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Effects of Amphetamine and Apomorphine on Locomotor Activity After 6-OHDA and Electrolytic Lesions of the Nucleus Accumbens Septi[1]

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KELLY, P. H. AND D. C. S. ROBERTS. *Effects of amphetamine and apomorphine on locomotor activity after 6-OHDA and electrolytic lesions of the nucleus accumbens septi.* PHARMACOL BIOCHEM BEHAV **19**(1) 137–143, 1983.— Spontaneous locomotor activity was markedly elevated by electrolytic lesions of the nucleus accumbens. This was true whether or not the dopaminergic input to this nucleus was previously destroyed by injection of 6-hydroxydopamine (6-OHDA) into the region. In animals with electrolytic lesions the locomotor stimulant action of d-amphetamine sulfate (1.5 mg/kg SC) was occluded, while a moderately low dose of apomorphine (0.25 mg/kg SC) produced a striking decrease of locomotor activity. The results are consistent with the view that the efferents of neurons in the nucleus accumbens exert an inhibitory influence on locomotor activity. Hyperactivity results when these efferents are destroyed. The results are also consistent with the view that the locomotor depressant action of apomorphine is mediated, at least partly, by an action at a site other than the nucleus accumbens.

Nucleus accumbens Hyperactivity Locomotor activity Amphetamine Apomorphine Dopamine

CONSIDERABLE evidence suggests that a primary event in the stimulation of locomotor activity by amphetamine is facilitation of the release of dopamine from terminals of mesolimbic dopaminergic neurons innervating the nucleus accumbens and olfactory tubercle. For example, dopamine and dopaminergic agonists microinjected into the nucleus accumbens elicit a marked stimulation of locomotor activity [33,34]. Microinjections of cholera toxin, an irreversible activator of adenylate cyclase, into the nucleus accumbens elicit a similar, but more prolonged behavioral effect [23], supporting the suggestion that cyclic AMP may be an intracellular second messenger mediating some of the effects of dopamine.

In agreement with these chemical stimulation studies, lesion studies have shown that microinjections of 6-hydroxydopamine (6-OHDA) into the nucleus accumbens preferentially destroy mesolimbic and mesocortical dopaminergic neurons [15,18] and greatly reduce the stimulation of locomotor activity by systemically administered amphetamine or cocaine [14, 16, 36]. Preferential destruction of dopamine terminals in frontal cortex does not reduce amphetamine-induced locomotor activity [38]. Moreover, dopamine antagonists, microinjected into the nucleus accumbens also reduce or abolish amphetamine-induced locomotor activity [32]. Subsequent studies have provided evidence that a number of neurotransmitters, neuropeptides and hormones influence locomotor activity by acting either at the cell bodies or terminal regions of the mesolimbic dopamine system. These substances include serotonin [6,20], acetylcholine [5], GABA [26,30], substance P [13], enkephalins [1,31] and thyrotropin releasing hormone [24].

In contrast to the blockade of amphetamine-induced locomotor activity after injections of 6-OHDA into the nucleus accumbens, amphetamine-induced locomotor activity is reportedly still present after electrolytic lesions of the nucleus accumbens [41]. Since part of the nucleus accumbens was spared by the lesion a possible explanation of this result is that the amphetamine-induced locomotor activity was mediated by dopamine release onto the remaining intact neurons of this nucleus. Such an explanation would not apply, however, if an electrolytic lesion were capable of restoring amphetamine-induced locomotor activity after it had been blocked by previous destruction of the mesolimbic dopamine innervation with 6-OHDA. This result is predicted

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if amphetamine-induced locomotor activity is indeed blocked by 6-OHDA lesions, but not by electrolytic lesions, of the nucleus accumbens. The present study was therefore designed with three aims in mind: first, to re-investigate if amphetamine-induced locomotor activity is present after electrolytic lesions of the nucleus accumbens; second, to investigate if electrolytic lesions are capable of restoring amphetamine-induced locomotor activity previously blocked by a 6-OHDA-induced lesion; and third, to examine the effect of the dopamine agonist apomorphine in rats with electrolytic lesions of the nucleus accumbens.

