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

S.D. IVERSEN, P.H. KELLY*,
R.J. MILLER & P. SEVIOUR
(introduced by L.L. IVERSEN)

Psychological Laboratory, Downing Street, Cambridge and M.R.C. Neurochemical Pharmacology Unit, Department of Pharmacology, Medical School, Hills Road, Cambridge

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

T.W. STONE

Department of Physiology, University of Aberdeen, Marischal College, Aberdeen

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-

paratyrosine methyl ester in saline; 10 mg/kg reserpine suspended in Tween 80.

For the acute experiments animals were anaesthetized with 1-1.25 g/kg urethane, and the frontoparietal cerebral cortex was exposed. To compare responses in normal and amine-depleted animals only one type of cell was studied. These were pyramidal tract cells with antidromic latencies of less than 3.0 ms. Five-barrelled micropipettes filled with 200 mM solutions of the various drugs were used for microiontophoresis. Ejecting currents of 60 nA were applied for 15 s in all cases. Three parameters of the neuronal response were measured to allow comparison of the normal and treated animals. These were *h*, the maximum change of firing rate produced, *t*, the time taken to reach that maximum, and *d*, the total duration of the response.

The reduction of amine levels was confirmed by fluorimetric estimation of noradrenaline and dopamine in the cortex.

Dopamine responses were unchanged in the amine depleted animals when compared to controls. Responses to amphetamine and amantadine were significantly reduced in amplitude *h*, but were not abolished. The parameters *t* and *d* were unchanged.

Failure to abolish amphetamine responses by amine depletion has been reported in the cerebellum (Kostopoulos & Yarborough, 1974) and caudate nucleus (Feltz & de Champlain, 1972) and seems to indicate an important difference in the action of amphetamine in these areas and in the brain stem (Boakes, Bradley & Candy, 1972).

The present experiments suggest that on pyramidal tract cells amphetamine and amantadine do not act solely by releasing stored catecholamines.

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Effect of dopamine-β-hydroxylase inhibitors and centrally administered noradrenaline on (+)-amphetamine anorexia in mice.

S. DOBRZANSKI* & N.S. DOGGETT

Department of Applied Pharmacology, Welsh School of Pharmacy, UWIST, Cardiff

Whilst the finding that α-methyl p-tyrosine antagonizes (+)-amphetamine anorexia in mice (Abdallah, 1971) implied possible involvement of catecholamines in the production of (+)-amphetamine anorexia in this species, resolution of the individual function of dopamine and noradrenaline in this capacity has not been attempted. Consequently, we have undertaken a preliminary study of the interactions between (+)-amphetamine, noradrenaline and centrally acting dopamine-β-hydroxylase inhibitors in mice.

Male albino mice of an ICI strain, weighing 20-25 g were housed in groups of 8 at an environmental temperature of 25 ± 1°C and trained over 10 days to adapt to a daily 3 h period of a 41B cube diet consumption. Water was given *ad libitum*. In trained mice, (+)-amphetamine injected subcutaneously, 15 min before feeding, produced a dose related depression of food intake during the first hour of feeding, and 2 mg/kg which produced a submaximal response, was subsequently used as the standard anorexic dose.

Intracerebroventricular (icv) injection of noradrenaline (4 and 8 μg in 5 μl saline) 25 min before feeding, potentiated (+)-amphetamine anorexia significantly ($P < 0.01$) only at the higher dose level. At doses of 250 and 500 mg/kg both disulfiram given orally 3 h before food and sodium diethyldithiocarbamate (DDC) given intraperitoneally 2 h before food markedly potentiated (+)-amphetamine anorexia ($P < 0.001$, $P < 0.001$). Neither noradrenaline nor the dopamine-β-hydroxylase inhibitors significantly influenced feeding when given alone at these dose levels. However, the potentiation of (+)-amphetamine anorexia by DDC was partially, though significantly reversed by noradrenaline (4 and 8 μg icv ($P < 0.05$, $P < 0.001$), although noradrenaline and DDC in combination did not significantly alter feeding compared with saline controls.