Effects of the (+)- and (−)-enantiomers of 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene on dopamine receptors and on dopamine uptake

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We have previously shown that 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) is a potent agonist at postsynaptic dopamine receptors and is accumulated by presynaptic dopamine uptake processes. The bilateral injection of ADTN into the nucleus accumbens of conscious rats causes a strong and long-lasting stimulation of locomotor activity, this response being blocked by low doses of neuroleptic drugs. ADTN contains an asymmetric carbon atom and thus exhibits stereoisomerism. All previous studies with ADTN have been carried out using the racemic mixture. In the present investigation we have compared the pharmacological actions of the (+)- and (−)-enantiomers of ADTN.

The effects of (+)- and (−)-ADTN HBr on rat striatal dopamine sensitive adenylate cyclase and on locomotor activity following bilateral injections into the nucleus accumbens were assessed using previously-described techniques (Woodruff, Watling, Andrews, Poat & McDermed, 1977). The effects of the two enantiomers on the uptake of [^{3}H]-dopamine (specific activity 0.5 Ci/mmol) and of [^{3}H]-(±)-ADTN (specific activity 0.4 Ci/mmol) into synaptosomes prepared from rat striatum were investigated by the method described by Davis, Roberts & Woodruff (1978).

On the striatal dopamine-sensitive adenylate cyclase (+)-ADTN was approximately 100 times more active than (−)-ADTN in increasing cyclic AMP production, the EC50 values (concentrations, in μM, producing 50% of maximum response) being 0.8 ± 0.1 (s.e. mean, n = 5) and 87.0 ± 7.8 (n = 10) respectively. The EC50 value for dopamine on the adenylate cyclase was 3.5 μM (n = 8). All compounds give identical maximum responses.

The IC50 values (concentration, in μM, causing 50% inhibition) for [^{3}H]-dopamine uptake were dopamine, 0.16 ± 0.03 (n = 4); (+)-ADTN, 0.36 ± 0.04 (n = 4); (−)-ADTN, 1.07 ± 0.23 (n = 4). (+)-ADTN was similarly more active than (−)-ADTN in inhibiting the uptake of [^{3}H]-(±)-ADTN, the IC50 values being 0.69 ± 0.12 μM (n = 4) and 2.4 ± 0.16 μM (n = 4) respectively. The IC50 for dopamine in inhibiting the uptake of (±)-ADTN was 0.17 ± 0.02 μM (n = 4).

Bilateral injections of as little as 5 nmol (+)-ADTN, each side, into the nucleus accumbens of conscious rats caused a strong locomotor stimulation. Maximum locomotor stimulation was produced by about 100 nmol (+)-ADTN each side. In terms of its locomotor stimulant action (+)-ADTN was approximately 13 times more active than the (−)-enantiomer.

Thus, in all tests (+)-ADTN was more active than (−)-ADTN, the difference in potency being particularly pronounced in the adenylate cyclase assay. The method of synthesis used does not preclude the possibility of a slight degree of cross contamination between the two enantiomers. Hence the true potency of (−)-ADTN may be even lower than our data suggests.

References

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