Dihydrexidine — The First Full Dopamine D₁ Receptor Agonist

Peter Salmi, Ruben Isacson, Björn Kull

Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

The functional role of dopamine D₁ receptors is still controversial. One reason for this controversy is that for a long time the only available agonists for in vivo characterization of dopamine D₁ receptors were benzazepines. Among them was the prototype dopamine D₁ receptor partial agonist, SKF 38393. The lack of a selective and fully efficacious dopamine D₁ receptor agonist hampered basic research on dopamine D₁ receptors and left the potential clinical utility of dopamine D₁ receptor agonists elusive. The research situation improved when the first potent full dopamine D₁ receptor agonist dihydrexidine, a phenanthridine, was introduced in the late 1980s. In contrast to SKF 38393, dihydrexidine was shown to stimulate cyclic AMP synthesis just as well or better than dopamine, and potently displaced [³H]SCH 23390 from rat and monkey striatal membranes. Also, dihydrexidine was the first dopamine D₁ receptor agonist that had potent antiparkinsonian activity in a primate model of Parkinson’s disease. This finding suggested clinical utility for dopamine D₁ receptor agonists in Parkinson’s disease and that this utility might be critically dependent on the intrinsic efficacy of the drug. Clinical utility for dopamine D₁ receptor agonists in other central nervous disorders might also be dependent on the intrinsic efficacy of the drug. However, even though studies with dihydrexidine as a pharmacological tool have pointed to the clinical use for dopamine D₁ receptor agonists, dihydrexidine’s unfavorable pharmacokinetic profile and various adverse effects are likely to restrict or even preclude its use in humans. This review article provides an updated overview of the pharmacology of dihydrexidine and discusses possible clinical utility of dopamine D₁ receptor agonists in various central nervous system disorders.