Dissociation by the aporphine derivatives of the stereotypic and hyperactivity responses resulting from injections into the nucleus accumbens septi

Recent studies have focussed interest on the nucleus accumbens septi (ACB) as a site for the initiation of hyperactivity responses in the rat. In particular, dopamine injections into the ACB have been shown to induce a marked hyperactivity which is antagonized by low doses of neuroleptic agents (Pijnenburg & van Rossum, 1973; Pijnenburg, Honig & van Rossum, 1975; Costall & Naylor, 1975). Thus, we considered the possibility of using this injection procedure as a model for dopamine agonist activity. However, whether the hyperactivity response from the ACB represents dopaminergic agonist activity *per se* or whether this reflects a true ability to increase locomotor activity remains unclear since it has been reported that apomorphine and (±)-*N*-n-propylnorapomorphine, dopaminergic agonists which lack the ability to increase locomotor activity in normal animals, are able to cause a hyperactive response following the injection of 6-hydroxydopamine into the ACB (Iversen, Kelly & others, 1975; Kelly, Miller & Neumeyer, 1975). Therefore, the present studies were designed to determine whether apomorphine and other aporphine derivatives, which normally lack the ability to increase locomotor activity although they possess marked dopaminergic agonist properties as measured by their ability to induce stereotyped responses, are able to cause hyperactivity following their direct injection into the ACB.

All experiments utilized male Sprague–Dawley (C.F.E.) rats, 250–300 g, and were carried out between 08.00 and 18.00 h in a sound-proofed, diffusely illuminated room maintained at 21 ± 1°. Activity boxes measured 30 cm × 20 cm and 15 cm high and were fitted with photocells. Activity was characterized by counting the number of interruptions of the light beam occurring during each 5 min period. Activity boxes were used in banks of 30 and were individually screened. Stereotyped behaviour was assessed simultaneously with activity through a one-way mirror and in separate experiments. Two components of stereotypy were individually assessed (sniffing and gnawing/biting/licking) and scored 0—no sniffing or gnawing/biting/licking, 1—very periodic sniffing or gnawing/biting/licking (intervals of no response greater than 1 min), 2—periodic sniffing or gnawing/biting/licking (intervals of no response less than 1 min), 3—continuous sniffing or gnawing/biting/licking.

Activity and stereotyped behaviour were assessed both after the peripheral (subcutaneous) administration of aporphine derivatives and after their injection into the ACB. Dopamine was also injected into the ACB. For peripheral administrations (−)-apomorphine HCl (Macfarlan Smith), (±)-*N*-n-propylnorapomorphine HI [(±)-NPA] and (−)-*N*-n-propylnorapomorphine HCl [(−)-NPA] were prepared in 0·1% sodium metabisulphite. For intracerebral injection, dopamine HCl (Koch–Light), apomorphine, (±)-NPA, (−)-NPA, (−)-1,2-dihydroxyaporphine HI, (+)-1,2,9,10-tetrahydroxyaporphine HI and (±)-isoapomorphine HBr (Pinder) were prepared immediately before use in nitrogen bubbled distilled water and (−)-1,2-dimethoxyaporphine in a minimum quantity of HCl.

Guide cannulae for intracerebral injections were chronically implanted using the stereotaxic techniques previously described (Costall & Naylor, 1975). Briefly, bilateral stainless steel guide cannulae (0·65 mm diameter) were implanted with their tips at Ant. 9·0, Vert. +2·5, Lat. ±1·5 (De Groot, 1959) and stainless steel injection units (0·3 mm diameter) were made to extend 2·5 mm beyond the tips and deposit drug at the centre of the ACB. Drugs or solvent were delivered bilaterally into the ACB in a volume of 2 μl during a 1 min period after a 2 h pretreatment of rats with

100 mg kg^{-1} intraperitoneal nialamide. Animals were first used 10 to 14 days after the operation and were used on a total of two occasions only with an intervening 14 day recovery period. Upon completion of the studies the locations of guide cannulae tips were determined histologically and were found to be correct for injections into the area of the ACB (see Costall, Naylor & Neumeyer, 1975).

The peripheral administration of apomorphine (0·125–2·0 mg kg^{-1}, s.c.), (−)-NPA (0·0032–0·1 mg kg^{-1}, s.c.) and (±)-NPA (0·016–1·0 mg kg^{-1}, s.c.) induced stereotyped behaviour patterns characterized by both sniffing and gnawing/biting/licking although the biting response was the dominant effect of (−)-NPA (see Costall & others, 1975). However, using these wide dose ranges of apomorphine, (−)-NPA and (±)-NPA no significant increase in activity was recorded. Constant observation was required throughout the experiments in order to differentiate between interruptions of the light beam caused by stereotyped movements or by active movements about the cage.

