

## Functional Selectivity of D<sub>2</sub> Receptor Ligands in a Chinese Hamster Ovary hD<sub>2L</sub> Cell Line: Evidence for Induction of Ligand-Specific Receptor States

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### ABSTRACT

There are now several examples of single G protein-coupled receptors to which binding of specific agonists causes differential effects on the associated signaling pathways. The dopamine D<sub>2</sub> receptor is of special importance because the selective activation of functional pathways has been shown both *in vitro* and *in situ*. For this reason, the present work characterized a series of rigid D<sub>2</sub> agonists in Chinese hamster ovary cells transfected with the human D<sub>2L</sub> receptor using three distinct functional endpoints: inhibition of cAMP synthesis, stimulation of mitogen-activated protein (MAP) kinase phosphorylation, and activation of G protein-coupled inwardly rectifying potassium channels (GIRKs). In this system, S-propylnorapomorphine (SNPA), R-propylnorapomorphine (RNPA), dihydrexidine (DHX), dinapsoline (DNS), and dinoxylone (DNX) all inhibited forskolin-stimulated adenylate cyclase activity to the same extent as the

prototypical D<sub>2</sub> agonist quinpirole (QP). The rank order of potency was the following: RNPA ≫ QP = DNX > SNPA > DHX = DNS. For MAP kinase phosphorylation, DHX, DNS, DNX, and RNPA had efficacy similar to QP, whereas SNPA was a partial agonist. The rank order of potency for MAP kinase phosphorylation was RNPA ≫ QP = DNX > DHX > DNS = SNPA. DNX activated GIRK channels to the same extent as QP, whereas DHX and DNS were partial agonists, and RNPA and SNPA caused no appreciable activation. These findings indicate that DHX, DNS, RNPA, and SNPA have atypical functional properties at the hD<sub>2L</sub> receptor and display different patterns of functional selectivity. We hypothesize that this functional selectivity may be a result of ligand induction of specific conformations of the D<sub>2L</sub> receptor that activate only selected signaling pathways.