Chronic amphetamine administration and central dopamine receptor sensitivity

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Some psychotic disturbances in man may be associated with overstimulation of cerebral dopamine (DA) receptors and the chronic administration of amphetamine to animals may provide a model of these disorders (Snyder, 1973). Such administration potentiates stereotyped behaviour in rodents (Klawans, Margolin, Dana & Crossett, 1975) but it is difficult to explain why continued receptor stimulation should evoke an apparent hypersensitive response. We have therefore used the circling mouse, a model of dopamine receptor imbalance, to assess possible changes in DA receptor sensitivity during chronic (+)-amphetamine sulphate administration and following its withdrawal.

Male 'Swiss S' mice (20–25 g) showing consistent ipsiversive turning to (+)-amphetamine sulphate (4 mg/kg i.p.) and contraversive turning to apomorphine hydrochloride (0.25 mg/kg s.c.) two weeks following a 6-hydroxydopamine (16 μg in 4 μl 0.9% saline) induced lesion of one nigro-striatal pathway (von Voigtlander & Moore, 1973) were utilized. Animals were randomly divided into two groups ($n=30$). One group received increasing amounts of (+)-amphetamine sulphate in the drinking water until an approximate daily dosage of 20 mg/kg was reached after 1 month. This dosage level was continued for a further 2 months and then withdrawn. Control animals received drug-free drinking water during the experiment.

Chronic amphetamine administration was associated with an increase in spontaneous locomotor activity ($P<0.05$ at 2 and 3 months), as judged in Animex activity meters, although little (<1 turn/min) spontaneous circling behaviour was observed. Apomorphine-induced circling (0.01–0.5 mg/kg s.c.) when tested immediately prior to amphetamine administration and then at 1 week, 1, 2 and 3 months following drug administration was progressively reduced in comparison to control animals ($P<0.05$ at 2 and 3 months).

Spontaneous locomotor activity was decreased ($P<0.05$) up to 1 month following drug withdrawal and the circling response to apomorphine (0.01–0.5 mg/kg s.c.) remained depressed in comparison to control animals ($P<0.05$). Two months after drug withdrawal, spontaneous locomotor activity had returned to control values, although apomorphine-induced circling remained depressed.

Forebrain DA was decreased by 43% on the intact side after 2 months of chronic amphetamine administration and by 20% 1 month following drug withdrawal ($P<0.05$). The DA content of the lesioned side (27% of the intact side; $P<0.05$) was not further reduced by amphetamine administration.

Thus, chronic amphetamine administration inhibits apomorphine-induced circling, which might be due to increased stimulation of the intact striatal dopamine receptors. On the basis of this explanation the continued reduction in apomorphine-induced circling after amphetamine withdrawal would presume the development of supersensitivity of innervated striatal receptors. However, an alternative explanation might be that amphetamine administration decreases the response of nucleus accumbens to apomorphine and its withdrawal leaves accumbens receptors sub-sensitive to apomorphine.

References

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Transport of dopamine by rat blood platelets

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Blood platelets have been proposed as models for studying the uptake mechanisms in central aminergic neurones (Sneddon, 1973). Under conditions where initial rates of uptake are measured (i.e. using low substrate concentrations and short incubation times) the kinetics of platelet 5-hydroxytryptamine (5-HT) uptake and its pharmacological inhibition closely resemble the uptake of 5-HT by synaptosomes (Tuomisto, 1974). Human blood platelets also accumulate dopamine against a concentration gradient by a mechanism which is energy dependent and temperature sensitive (Boullin & O'Brien, 1970; Solomon, Spirt & Abrams, 1970). It is, however,