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Brain dopamine and the amphetamine-reserpine interaction

SIR,—It seems that in rats the amphetamine excitatory response including stereotyped activity (continuous sniffing, licking and biting) is effected by some interaction or synergism of amphetamine with the brain catecholamines, dopamine and noradrenaline. It can be prevented by inhibition of the synthesis of dopa, the physiological precursor of these amines (Weissman, Koe & Tenen, 1966; Randrup & Munkvad, 1966a) and then restored by the injection of dopa (Randrup & Munkvad, 1966a; Hanson, 1966). In very large doses dopa alone can produce stereotyped activity (Randrup & Munkvad, 1966b; Ernst, 1965).

Further experiments showed that specific inhibition of the synthesis of noradrenaline did not affect the stereotyped activity induced by amphetamine or dopa. This activity, therefore, seems to depend exclusively on dopamine, while noradrenaline seems to be involved in other forms of activity such as locomotion and aggressive behaviour (Randrup & Scheel-Krüger, 1966; Scheel-Krüger & Randrup, 1967).

With this background it becomes necessary to explain why reserpine, which completely depletes the brain both of dopamine and noradrenaline, does not prevent the amphetamine excitatory response.

To investigate this problem we made some experiments on the influence of reserpine and amphetamine upon brain catecholamines. Male Wistar rats weighing 210 to 280 g were injected with various combinations of reserpine (7·5 mg/kg s.c. 20 to 20½ hr before death), the monoamine oxidase inhibitor, nialamide (100 to 500 mg/kg s.c. 2½ hr before death), and (+)-amphetamine sulphate (10 mg/kg s.c. 2 hr before death). The rats were killed by a blow on the back of the neck and the catecholamines together with their *O*-methylated metabolites were measured in brain (Häggendal, 1962, 1963; Scheel-Krüger & Randrup, 1967; Carlsson & Waldeck, 1964).

When reserpine was given alone, none of the four amines, noradrenaline, *O*-methylated noradrenaline, dopamine or *O*-methylated dopamine, could be detected in the rat brains (concentrations below 0·02, 0·01, 0·08 and 0·04 μg/g respectively), and even after the addition of nialamide in the highest dose (500 mg/kg, 5 experiments) they remained undetectable. When, however, amphetamine was added after reserpine and nialamide, *O*-methylated dopamine appeared in measurable amounts.

In five experiments, in which amphetamine was given after reserpine and the highest dose of nialamide, the amounts were 0·35, 0·24, 0·32, 0·50 and 0·07 μg/g tissue, respectively. In three experiments with lower doses of nialamide (100–200 mg/kg) the values were 0·10, 0·27 and 0·14 μg/g, respectively. The other three amines remained undetectable.

In all the experiments amphetamine produced the characteristic stereotyped behaviour. In the dose used (10 mg/kg) it also produces stereotypy when given after reserpine alone, nialamide alone or without pretreatment. In this laboratory 10 mg/kg s.c. is the standard dose used to produce amphetamine-stereotypy. The present experiments thus show that although this stereotypy-producing dose of amphetamine does not alter the level of dopamine in the brain of reserpinized rats, it does interfere with the turnover or metabolism of this amine.

Although this isolated effect of amphetamine upon *O*-methylated dopamine may seem surprising it is in agreement with recent findings about the influence of reserpine and amphetamine on the turnover and metabolism of catecholamines in brain (Andén, Roos & Werdinius, 1964; Glowinski, Axelrod & Iversen, 1966; Carlsson, Fuxe & others, 1966). Thus it has been found that the synthesis of dopamine is not affected by reserpine as evidenced by the undiminished level of the dopamine metabolites dihydroxyphenylacetic acid and homovanillic acid (Andén & others, 1964). Noradrenaline synthesis, however, seems to be inhibited (Stjärne, 1966; Scheel-Krüger & Randrup, 1967).

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