Since these experiments were performed several other conflicting reports have appeared concerning the effects of electrolytic and radio-frequency lesions of the nucleus accumbens on spontaneous and amphetamine-induced locomotor activity [2, 7, 12, 21, 40]. One factor which appears to be important in determining whether such lesions block amphetamine-induced locomotor activity is the exact location of the lesion [40]. In the present report, therefore, lesion sites are presented visually at several levels along their anterior-posterior extent, in preference to the less informative written descriptions or illustrations of a representative lesion at a single anterior-posterior level, which have generally sufficed in previous reports. Another factor of importance appears to be the method used to record locomotor activity [12]. This factor is therefore discussed later.

METHOD

Subjects were male Charles River Wistar rats weighing 290–310 g at the start of the experiment. Pairs of rats were housed in plastic cages with ad lib food and water. A 12 hr light/dark cycle was maintained in the colony. All animals received bilateral injections into the nucleus accumbens under Equithesin anesthesia (3 ml/kg). One group received 6-OHDA (8 μg/2 μl, dose as the free base) in saline containing ascorbic acid (0.2 mg/ml). The control group received identical injections of the ascorbic acid/saline solution. Injection rate was 2 μl/5 min.

Coordinates were as follows: Incisor bar at +5.0 mm, AP +3.4 mm from Bregma, ML ±1.7 mm, DV −7.2 mm from dura. Immediately following the 6-OHDA or vehicle injections, all animals were implanted with stainless steel wire electrodes so that the tip of the electrode corresponded to the site of the injection. The electrodes, insulated except for the cross sectional area of the tip, were permanently fixed to the skull with dental cement and skull screws. Approximately 3–4 mm of electrode was left clear of cement and bent flat to the skull mount.

The animals were allowed four days recovery prior to initial testing in photocell activity cages. Animals were habituated and tested in these cages for 4 hr/day for 4 days. On postoperative day 10 the animals were habituated for 1 hr then injected with 1.5 mg/kg d-amphetamine sulfate SC, returned to the testing cages and their activity measured for 2 hr. This dose of d-amphetamine was chosen as one which markedly stimulates locomotor activity without causing stereotyped licking and biting [16].

After three drug free days, all rats were again tested with apomorphine hydrochloride (0.25 mg/kg SC) in the same way. This dose of apomorphine was chosen as one which produces locomotor depressant effects but little stimulatory action in intact animals [3,39] (unpublished observations). Four days after the apomorphine test, half the animals in each group received bilateral electrolytic lesions through the implanted electrodes. Rats were anesthetized briefly with halothane before a current 1 mA was passed for 30 sec between the previously implanted electrode and a rectal cathode. The remaining animals were handled identically except that no current was passed.

This procedure created four groups: 6-OHDA-sham lesion (n=7); 6-OHDA-electrolytic lesion (n=8); vehicle-sham lesion (n=7); and vehicle-electrolytic lesion (n=8).

The animals were again tested in the photocell cages for their response to amphetamine (1.5 mg/kg, SC) four days and eighteen days post operatively, and with apomorphine (0.25 mg/kg SC) eight days postoperatively, and with saline fourteen days postoperatively.

After behavioral testing all animals with electrolytic lesions were perfused transcardially with saline and formalin under deep anesthesia. Histological examinations of lesions were made on cresyl violet stained sections.

The remaining animals were decapitated and their brains were dissected on ice, into the following brain areas: olfactory tubercle, nucleus accumbens, caudate and neocortex. Catecholamines were measured by a radioenzymatic assay [27].

Results were analyzed by a two factor repeated measures ANOVA. Post hoc comparisons were made using *t*-tests or paired *t*-tests as appropriate, with the significance level set at 0.01 to compensate for the use of multiple comparisons.

RESULTS

Amphetamine-Induced and Apomorphine-Induced Locomotor Activity Prior to Electrolytic Lesions

As previously described amphetamine-induced locomotor activity was greatly reduced in animals which had received microinjections of 6-OHDA into the nucleus accumbens, whereas apomorphine-induced activity was substantially increased compared to animals which had received intra-accumbens vehicle (Table 1).

Spontaneous Locomotor Activity and Drug Effects on Locomotor Activity After Electrolytic Lesions of the Nucleus Accumbens

Total locomotor counts after drug and saline treatments are summarized in Table 2, and time courses illustrated in Figs. 1–4. Two factor, repeated measures ANOVA of the results summarized in Table 2 revealed a significant main effect of group, $F(3,26)=8.35$, $p<0.001$, drug treatment, $F(3,78)=13.52$, $p<0.001$, and a significant group × drug treatment interaction, $F(9,78)=4.15$, $p<0.001$.

