DEMONSTRATIONS

Effect of aporphine alkaloids on central dopamine receptors

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(introduced by L.L. IVERSEN)

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The behavioural syndrome produced in rats after injection of (−)-apomorphine is believed to result from the stimulation of central dopamine receptors. In the present study we have used both *in vivo* and *in vitro* test systems to examine the dopamine-like properties of a series of aporphine alkaloids. Among the compounds tested only (−)-apomorphine and (±)-*N*-n-propylnorapomorphine ((±)-NPA) were effective in stimulating adenylate cyclase activity in homogenates of rat striatum under conditions in which dopamine is known to be effective (Miller, Horn, Iversen & Pinder, 1974). (−)-Apomorphine was slightly more potent than (±)-NPA, but the maximal stimulation seen with both substances was not significantly different. At higher concentrations both compounds caused some inhibition of adenylate cyclase activity. Compounds with the catechol group in a different position, such as (−)-isoapomorphine or (−)-1,2-dihydroxyaporphine, or those lacking one or both of the hydroxyl groups, as in (±)-10-hydroxy-*N*-n-propylnorapomorphine or (−)-aporphine, were found to be inactive in stimulating adenylate cyclase. Several compounds had some ability to inhibit the stimulating effects of 10^{-4} M dopamine on striatal adenylate cyclase. (+)-Bulbocapnine was the most potent compound in this respect, the inhibition was of a competitive nature with a K_i of 1.6×10^{-7} M. 10^{-5} M (+)-Bulbocapnine also inhibited the effects of 10^{-5} M (−)-apomorphine on striatal adenylate cyclase. As (±)-10-hydroxy-*N*-n-propylnorapomorphine has been reported to have some central effects (Neumeyer, Granchelli, Fuxe, Ungerstedt & Corrodi, 1974) we investigated its action following intraventricular injection into rats with unilateral lesions of the nigrostriatal pathway induced with 6-OH dopamine. Injection of 5 μg of (−)-apomorphine produced turning away from the side of the lesion for 40 minutes. However, injection of 25 μg of (±)-10-hydroxy-*N*-n-propylnoraporphine (NPA) was without effect.

Some of the aporphines were also tested for their ability to produce locomotor stimulation in rats with bilateral 6-OH dopamine induced lesions of the nucleus accumbens (see Iversen, Kelly, Miller & Seviour, C.30—this meeting). (±)-NPA was considerably more potent than (−)-apomorphine in producing a stimulation of locomotor activity. Doses of (±)-NPA as low as 0.05 mg/kg (i.p.) produced locomotor stimulation lasting for more than two hours. (−)-Aporphine, (−)-isoapomorphine, (−)-1,2-dihydroxyaporphine and (−)-nuciferine were all without effect. (±)-*N*-n-Propylnorapocodeine, however, produced a long term stimulation of locomotor activity although this compound did not stimulate striatal adenylate cyclase. (−)-Apocodeine has been shown previously to produce stereotypy in rats (Lal, Sourkres, Missala & Belendiuk, 1972). The central activity of (±)-*N*-n-propylnorapocodeine is probably due to its conversion to (±)-NPA in a similar fashion to the conversion of the anti-parkinsonian drug ET495 to its active metabolite S584 (Miller & Iversen, 1974).

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