a limited duration of efficacy and have significant drawbacks, including induction of psychosis and compulsive behaviours. Similarly, while orthosteric D2-likeR antagonism is sufficient for antipsychotic activity, it can be associated with extrapyramidal side effects and tardive dyskinesia. Such side-effects can be attributed, in part, to a lack of target specificity and/or the inability of orthosteric drugs to replicate the spatiotemporal pattern of endogenous dopamine signalling in the brain. Drugs that bind topographically distinct allosteric sites can display greater subtype-selectivity and, because they still allow the endogenous agonist to bind, maintain endogenous spatiotemporal patterns of signalling. Allosteric drugs that target the D2-likeR and act to tune up (Positive Allosteric Modulator, PAM) or tune down (Negative Allosteric Modulator, NAM) the action of dopamine may present a safer, more effective therapeutic approach. While this approach has yet to be therapeutically exploited, recent years have seen the identification of novel allosteric scaffolds for the dopamine receptors. I will present our findings regarding the binding mode and mechanism of action of novel NAMs and PAMs of the D2-likeRs. In particular we have explored the relationship between interactions with distinct allosteric binding pockets and patterns of modulatory effects. We reveal effects upon both orthosteric agonist affinity and efficacy, modulatory effects that are biased towards particular signalling pathways and unique patterns of subtype selectivity. We also explore the pharmacology of bitopic (dual allosteric/orthosteric) ligands and how the pharmacology of clinically-used antipsychotics might be derived from such a binding mode. In summary, our studies of D2-likeR allosteric modulators illustrate how the complex pharmacology of such ligands can sculpt dopamine receptor responses in a manner that cannot be achieved through the action of orthosteric drugs. Understanding the mechanism of action of such allosteric ligands can provide a platform for the development of improved therapeutics that target these receptors.