Hyperactivity response to apomorphine and amphetamine in the mouse: the importance of the nucleus accumbens and caudate-putamen

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A disadvantage to the use of locomotor hyperactivity responses in normal animals (such as those measured in photocell cages or in activity wheels) as tests for the specific locomotor depressant actions of neuroleptic agents is their general failure to detect atypical neuroleptics such as sulpiride. Interest has, therefore, focused on a hyperactivity response in the mouse to apomorphine which will detect sulpiride and similar agents and allow the elimination of non-neuroleptic agents such as metoclopramide by simple drug interactions (Protais et al 1976; Costall et al 1978). Of two brain regions known to be important for motor control, the nucleus accumbens and striatum (see review by Costall & Naylor 1977), the striatum, rather than the nucleus accumbens, has been indicated by brain lesion studies to be the site at which apomorphine can induce the hyperactivity response, which has been quantified as a climbing behaviour (Protais et al 1976). However, it is difficult to reconcile this finding with the novelty of climbing behaviour to 'detect' the actions of sulpiride and other atypical agents since changes in the mesolimbic regions such as the nucleus accumbens are now considered to be at least as important as changes in striatal function for the neuroleptic effect (Costall & Naylor 1976; Waldmeier & Maitre 1976; Elliott et al 1977). This has been exemplified by studies on circling behaviour, which can be modulated by neuroleptic agents, showing that whilst striatal damage may cause asymmetry, it is the nucleus accumbens which can provide a component of motor drive (Pycock & Marsden 1978). Therefore, the present studies were designed to re-evaluate the importance of the nucleus accumbens and striatum for the induction of climbing behaviour induced by apomorphine in the mouse. Comparisons were made with amphetamine-induced hyperactivity since apomorphine failed to induce a locomotor hyperactivity, expressed in a form other than climbing, in the strain of mouse used. Amphetamine was also selected on the basis of its ability to cause hyperactivity via the mesolimbic areas (Costall & Naylor 1977).

The studies used male albino mice, BKW strain, 25–30 g at the beginning of an experiment or 35–40 g at the time of operation. Stereotaxic surgery was carried out using a Kopf stereotaxic instrument and ear bars and incisor bar (raised 2·0 mm above the inter-aural line) supplied for the rat. Mice were anaesthetized with chloral hydrate, 450 mg kg^{-1} i.p., and electrolesions were induced in the caudate-putamen using a stainless steel electrode (0·65 mm diam.) insulated except at the tip, and passing 1·5 mA for 15 s, or in the nucleus accumbens using an electrode 0·3 mm diam. and passing a current of 1·0 mA for 10 s. Lesions were induced bilaterally in the nucleus accumbens but mortality rates were unacceptably high when bilateral lesions were induced in the caudate-putamen on the same occasion: the latter lesions were, therefore, initially placed unilaterally and the second lesion was placed after a 14 day recovery period. Lesion locations were determined with reference to the atlas of Lehmann (1974). The electrode locations for caudate-putamen lesions were 1·0 mm anterior to bregma, 2·3 mm lateral to the midline, vertical 3·5 mm from the skull surface, and 2·3 mm anterior to bregma, 0·8 mm lateral to the midline, vertical 3·7 mm from the skull surface for lesions of the nucleus accumbens. These locations were confirmed histologically on completion of the studies (caudate lesions were essentially confined to the body and head of the caudate-putamen complex: slight damage to the cerebral cortex was infrequent except at the point of the electrode insertion. Lesions of the nucleus accumbens were confined to this area with minimal damage to the medio-anterior caudate and frontal cortex). Sham operated animals were treated exactly as above excepting that a current was not passed after electrode insertions to the appropriate coordinates. The responses of operated and sham operated animals to apomorphine (apomorphine hydrochloride, Macfarlan Smith, prepared in distilled water containing 0·1% sodium metabisulphite) and amphetamine ((+)-amphetamine sulphate, Sigma, dissolved in distilled water) were assessed 14 days after surgery (14 days after the second lesion of the caudate-putamen), and on the 28th and 56th postoperative days.

Behavioural experiments were carried out between 09.00 and 18.00 h in a diffusely illuminated room maintained at a temperature of 21 ± 1 °C. Mice exhibited climbing behaviour following s.c. apomorphine. To quantify this behaviour, animals were placed in individual Perspex cages, 20 × 15 × 15 cm, lined with 1 cm^2 wire mesh, made of wire 2 mm in diameter. 30 min were allowed for animals to acclimatize to the new environment. Animals then given control solvent injections exhibited normal exploratory behaviour about the floor of their individual cages, whilst normal animals receiving apomorphine climbed about the sides and tops of the cages, moving constantly and holding on to the wire mesh with their four paws. Mice were individually tested for climbing behaviour taking 'the percentage of time spent climbing during the 30 min after the first climb' as a measure of climbing (the 'climbing index', see Costall et al 1978).