The injections of dopamine (5–100 μg), apomorphine (12·5–50 μg) and (−)-NPA (6·25–25 μg) into the ACB each induced stereotyped behaviour patterns of intensity related to dose but the nature of the responses differed; dopamine caused only a sniffing response, apomorphine induced sniffing and a weak biting whilst the effect of (−)-NPA was predominantly biting (Fig. 1). In addition, dopamine (5–100 μg) and (−)-NPA (6·25-25 μg) caused dose-dependent increases in activity, although the maximum effect of (−)-NPA was much less than that of dopamine (Fig. 1). The activity recorded after injections of apomorphine into the ACB (12·5–50 μg) was indistinguishable from that exhibited by animals receiving solvent injections only.

The injections of 12·5–50 μg (±)-NPA, (−)-1,2-dihydroxyaporphine, (+)-1,2,9,10-tetrahydroxyaporphine, (−)-1,2-dimethoxyaporphine or isoapomorphine into the ACB failed to induce either stereotyped or hyperactive behaviour.

Therefore, the present results show that agents which have marked dopaminergic agonist properties as indicated by the induction of stereotyped behaviour (Costall & others, 1975; Schoenfeld, Neumeyer & others, 1975), may not mimic the effects of dopamine in causing a hyperactivity response after injections into the ACB. If it is accepted that apomorphine and the more recently introduced (±)- and (−)-NPA are able to directly stimulate dopamine receptors (Andén, Rubenson & others, 1967;

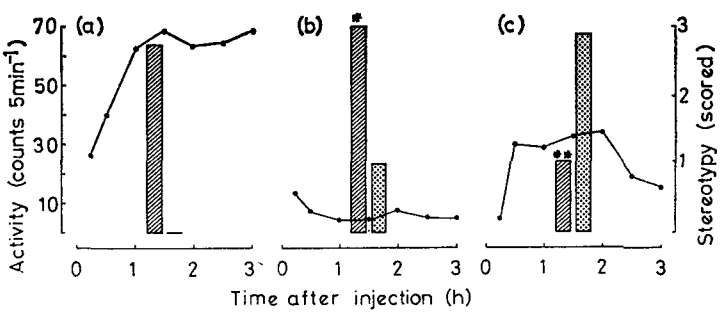

FIG. 1. The induction of hyperactivity (●——●) and stereotyped sniffing behaviour (hatched columns) or biting/gnawing/licking (dotted columns) following the bilateral injections of 50 μg dopamine (a), 50 μg apomorphine (b) and 25 μg (−)-*N*-n-propylnorapomorphine (c) into the nucleus accumbens septi. Doses selected for graphical representation are those causing the maximum increase in activity and/or intensity of stereotyped behaviour. Stereotyped sniffing or gnawing/biting/licking were assessed on a 1–3 scoring system (see text) *2/6 or **4/6 animals only gave these responses, others failed to respond. All other values are the means of responses from 6–10 animals. Standard errors are all less than 20% of the means.

Costall & others, 1975), their failure to cause marked hyperactivity after injections into the ACB indicates a relative inability to stimulate a mechanism sensitive to dopamine. Similar observations have been made following the injection of such aporphines into the striatum; they do not mimic the hyperactivity response to dopamine (Costall & Naylor, unpublished observations). Thus, in normal rats apomorphine, (±)-NPA, (−)-NPA and the other aporphine derivatives evaluated lack the ability to induce hyperactivity following peripheral administration and have a weak action or lack effect following intracerebral application to the ACB or striatum. The use of a hyperactivity response as a behavioural index of dopaminergic stimulation in normal rats may, therefore, exclude the most potent dopaminergic agonists known. The locomotor response obtained after the peripheral injection of apomorphine and (±)-NPA to rats with 6-hydroxydopamine lesions of the ACB (Iversen & others, 1975; Kelly & others, 1975) may, therefore, indicate a change in receptor sensitivity *and specificity* presumably involving dopaminergic mechanisms within the ACB or in the associated dopamine-containing tuberculum olfactorium.

This work was supported by the Medical Research Council and the State of New Jersey, Department of Health, Division of Narcotic and Drug Abuse Control. Dr. R. M. Pinder kindly provided isoapomorphine and Miss M. Y. Green gave excellent technical assistance with the animal studies.

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April 25, 1975

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