Amphetamine and apomorphine responses in the rat after lesion of mesolimbic or striatal dopamine neurones

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While low doses of amphetamine increase locomotor activity in the rat, higher doses produce stereotyped behaviour. There is evidence that release of dopamine (DA) in the brain is responsible for these actions of amphetamine. Dopamine is principally localized in two systems of neurons, the nigrostriatal pathway, and the mesolimbic dopaminergic system arising in the A 10 group of neurons and terminating in the nucleus accumbens, olfactory tubercle and frontal cortex. Selective lesions have been made of one or other of these systems using stereotaxic injection of the selective neurotoxic agent 6-hydroxydopamine (6-OHDA). The behavioural effects elicited by low and high doses of d-amphetamine and by the dopamine agonist apomorphine were examined in these two preparations. Locomotor activity was measured in photocell cages, and the intensity of the stereotyped behaviour was evaluated with a 1-6 rating scale.

Eight μg of 6-OHDA injected into the nucleus accumbens septi (NAS) in a volume of 2 μl reduced the DA content of the NAS to 7% of control and that in the olfactory tubercle to 22% of control when brains were assayed 18 days later. Striatal DA was only depleted by 17%. When brains were assayed 90-100 days after the lesion the DA concentration in the NAS had recovered to values significantly greater (21% of control), although there was no similar recovery of amine levels in the other regions studied. Injections of 8 μg of 6-OHDA into the caudate nucleus reduced caudate DA levels by 51% when assays were performed 90-100 days later, but did not affect DA in the nucleus accumbens or olfactory tubercle. The caudate lesion attenuated the intense stereotyped behaviour produced by 5 mg/kg (i.p.) of d-amphetamine, but did not alter the locomotor stimulation produced by 1.5 mg/kg (i.p.) of d-amphetamine. The dopamine agonist apomorphine (1 mg/kg i.p.) produced more intense stereotyped behaviour in the caudate lesioned animals, which may be attributed to supersensitivity of the denervated striatal DA receptors. By contrast the NAS lesion severely attenuated the locomotor response to 1.5 mg/kg (i.p.) of d-amphetamine, whereas the locomotor response to apomorphine (0.1-1.0 mg/kg i.p.) was greatly enhanced. The locomotor stimulant effect of apomorphine was blocked by the DA antagonist pimozide (0.5 mg/kg). The stereotyped behaviour produced by 5 mg/kg of d-amphetamine was not attenuated. These behavioural effects of the NAS lesion were maximal 14-22 days after the lesion. Thereafter there was a gradual recovery, with an increase in the locomotor response to d-amphetamine (1.5 mg/kg) and a corresponding decline in the locomotor response to apomorphine. The behavioural changes correlate with the recovery of DA content in the NAS.

The NAS lesioned animal offers a convenient *in vivo* model for studying the effects of dopamine agonists and antagonists on mesolimbic DA receptors (Kelly, Miller & Neumeyer, D.1, this meeting).

Responses of cortical pyramidal tract cells to amantadine and amphetamine after depletion of central catecholamines

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Amantadine is an anti-Parkinsonian drug for which there is evidence for three possible modes of action: (a) a direct stimulation of postsynaptic receptors; (b) An amphetamine-like action to release presynaptic catecholamines; (c) Inhibition of reuptake of released catecholamines.

From previous experiments we concluded that (c) did not contribute to the depression of neurones seen with iontophoretically applied amantadine (Stone & Bailey, 1975). The present experiments were an attempt to assess the contribution of (a) and (b) to the depressions produced by amantadine.

Male hooded Wistar rats weighing 250-300 g were pretreated 24 h before the acute experiments with one of the following: 1 ml/kg of 0.9% saline; 1 ml/kg Tween 80; 200 mg/kg alpha-methyl-