Amphetamine-induced hyperactivity was measured

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by placing mice in individual Perspex boxes, 30 × 20 × 15 cm, each fitted with one photocell unit set off-centre with the beam 2·5 cm above the cage floor. Hyperactivity was recorded electromechanically as the number of interruptions of the light beam occurring in a 5 min period. Animals were also visually observed and any change in the nature of the amphetamine response, e.g. to a stereotyped behaviour, was noted.

Apomorphine caused dose-dependent climbing behaviour in doses of 0·5–1·5 mg kg^{-1} s.c. (stereotypy interfered with this behaviour at 2·0 mg kg^{-1} s.c.). 1·0 mg kg^{-1} s.c. apomorphine was selected as a sub-maximal dose for subsequent studies (Fig. 1). Normal

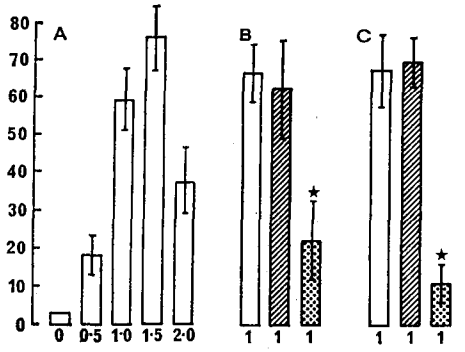

FIG. 1A. Dose-dependency of the climbing behaviour induced by 0·5–2·0 mg kg^{-1} s.c. apomorphine in the mouse. The onset of climbing behaviour was within 5–7 min of drug administration, and the duration approximately 40–50 min. The climbing index represents the percentage of time spent climbing during the 30 min following the first climb. B. The climbing behaviour induced by 1·0 mg kg^{-1} s.c. apomorphine in normal mice, open columns, sham operated mice, hatched columns and mice with bilateral electrolesions of the nucleus accumbens stippled columns on the the 14th and C.56th postoperative days. n = 6–8. The s.e. of the mean is shown. *P<0·001. Ordinate: climbing index (%). Abscissa: dose (mg kg^{-1}).

solvent treated mice exhibit a low intensity climbing behaviour, the 'climbing index' being less than 5% (see Costall et al 1978b). On the 14th, 28th and 56th post-operative days, bilateral electrolesions of the nucleus accumbens were shown to significantly reduce the climbing response to apomorphine, while the responses of sham operated animals were indistinguishable from the measures made for control, solvent treated animals (Fig. 1). Increasing the dosage of apomorphine to 2–10 mg kg^{-1} s.c. did not overcome the reduction in effect caused by the lesions (although stereotypy did develop at these doses). Climbing behaviour was not observed when animals with bilateral lesions of the caudate-putamen were given 1·0 mg kg^{-1} s.c. apomorphine. On the 14th and 28th post-operative days animals tended to circle ipsilateral to the first lesion. Insufficient animals survived for testing on the 56th postoperative day.

1·0–2·5 mg kg^{-1} i.p. amphetamine caused a dose-dependent hyperactivity in normal mice (Fig. 2). Reduced hyperactivity recordings at 4·0 mg kg^{-1} i.p. coincided with the development of stereotyped biting (Fig. 2A). Untreated animals, or animals given solvent, exhibited a period of exploration when placed in the activity boxes: this was most marked in the initial 10 min period and declined over the following 50–80 min to a basal level of <5 counts/5 min (Figs 2A and B). The hyperactivity recorded during this exploratory period was maintained at a more intense level (approx. 70–90 counts/5 min) in animals with bilateral lesions of the nucleus accumbens (P<0·001 compared with normal or sham operated mice), whilst the response of sham-operated animals closely followed that of normal mice (Fig. 2B). 2·0 mg kg^{-1} i.p. amphetamine failed to enhance the activity of lesioned animals 14 days after surgery (Fig. 2C) whilst the activity of normal animals given this dose of amphetamine was enhanced above that of normal mice given solvent (P<0·001) or lesioned animals receiving solvent or the same dose of amphetamine (P<0·01) (Fig. 2C). The inability of amphetamine to enhance activity above basal levels in the lesioned mice could not be overcome by increasing the dose of amphetamine (although stereotyped behaviour did develop). Data obtained 28 or 56 days after surgery were indistinguishable from those in Figs 2B and C for the 14th postoperative day.

Bilateral lesions of the caudate-putamen failed to modify either normal exploration or the response of mice to amphetamine on any day, or at any time of testing.

The present studies indicate that the nucleus accumbens may be directly and/or indirectly involved with the mediation of apomorphine climbing in mice. Differences in lesion location and extent may account for the report by Protais et al (1976) that accumbens lesions fail to modify apomorphine climbing. The reduction obtained in the present work, which persisted for at least 56 days after surgery, could not be related to any non-specific depression of motor function, indeed the mice with accumbens lesions were demonstrably more active than normal or sham operated mice. Nevertheless, in accord with studies in the rat (Kelly et al 1975; Costall et al 1977), the importance of the nucleus accumbens for locomotor responding in the mouse was emphasized by the marked reduction in amphetamine-induced hyperactivity by lesions of this area.