Post hoc comparisons of the spontaneous activity (i.e., after saline injection) of the various groups showed no difference between the activity of the vehicle-sham and 6-OHDA-sham groups, $t(12)=1.08$, $p>0.05$, and no difference between the activity of the vehicle-electrolytic lesion and 6-OHDA-electrolytic lesion groups, $t(14)=0.48$, $p>0.05$. The vehicle-electrolytic lesion group was significantly more active than both the vehicle-sham group, $t(13)=4.40$, $p<0.01$, and the 6-OHDA-sham group, $t(13)=3.60$, $p<0.01$. The 6-OHDA-electrolytic lesion group was also significantly more active than both the vehicle-sham group, $t(13)=3.47$, $p<0.01$, and the 6-OHDA-sham group, $t(13)=3.01$, $p<0.01$. In summary, these results show that electrolytic lesions of the nucleus accumbens result in significant locomotor hyperactivity irrespective of whether the nucleus accumbens has previously received a 6-OHDA injection.

TABLE 1

TOTAL PHOTOCELL COUNTS AFTER DRUG INJECTION

Drug treatment	Vehicle-sham group	Vehicle-electrolytic lesion group	6OHDA-sham group	6OHDA-electrolytic lesion group
D-amphetamine (1.5 mg/kg SC)	3025 ± 647	3553 ± 576	1189 ± 342*	1571 ± 465*
Apomorphine (0.25 mg/kg SC)	203 ± 72	349 ± 62	1041 ± 242†	1289 ± 295†

Total photocell counts were recorded for 120 min after amphetamine and for 90 min after apomorphine. Results were obtained after animals had been assigned to their final groups but before they had received an electrolytic lesion or sham procedure. *$p<0.05$ vs. vehicle-sham group and $p<0.01$ vs. vehicle-lesion group. †$p<0.01$ vs. vehicle-sham group and vehicle-lesion group (t-tests).

TABLE 2

TOTAL PHOTOCELL COUNTS PER 90 MINUTES (MEAN ± S.E.M.)

	Vehicle-sham (n=7)	6-OHDA-sham (n=7)	Vehicle-electrolytic lesion (n=8)	6OHDA-electrolytic lesion (n=8)
D-amphetamine (1.5 mg/kg SC) 4 days	2478 ± 378	1285 ± 375	1885 ± 564	1996 ± 371
Apomorphine (0.25 mg/kg SC) 8 days	370 ± 111	1618 ± 81	1240 ± 188	1762 ± 436
Saline (1 ml/kg SC) 14 days	662 ± 170	1066 ± 334	3843 ± 657	4415 ± 996
D-amphetamine (1.5 mg/kg SC) 18 days	2688 ± 333	1679 ± 184	4062 ± 606	4462 ± 845

Results obtained after both surgical procedures. See text for further details.

Post hoc comparisons of the effect of amphetamine revealed that in the vehicle-sham group amphetamine produced a significant stimulation of locomotor activity on day 4, $t(6)=5.84$, $p<0.01$ vs. saline, and on day 18, $t(6)=4.81$, $p<0.01$ vs. saline. In the 6-OHDA-sham group amphetamine produced no significant effect either on day 4, $t(6)=0.97$, $p>0.05$ vs. saline, or on day 18, $t(6)=2.56$, $p>0.01$ vs. saline. By a less stringent criterion ($p<0.05$) the effect of amphetamine on day 18 was significant, but by this criterion the amphetamine-induced locomotor activity in the 6-OHDA-sham group was less than that in the vehicle-sham group, $t(12)=2.65$, $p<0.05$. Thus, by either criterion amphetamine-induced activity in the 6-OHDA-sham group was still at least partially blocked compared to that in the vehicle-sham group by day 18. In the vehicle-electrolytic lesion group amphetamine exerted no significant effect either on day 4, $t(7)=2.07$, $p>0.05$ vs. saline, or on day 18, $t(7)=0.26$, $p>0.05$ vs. saline. Also in the 6-OHDA-electrolytic lesion group amphetamine exerted no significant effect on either day 4, $t(7)=2.12$, $p>0.05$ vs. saline, or on day 18, $t(7)=0.04$, $p>0.05$ vs. saline. In summary, these results show that amphetamine stimulated locomotor activity in the vehicle-sham group, that this stimulation was absent (day 4) or reduced (day 18) in the 6-OHDA-sham group, and was absent in both the vehicle-electrolytic lesion group and the 6-OHDA-electrolytic lesion group.

