Central actions of amphetamines and ephedrines after unilateral lesions of dopamine neurones

J. E. CHRISTIE* and T. J. CROW (introduced by J. L. MALCOLM), *Departments of Physiology and Mental Health, University of Aberdeen*

Anden (1966) has suggested that the actions of drugs on the central dopamine neurones arising from the pars compacta of the substantia nigra can be studied in animals with unilateral lesions of the nigro-striatal pathway. Such animals show a marked tendency to turn towards the lesioned side when treated with drugs of the amphetamine group (Ungerstedt, 1969; Crow & Gillbe, 1970) and such turning can be used as an index of drug action.

We have compared the relative potencies of amphetamine derivatives in eliciting turning in rats with unilateral nigral lesions. In contrast to its relative ineffectiveness in releasing central noradrenaline (−)-amphetamine is nearly as potent as (+)-amphetamine in its effects on central dopamine stores (Snyder & Taylor, 1970) and is almost as effective in provoking turning. Neither isomer, however, has as marked an effect as methylamphetamine.

To test whether the postulated specificity of the uptake process into dopamine neurones (Jonason & Rutledge, 1968) prevents β-hydroxylated phenylethylamines from releasing central dopamine stores we have tested a number of ephedrine derivatives. These compounds also cause turning although at somewhat higher doses than the amphetamines. The most effective compound is (+)-norpseudoephedrine which is also the derivative most active on general activity (Fairchild & Alles, 1967). Neither the ephedrines nor the amphetamines were diminished in their activity by the administration of reserpine (4 mg/kg 24 h before testing), this finding being in accordance with other reports that this alkaloid differs from α-methyl-*p*-tyrosine in its ability to inhibit the central actions of catecholamine-releasing drugs (Fig. 1).

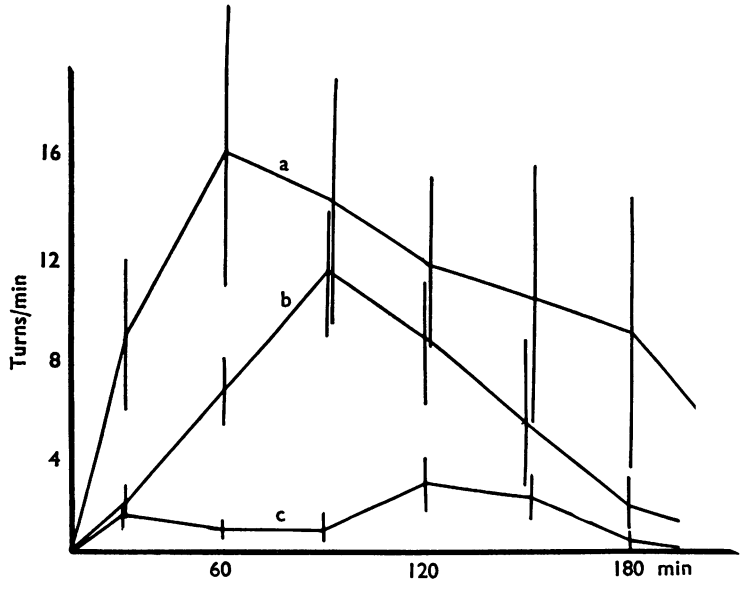

FIG. 1. Number of turns provoked in rats with substantia nigra lesions by (−) ephedrine hydrochloride (100 mg/kg) alone (b), 24 h after reserpine (4 mg/kg) (a), and 14 h after α-methyl-*p*-tyrosine (150 mg/kg) (c).

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Role of cerebral dopamine in the action of psychotropic drugs

G. M. ANLEZARK, G. W. ARBUTHNOTT, J. E. CHRISTIE and T. J. CROW* (introduced by J. L. MALCOLM), *Departments or Physiology and Mental Health, University of Aberdeen*

Biochemical evidence suggests that the turnover of cerebral dopamine is increased by administration of drugs of both the phenothiazine (Anden, Roos & Werdinius, 1964; O'Keefe, Sharman & Vogt, 1970) and amphetamine (Jonas & Scheel-Kruger, 1969) groups. A high proportion of the dopamine in the central nervous system is contained in the terminal varicosities of neurones originating in groups of cell bodies in the ventral mesencephalon (Hillarp, Fuxe & Dahlstrom, 1966). Two behavioural effects of drug action have been suggested to depend upon dopamine release—the stereotyped licking, sniffing, and gnawing behaviour which follows the administration to rats of fairly large doses of the amphetamines (Randrup & Munkvad, 1967), and the turning elicited by similar doses of amphetamines in rats with unilateral nigrostriatal lesions (Anden, 1966). In both cases the behavioural effects of the amphetamine group of drugs are inhibited by administration of phenothiazine derivatives, and the tyrosine hydroxylase inhibitor α-methyl-*p*-tyrosine, but not by the dopamine-β-hydroylase inhibitor FLA 63 (a derivative of disulfram).

In this communication we wish to report some similarities between the behavioural actions of amphetamine-like drugs and the effects of stimulation through electrodes chronically implanted in the region of the ventral mesencephalon. In particular we have found that there is a close correspondence between the sites from which electrical self-stimulation can be obtained and the location of dopamine-containing cell bodies. Sniffing, licking and gnawing can be elicited by stimulation through the same electrodes, and are frequently accompanied by an increase in locomotor activity. From electrode sites in the lateral parts of this region contralateral turning behaviour is provoked by stimulation (Arbuthnott, Crow, Fuxe & Ungerstedt, 1970). The results of experiments with catecholamine synthesis inhibitors, and with electrodes implanted in other neural pathways through this area, support the hypothesis that all three effects of stimulation are related to activation of dopamine-containing neurones.

These results lead us to suggest that the dopamine-containing system arising from the ventral mesencephalon may function as an activating system involved in the effects of positive reward on operant behaviour. This concept of the role of dopamine in the central nervous system may be of significance for understanding some actions of neuroleptic and activation-producing drugs.