The Effects of 5,7-Dihydroxytryptamine Lesions of Extrapyramidal and Mesolimbic Sites on Spontaneous Motor Behaviour, and Amphetamine-Induced Stereotypy

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Summary. 5,7-Dihydroxytryptamine lesions of the nucleus accumbens septi, or substantia nigra, resulted in a twofold increase in spontaneous locomotor activity. Striatal 5HT depletion also raised basal activity levels, as well as increasing rearing behaviour in an open field. The stereotyped responses to all doses of amphetamine tested (2.5 - 10 mg/kg, i.p.) were enhanced by lesions of the nucleus accumbens or substantia nigra. Stria
tal lesions only affected the response to the lowest dose of amphetamine. Lesions of the tuberculum olfactorium were without effect on spontaneous or amphetamine induced responses. The results support the concept of a modulatory 5HT influence on nigro-striatal function, and suggest that 5HT in the nucleus accumbens has an antagonistic role with respect to dopamine function in this site.

Key words: Dopamine - 5-Hydroxytryptamine - Activity - Stereotypy - Amphetamine.

Introduction

The control of motor behaviour, and the induction of stereotyped behaviour by agents such as apomorphine or amphetamine, are thought to depend largely upon the integrity of central dopaminergic mechanisms localised within extrapyramidal and mesolimbic brain systems (Kelly et al., 1975; Costall et al., 1977).

Recent studies have shown that manipulation of other central neurotransmitter systems — particularly y-aminobutyric acid (GABA) and 5-hydroxytryptamine (5HT) can also affect such behaviour. Hyperactivity may be produced or enhanced by lowering central serotonergic or GABA-ergic function, for instance by raphé nucleus lesions (Kostowski et al., 1972), p-chlorophenylalanine (PCPA) pretreatment (Segal, 1976; Marsden and Curzon, 1977), 5HT receptor blockade (Carter and Pycock, 1978b), or by putative GABA receptor antagonists (Pycock and Horton, 1979). Some of these effects may be explained by the known inhibitory effects of GABA and 5HT on nigro-striatal dopamine function. The roles of 5HT or GABA in stereotyped behaviour however appear to be more complex. Raphé lesions, PCPA pretreatment, or 5HT receptor antagonism, have been shown to reduce components of apomorphine or amphetamine-induced stereotyped behaviour (Costall et al., 1975; Segal, 1976; Carter and Pycock, 1978b) while injections of the putative GABA agonist muscimol, into the nucleus accumbens, convert the hyperactivity produced by dopamine injections into this site, to intense stereotyped gnawing or licking (Scheel-Krüger et al., 1977).

In this study, we have investigated the effects of localised 5HT depletion in selected DA containing brain areas, on spontaneous locomotor activity and amphetamine-induced stereotyped behaviour. The neurotoxin 5,7-dihydroxytryptamine (Baumgarten et al., 1973) was used to lesion 5HT terminals within the substantia nigra, striatum, nucleus accumbens septi or tuberculum olfactorium.

Methods

Surgery. Male Porton rats (200—250 g) were anaesthetised with chloral hydrate (300 mg/kg i.p.) and immobilised in a Kopf stereotaxic frame. 5,7-Dihydroxytryptamine (Sigma) (10 μg/2 μl saline containing 0.1% ascorbic acid) was injected bilaterally into the striatum (A + 8.0, L ± 3.0, V + 1.0), nucleus accumbens septi (A + 9.4, L ± 1.5, V — 0.5), tuberculum olfactorium (A + 8.5, L ± 2.5, V — 2.5, and A + 9.5, L + 2.0, V — 2.0) and substantia nigra (A + 1.8, L ± 2.5, V — 3.0) (co-ordinates from De Groot, 1959) through a stainless steel cannula (O.D., 0.3 mm) at a rate of 1 μl/min. Striatally lesioned animals received 15 μg of neurotoxin in 3 μl solvent. Sham-operated animals received solvent alone.
**Behavioural Testing.** Ten days after surgery, spontaneous motor behaviour of lesioned or sham-operated animals was assessed in an open field apparatus (88 x 88 cm with 15 cm retaining walls, divided into 25 squares of equal size). Rats were placed in the centre of the open field, and the number of lines crossed in the central or perimeter area noted during a 5-min test session. Incidences of rearing or grooming were also recorded. Groups of 6 rats were randomly selected for biochemical determination of the effects of the lesion, and the remaining animals were transferred to perspex observation cages (30 x 20 x 15 cm). After 30 min acclimatisation groups of 6 rats were injected with dexamphetamine sulphate (2.5 – 10.0 mg/kg i.p.) and stereotyped behaviour recorded at 10 min intervals for 3 h. The following scoring system was adopted. 0 = the appearance of the animals is the same as that of saline-treated controls; 1 = periodic sniffing with some locomotion; 2 = continuous sniffing with little locomotor component; 3 = periodic biting, gnawing or licking; 4 = continuous biting, gnawing or licking, no locomotion (Costall and Naylor, 1973).

**Biochemical Analysis.** Rats were killed by cervical dislocation, and the brains removed and dissected over ice into the following regions — striatum, nucleus accumbens septi, tuberculum olfactorium, substantia nigra, and frontal cortex (see Horton et al., 1978). Following homogenisation in acidified butanol and back-extraction into 0.1 N HCl, 5HT was assayed fluorimetrically after condensation with o-phthalaldialdehyde (Curzon and Green, 1970).

**Statistics.** Mean scores for stereotyped behaviour in sham and lesioned animals were compared using the Mann-Whitney ‘U’ test for non-parametric data. Results from observations in the open field, or biochemical data were subjected to a Student’s ‘t’ test. At least 6 animals were used in each control or treated group.

**Drugs.** 5,7-Dihydroxytryptamine (Sigma) was dissolved in 0.9% saline containing 0.1% ascorbic acid. Dexamphetamine sulphate (Smith, Kline and French) was dissolved in 0.9% saline.

**Results and Discussion**

Animals with 5,7-DHT lesions of the nucleus accumbens or substantia nigra were noticeably more active when handled or disturbed in the home cage. Such lesions produced a twofold increase in activity in the perimeter squares of the open field (P < 0.05) (Fig. 1). Activity in the central squares, or rearing and grooming behaviour were not significantly affected. Striatal 5,7-DHT lesions also produced an increase in perimeter activity (≈ 1.6 x basal control levels), (P < 0.05) and in addition, produced a significant increase in the incidences of rearing (P < 0.01, Fig.1). Lesions of the tuberculum olfactorium had no effect on any of the behavioural parameters assessed.

The peak effect of each dose of amphetamine was significantly enhanced by 5,7-DHT lesions of either the nucleus accumbens or substantia nigra (P < 0.05, Fig. 2), although the effect was less noticeable at the highest dose, possibly because of the near maximal effect produced in control animals. Lesions of the tuberculum olfactorium had no significant effect upon any components of the stereotyped response, but striatal lesions significantly enhanced the effects of the lowest dose (2.5 mg/kg) of amphetamine (P < 0.05) which, in lesioned rats produced continuous, rather than periodic sniffing behaviour. The qualitative nature of the amphetamine response was unaltered by any of the lesions. Each lesion produced a significant reduction in 5HT concentrations within the lesion site (P < 0.01). Lesions of the tuberculum olfactorium,