Because the effects of apomorphine are known to be short-lasting, scores in the first 60 minutes following its administration were subjected to further comparisons. These comparisons revealed that apomorphine produced no significant effect in the vehicle-sham group, $t(6)=2.45$, $p=0.05$ vs. saline, a significant enhancement of activity in the 6-OHDA-sham group, $t(6)=3.73$, $p<0.01$ vs. saline, a significant inhibition of activity in the vehicle-electrolytic lesion group, $t(7)=4.11$, $p<0.01$ vs. saline, and a significant inhibition of activity in the 6-OHDA-electrolytic lesion group, $t(7)=3.51$, $p<0.01$ vs. saline.

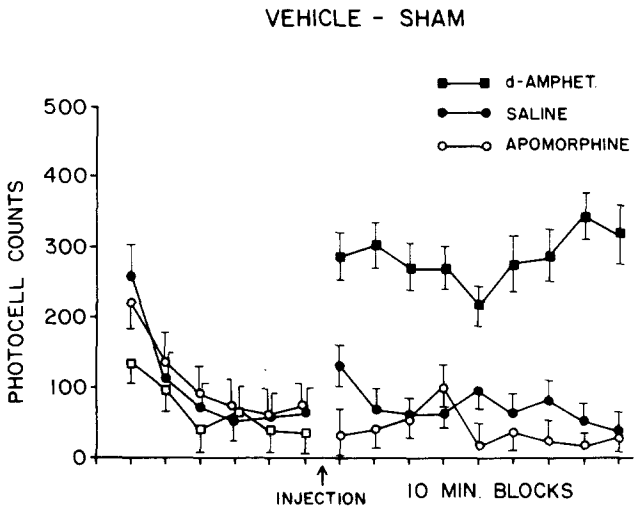

FIG. 1. Locomotor activity (mean±SEM), measured by photocell counts, in the vehicle-sham group before and after injection of saline (1 ml/kg, 14 days), d-amphetamine (1.5 mg/kg SC, 18 days) or apomorphine (0.25 mg/kg SC, 8 days).

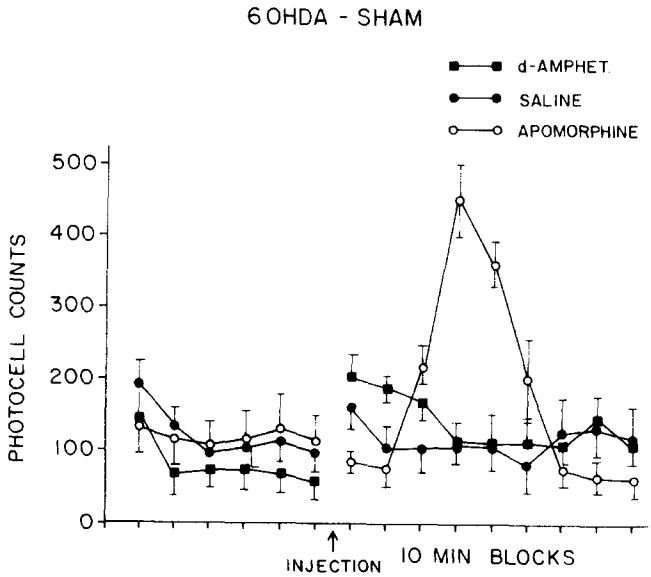

FIG. 2. Locomotor activity (mean±SEM), measured by photocell counts, in the 6-OHDA-sham group before and after injection of saline (1 ml/kg, 14 days), d-amphetamine (1.5 mg/kg SC, 18 days) or apomorphine (0.25 mg/kg SC, 8 days).