It was considered possible that the effects of accumbens lesions may reflect the interruption of an efferent system from other apomorphine sensitive area(s) involved in locomotor control, for example, the caudate-putamen. The effects of lesions of the caudate-putamen were therefore investigated, but difficulties arise in the interpretation of the data obtained since the lesioned animals invariably circled ipsilateral to the side of the

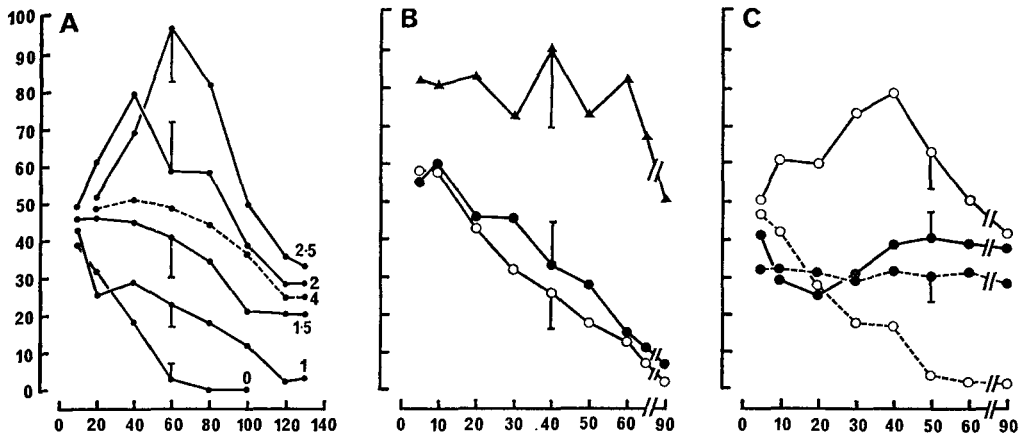

FIG. 2. A. Dose-dependency of the hyperactivity (ordinate: counts/5 min) induced by (+)-amphetamine 1·0–2·5 mg kg^{-1} i.p. Stereotyped behaviour developed at 4·0 mg kg^{-1} i.p. (- - - -). Doses are indicated in mg kg^{-1} i.p. Hyperactivity was measured as the number of interruptions of a photocell beam occurring within 5 min (counts/5 min). B. Spontaneous (exploratory) locomotor activity exhibited by normal mice (○——○) and mice with bilateral electrolesions of the nucleus accumbens (▲——▲) or the appropriate sham operation (●——●) (14th postoperative day). C. Hyperactivity induced by 2·0 mg kg^{-1} i.p. amphetamine in normal mice (○——○) and mice with bilateral lesions of the nucleus accumbens (●——●): effects of saline in normal mice (○- -○) and lesioned mice (●- -●) (14th postoperative day). n = 6–8. Representative s.e.s. given. Abscissa: time (min).

first lesion when challenged with apomorphine (and experiments using animals with unilateral lesions of the caudate-putamen have shown that the development of circling can prevent a climbing response; Costall, Naylor & Nohria, unpublished data). The histological examinations did not reveal any clear differences in the size of the areas damaged in the two striata, and repeat experiments paying careful attention to the lesion parameters did not eliminate the development of circling or asymmetry to doses of apomorphine which may be expected to cause a climbing behaviour. However, it should be noted that small electrolesions of the caudate-putamen have been reported to reduce apomorphine climbing (precise lesion location not specified, and it is presumed that the animals were in good health), whilst 6-hydroxydopamine lesions of the same area enhanced the climbing (although this potentiation persisted for an inexplicably short period of 6 days, and animals exhibited climbing in addition to circling behaviour) (Protais et al 1976). If the caudate-putamen is involved in the modulation of climbing behaviour, then this clearly differentiates a climbing 'hyperactivity' response from that induced by amphetamine (used in doses too low to reveal the inherent striatal asymmetry) which was not modified by lesions of the caudate-putamen.

It is suggested that the mesolimbic nucleus accumbens (possibly in addition to the caudate-putamen) may be involved with the hyperactivity responding to both apomorphine and amphetamine, and that this area cannot, therefore, be excluded as a site at which neuroleptic agents, including atypical drugs, may act to antagonize apomorphine climbing behaviour (Costall et al 1978). However, since amphetamine hyperactivity is known to be comparatively resistant to blockade by atypical neuroleptics such as sulpiride (Costall et al 1978a), the present data may be taken as further evidence that apomorphine and amphetamine, although both capable of affecting the function of the nucleus accumbens, may do so by interference with different mechanisms, the nature of the changes caused by apomorphine being the more appropriate for the detection of antischizophrenic drug activity.

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