

Aripiprazole has Functionally Selective Actions at Dopamine D₂ Receptor-Mediated Signaling Pathways

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Aripiprazole is a unique atypical antipsychotic drug with an excellent side-effect profile presumed, in part, to be due to lack of typical D₂ dopamine receptor antagonist properties. Whether aripiprazole is a typical D₂ partial agonist, or a functionally selective D₂ ligand, remains controversial (eg D₂-mediated inhibition of adenylate cyclase is system dependent; aripiprazole antagonizes D₂ receptor-mediated G-protein-coupled inwardly rectifying potassium channels and guanosine triphosphate nucleotide (GTP) γ S coupling). The current study examined the D_{2L} receptor binding properties of aripiprazole, as well as the effects of the drug on three downstream D₂ receptor-mediated functional effectors: mitogen-activated protein kinase (MAPK) phosphorylation, potentiation of arachidonic acid (AA) release, and D₂ receptor internalization. Unlike quinpirole (a full D₂ agonist) or (-)3PPP (*S*(-)-3-(3-hydroxyphenyl)-*N*-propylpiperidine hydrochloride, a D₂ partial agonist), the apparent D₂ affinity of aripiprazole was not decreased significantly by GTP. Moreover, full or partial agonists are expected to have Hill slopes <1.0, yet that of aripiprazole was significantly >1.0. Whereas aripiprazole partially activated both the MAPK and AA pathways, its potency vs MAPK phosphorylation was much lower relative to potencies in assays either of AA release or inhibition of cyclic adenosine 3',5'-cyclic monophosphate accumulation. In addition, unlike typical agonists, neither aripiprazole nor (-)3PPP produced significant internalization of the D_{2L} receptor. These data are clear evidence that aripiprazole affects D_{2L}-mediated signaling pathways in a differential manner. The results are consistent with the hypothesis that aripiprazole is a functionally selective D₂ ligand rather than a simple partial agonist. Such data may be useful in understanding the novel clinical actions of this drug. *Neuropsychopharmacology* (2007) **32**, 67–77. doi:10.1038/sj.npp.1301071; published online 22 March 2006

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