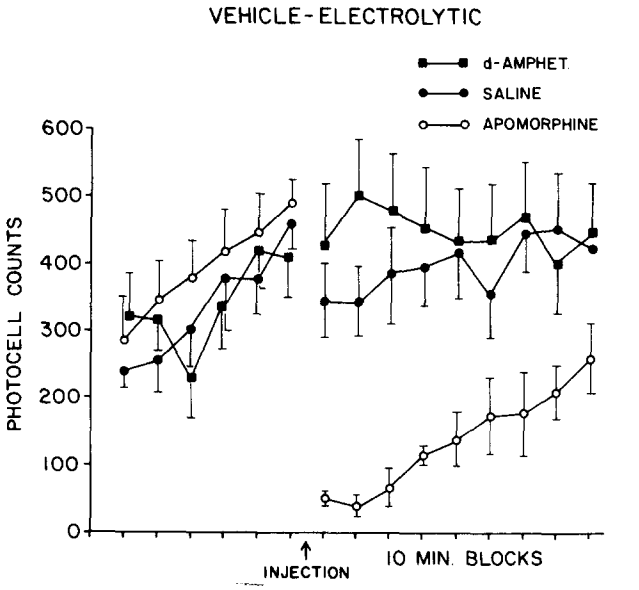

FIG. 3. Locomotor activity (mean±SEM), measured by photocell counts, in the vehicle-electrolytic lesion group before and after jection of saline (1 ml/kg, 14 days), d-amphetamine (1.5 mg/kg SC, 18 days) or apomorphine (0.25 mg/kg SC, 8 days).

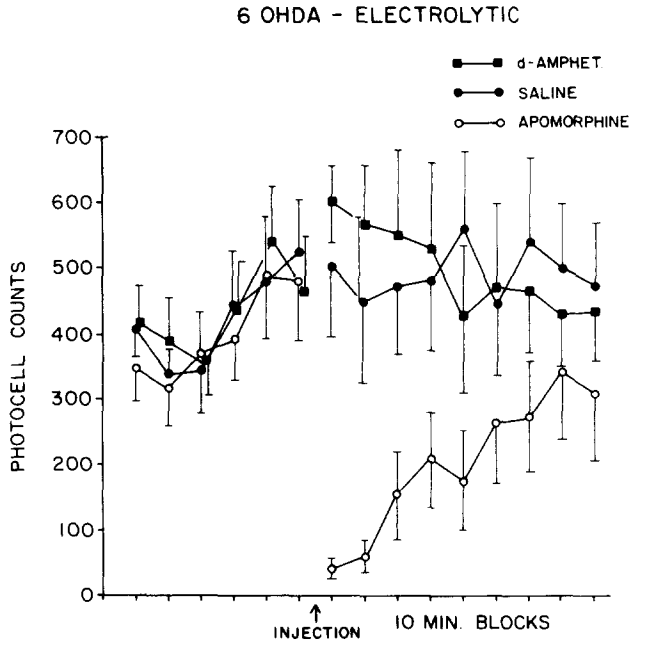

FIG. 4. Locomotor activity (mean±SEM), measured by photocell counts, in the 6-OHDA-electrolytic lesion group before and after injection of saline (1 ml/kg, 14 days), d-amphetamine (1.5 mg/kg SC, 18 days) or apomorphine (0.25 mg/kg SC, 8 days).

Histological Verification of Lesions

Lesion sites were verified in 6 randomly chosen rats. The behavioral results of these animals were typical of the group as a whole. Inspection of histological material revealed that the centers of the electrolytic lesions were consistently placed within the nucleus accumbens. All animals sustained extensive bilateral damage to this nucleus and to the anterior commissure. Variable damage was seen to occur to the medial anterior caudate and olfactory tubercle. The boundaries of necrotic tissue for those brains which were saved for histology are displayed in Fig. 5. Also shown is the area common to all lesions. Much of the ventral tissue had collapsed in toward the lesion causing an alteration of the outline of the ventral surface. To better represent the damaged areas, this collapse is not shown in Fig. 5.

