Effect of the (+)- and (−)-enantiomers of sulpiride on ADTN-induced hyperactivity in the rat

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Bilateral injections of the dopamine analogue ADTN (2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene) into the nucleus accumbens of conscious rats causes a strong stimulation of locomotor activity which is believed to be due to the direct activation of postsynaptic dopamine receptors (Elkhawad & Woodruff, 1975; Woodruff, Watling, Andrews, Poat & McDermed, 1977). In the present study we have studied the actions of the (+) and (−) enantiomers of sulpiride, together with some other drugs, in terms of their ability to block ADTN-induced hyperactivity.

ADTN injections were carried out via permanently implanted cannulae and motor activity was recorded as described by Elkhawad & Woodruff (1975). Drugs were dissolved in 0.9% w/v NaCl solution except sulpiride which was dissolved in a tartaric acid solution (1 mg/ml pH 7.4). Rats were injected with neuroleptics or with other potential antagonists 3 h after the ADTN injections, at a time when a high degree of locomotor stimulation was apparent; these injections were performed either intraperitoneally or bilaterally into the nucleus accumbens (1 μl each side).

The bilateral injection of ADTN into the nucleus accumbens caused a potent, dose-related stimulation of locomotor activity. The threshold dose for ADTN was about 23 nmol each side and the maximum response was produced by 116 nmol each side. With this highest dose, which was the dose used in all antagonist studies, the duration of action of ADTN was about 20 hour.

The intraperitoneal injection of fluphenazine (0.2 mg/kg) completely blocked the response to ADTN. (±)-Sulpiride was much less active, causing complete abolition of ADTN-induced locomotor stimulation at a dose of 20 mg/kg i.p., and only partial inhibition of the response following a dose of 10 mg/kg i.p. In contrast, following bilateral injection into the nucleus accumbens, sulpiride was extremely potent in blocking the action of ADTN, the (−)-enantiomer of sulpiride being approximately 25 times more active than the (+)-enantiomer. The ID50 values (dose required on each side of the nucleus accumbens to produce 50% inhibition of ADTN-induced locomotor activity) were (−)-sulpiride, 0.1 nmol; fluphenazine, 1.0 nmol; (+)-sulpiride, 2.6 nmol.

Neither naloxone (137 nmol each side) nor metoclopramide (167 nmol each side) caused significant attenuation of the ADTN response when similarly applied.

Our results support the suggestion of Honda, Satoh, Shimomura, Satoh, Noguchi, Uchida & Kato (1977) that peripherally administered sulpiride may penetrate relatively poorly into the brain.

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