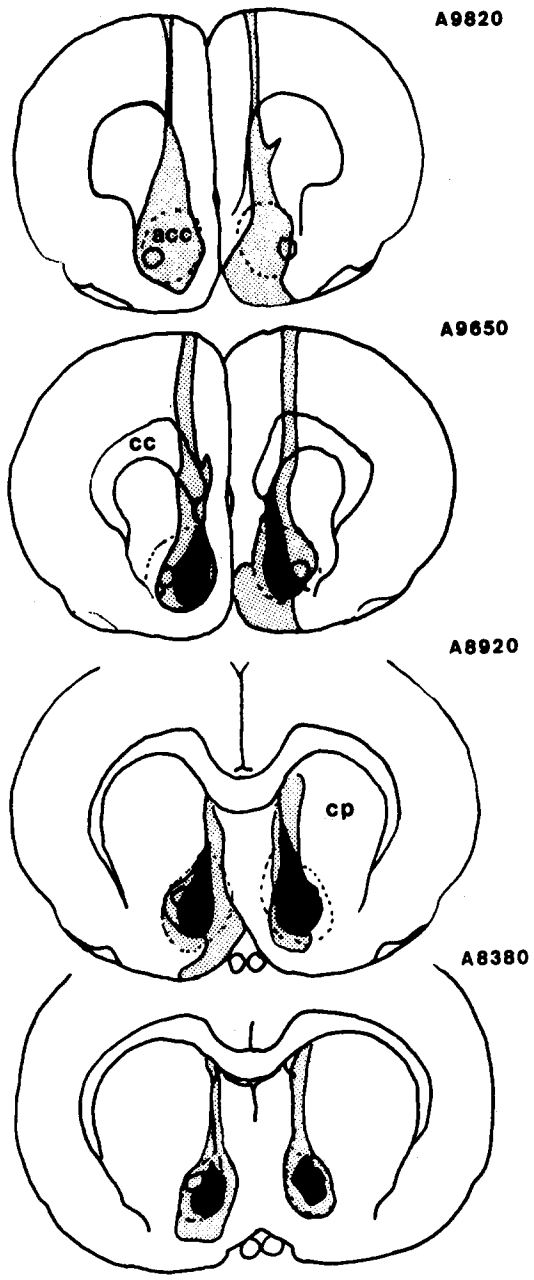

FIG. 5. Illustration of the extent of damage in animals sustaining electrolytic lesions of the nucleus accumbens. Stippled area represents tissue observed to be damaged in at least one animal. Blackened areas represent tissue damaged in all animals examined. Numbers correspond to sections in König and Klippel [14] from which the figures were redrawn. Abbreviations: CP=caudate-putamen, CC=corpus callosum, acc=nucleus accumbens.

Catecholamine Levels

Dopamine levels, measured 80–85 days after the intra-accumbens microinjections are shown in Table 3. In the 6-OHDA-sham group the dopamine concentration in the olfactory tubercle was 49±14% of control ($p<0.01$), in the nucleus accumbens 30±11% of control ($p<0.01$) and in the striatum 83±10% of control ($p>0.1$). Norepinephrine in the neocortex was also significantly reduced in the 6-OHDA treated animals (0.09±0.01 μg/g compared to 0.23±0.02 μg/g, ($p<0.01$).

TABLE 3

DOPAMINE (μg/g)

Group	Olfactory tubercle	Nucleus accumbens	Striatum
Vehicle-sham	2.75 ± 0.19	4.44 ± 0.45	6.29 ± 0.64
6OHDA-sham	1.34 ± 0.38*	1.34 ± 0.47*	5.20 ± 0.61

*$p<0.01$ (t-tests) compared to corresponding region of vehicle-sham group. Means ± SEM.

DISCUSSION

The main findings of the present studies are first, that electrolytic lesions of the nucleus accumbens produce a pronounced hyperactivity. This confirms previous reports [2, 7, 19, 25, 41]. Second, amphetamine elicited no further stimulation of locomotor activity in rats with electrolytic lesions. This contrasts with some previous studies [2, 21, 41], but confirms others [7, 12, 40]. Third, apomorphine suppressed locomotor activity in the rats with electrolytic lesions. To our knowledge this is a new finding. Finally, the effects of electrolytic lesions were the same whether or not mesolimbic dopaminergic neurons had been previously destroyed by 6-OHDA.

Before considering possible explanations of these findings it is appropriate to relate them to the results of previous studies. Most previous studies have found some degree of hyperactivity after electrolytic or radio-frequency lesions of the nucleus accumbens [2, 7, 19, 25, 41]. However, the reported effects on amphetamine-induced locomotor activity are more variable. In some studies, this behavior has been blocked by such lesions [7, 12, 40], whereas in others it has not [2, 21, 41]. Possible reasons for this variability lie in the many procedural and technical differences between these various studies. These include the species used, the time after lesioning that testing occurred, whether the animals were habituated to the activity cages before drug injection, the interval between drug injection and measurement of locomotor activity, the duration of locomotor activity measurement, the method of locomotor activity measurement, and the exact location and extent of the lesion. There is evidence that at least two of these factors, the lesion placement and the method used to quantitate locomotor activity, are important determinants of whether a blockade of amphetamine-induced locomotor activity is observed. For example, Teitelbaum *et al.* [40] studied the effect of lesion location in mice. Amphetamine-induced locomotor activity was blocked by lesions of the posterior nucleus accumbens, but not by more anteriorly-placed lesions which included damage to the rostral pole of this nucleus. It is probably

therefore pertinent that in the present study posterior regions of the nucleus accumbens were consistently destroyed, whereas they were spared by lesions which did not block amphetamine-induced locomotor activity [41].

The importance of the method used to quantitate locomotor activity has recently been considered by Kehne *et al.* [12]. These authors tested their animals in an arena divided into a number of squares. From videotape recordings locomotor activity was quantitated by directly counting the number of squares entered. They found that electrolytic lesions of the nucleus accumbens blocked the locomotor stimulant effect of amphetamine, but not its effect on rearing. They suggested that the results of Wirtshafter *et al.* [41] were due to the use of stabilimeter cages which do not discriminate between locomotor activity and rearing. In the present study locomotor activity was quantitated by the interruption of infra-red light beams which illuminate photocells. Though such beams can be interrupted by both locomotor movements and by rearing [35], amphetamine-induced locomotor activity was blocked by electrolytic lesions of the nucleus accumbens. In a similar apparatus a similar result has been observed in mice [7]. In light of the results of Kehne *et al.* [12], it is suggested therefore, either that beam interruptions by rearing are quantitatively less signficant than those resulting from locomotor movements, or that with the present large lesions the effects of amphetamine on both locomotor movements and rearing were occluded. Further work is necessary to provide evidence on this issue.

In light of the above considerations a reasonable summary of the present results and those previously published is that there is no conclusive evidence to contradict the view that when methods are used which record predominantly large locomotor movements the stimulatory effect of amphetamine on such movements is blocked by lesions of the nucleus accumbens providing these lesions include its posterior extent.

We now suggest the following model as a possible explanation of our findings. At some extra-accumbens location in the brain there is a system which when active facilitates locomotor activity. Efferents from the nucleus accumbens, either directly or through polysynaptic effects, exert an inhibitory influence on this "activity system." Thus, when the nucleus accumbens is destroyed electrolytically the system is released from inhibition and hyperactivity results. Since the effect of dopamine in the nucleus accumbens also is to stimulate locomotor activity [33,34] the overall effect of dopamine on the nucleus accumbens efferents which inhibit the "activity system" should be inhibitory. According to this model amphetamine-induced activity is mediated by dopamine release in the nucleus accumbens. When dopaminergic terminals and their postsynaptic target neurons in the nucleus accumbens are destroyed by an electrolytic lesion the stimulating effect of amphetamine on locomotor activity is occluded. There are physiological and anatomical studies which are consistent with the above hypothesis. Locomotor activity is elicited in the decerebrate cat by electrical stimulation of the mesencephalic locomotor region [29,37]. Conceivably, this region is identical with or part of the "activity system" referred to above. Anatomical evidence suggests that the nucleus accumbens could polysynaptically influence the mesencephalic locomotor region. For example, the ventral pallidum and the substantia nigra are both major targets of efferents from the nucleus accumbens [11,28], and both the pallidum and the substantia nigra contain neurons which project to the mesencephalic locomotor region [9,10].

Another possible explanation of the failure of amphetamine to stimulate locomotor activity in rats with electrolytic lesions is that this result is due to a "ceiling effect." According to this explanation the neural substrate for amphetamine-induced locomotor activity is not damaged by electrolytic lesions of the nucleus accumbens. However, the lesion causes such a marked stimulation of locomotor activity that the animals are physically incapable of moving any faster in response to amphetamine. While we cannot definitively rule out this explanation the predominant behavior exhibited by lesioned animals was walking frequently interrupted by pauses to sniff at particular cage locations, rather than any continuous running activity. We are therefore inclined to reject the "ceiling effect" explanation.

Finally, apomorphine suppressed the locomotor hyperactivity of electrolytically lesioned rats in the present study. In previous studies low doses of apomorphine and other dopamine agonists have produced hypomotility and sedation in mice and rats [3, 8, 22, 39]. Dopamine antagonists are able to antagonize this effect of apomorphine [8]. The proposition that actions at presynaptic autoreceptors causing inhibition of dopamine release are responsible for these activity decreasing effects [3] has been widely accepted. In view of the relation between the action of dopamine in the nucleus accumbens and locomotor activity one might expect the relevant presynaptic receptors to be those in the nucleus accumbens. However, in the present study apomorphine exhibited activity-depressant effects in rats with electrolytic lesions of the nucleus accumbens, suggesting that at least one population of dopamine receptors mediating a depression of locomotor activity is outside this structure.

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