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Differential Effects of Mesocortical, Mesolimbic, and Mesostriatal Dopamine Depletion on Spontaneous, Conditioned, and Drug-Induced Locomotor Activity

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JONES, G. H. AND T. W. ROBBINS. *Differential effects of mesocortical, mesolimbic, and mesostriatal dopamine depletion on spontaneous, conditioned, and drug-induced locomotor activity.* PHARMACOL BIOCHEM BEHAV **43**(3) 887–895, 1992.—Groups of rats with 6-hydroxydopamine (6-OHDA) lesions of either the medial prefrontal cortex (PFC), nucleus accumbens (NAC), or caudate putamen (CPu) were given daily tests for locomotor activity in photocell cages while food deprived. Two separate groups of NAC-lesioned rats were prepared with either large [NACT (90% NAC dopamine depletion)] or partial [NACP (67% NAC dopamine depletion)] lesions. NACT rats were spontaneously hypoactive whereas NACP rats were hyperactive compared with sham-operated controls. PFC-lesioned rats were also hyperactive compared to their respective controls. Spontaneous locomotor activity in CPu-lesioned rats did not differ from shams. When daily food supplements were paired with the photocell cages, all subjects developed a conditioned locomotor response. During the first few days of conditioning, the response to this conditioning procedure was markedly greater in the NACP group whereas the response in the NACT group was unaffected initially and actually enhanced during the latter days of testing. The locomotor response to the conditioning procedure was unaffected in either the PFC- or CPu-lesioned groups. Both the NACT and NACP lesions attenuated the locomotor response to 1.5 mg/kg *d*-amphetamine sulphate IP, and the NACT group showed a supersensitive response to 0.1 mg/kg apomorphine HCl SC. PFC or CPu 6-OHDA lesions did not alter the response to either drug. These results differentiate the role of PFC, NAC, and CPu dopamine in spontaneous, conditioned, and drug-induced locomotor activity and further implicate dopaminergic mechanisms of the NAC in the magnitude of the behavioural response to incentive stimuli.

Locomotor activity Conditioning Dopamine Nucleus accumbens Caudate putamen
Medial prefrontal cortex 6-OHDA Amphetamine Apomorphine

MOTIVATIONAL behaviours have traditionally been divided into those that are appetitive or preparatory and those which are consummatory (18). Preparatory behaviours are those that generally lead to consummatory acts, and include approach and exploratory behaviours and instrumental responding for reward, whereas consummatory behaviours include eating and drinking. Dopamine (DA) has been widely implicated in both consummatory and preparatory behaviors. For example, forebrain DA activity is apparently increased following food consumption (25). In addition, either DA receptor blockade (65) or DA-depleting lesions of the forebrain (66) can produce severe aphagia and adipsia. Preparatory behaviour such as hoarding (38), lever pressing for food (21), and conditioned place preference for food (54) are also attenuated by disruption of central DAergic transmission.

Although preparatory and consummatory acts are obviously linked, they do have a degree of autonomy. For example, rats will still respond to cues predictive of reward even when sated (52). It has also been demonstrated that DA receptor blockade attenuates preparatory (latency to enter food niche), but not consummatory behaviour (amount of food consumed) in a conditioned feeding paradigm (3). This autonomy suggests that preparatory and consummatory acts to a certain extent may be under the influence of different DAergic pathways.

Mesolimbic DA has been implicated in all aspects of food-related preparatory behaviour, including exploration (23) and hoarding (38,57). Locomotor activity conditioned to food presentation is a clear example of preparatory behaviour. Explicit pairing of stimuli with biologically significant events, such as

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food presentation, invests these stimuli with incentive properties and by definition they are classified as incentive stimuli (2,5,6). Food-deprived rats on a scheduled food delivery regimen develop an anticipatory locomotor response (1,8,49,53) that can be demonstrated to depend upon these incentive stimuli (7).

The possible role of mesolimbic DA in conditioned locomotor activity for food is unknown. However, aspirative lesions of the hippocampal formation, whose efferent projection to the nucleus accumbens (NAC) is largely coincident with the DAergic projection to the NAC from the ventral tegmentum area (VTA) (33), greatly enhance this locomotor response to signalled reward (19). Other studies have also indicated a possible involvement of NAC dopamine in food-related conditioned locomotor activity (28). The fact that locomotor activity conditioned to amphetamine administration can be blocked by 6-hydroxydopamine (6-OHDA) lesions of the NAC (24) is a further indication that the DA innervation of the NAC may play a role in conditioned locomotor activity to stimuli predictive of food reward. Moreover, the dihydroxyphenylacetic acid (DOPAC)/DA ratio is increased in the NAC following presentation of stimuli predictive of food reward but not during consumption of an unsignalled meal (4), and 6-OHDA lesions of the NAC are also considered to block the motivational excitement produced by scheduled food delivery (51). These findings, together with demonstrations that NAC DAergic activity can increase prior to consummatory acts (28,46), are consistent with the view that NAC DA is implicated in preparatory behaviour or in the response to reward-related stimuli.

The present experiment investigated the effects of both NAC and caudate putamen (CPu) DA depletion on spontaneous locomotor activity, locomotor activity conditioned to food presentation, and locomotor activity induced by *d*-amphetamine or apomorphine. For comparison, a separate group of rats was included with 6-OHDA lesions of the medial prefrontal cortex (PFC), as this structure has been implicated in the regulation of locomotor activity (10,16,42,61) and in some classes of preparatory behaviour, such as exploration (23).

METHOD

Subjects

Subjects used in this experiment were 54 male Lister hooded rats weighing 250–300 g (Olac, Bicester, UK). Rats were housed in groups of five or six per cage and had free access to food and water. All rats were housed in a colony room maintained at 21°C on a 12 L : 12 D cycle (lights on 0700 h).

Surgical Procedures

All rats were anesthetised with 0.3 ml/100 g body weight Equithesin and placed in a Kopf (Tujunga, CA) stereotaxic frame. 6-OHDA (Sigma Chemical Co., St. Louis, MO) infusions were made via 30-g stainless steel cannulae connected by polythene tubing (PP 10) to 5-μl glass syringes mounted on a Harvard infusion pump (Harvard Apparatus, South Natick, MA). 6-OHDA (4 μg/μl; free base) was prepared immediately before surgery in a solution of ascorbic acid (0.01%) in saline (0.9%) and kept on ice. All rats, except the 67% NAC DA depletion (NACP) group, were pretreated with the monoamine oxidase inhibitor pargyline HCl (Sigma) to improve the efficacy of 6-OHDA (9). Pargyline HCl was administered 30 min before surgery at a dose of 25 mg/kg and in a volume of 0.1 ml/100 g body weight. Groups of rats received the following bilateral 6-OHDA or appropriate sham lesions (infused with vehicle only):

NAC. Two separate groups of NAC-lesioned rats were prepared, 90% NAC DA depletion (NACT) ($n = 8$) and NACP ($n = 5$), together with appropriate sham-operated controls ($n = 11$). Rats received 2 × 2-μl infusions of 6-OHDA or vehicle. Infusions were made over a 2-min period and a further 2 min allowed to elapse for diffusion. Coordinates were, from bregma: AP +3.4 mm, L +/− 1.7 mm, V −7.2 mm from dura, with the incisor bar set at +5.0 mm above the interaural line (43).

PFC. Rats received infusions of 6-OHDA ($n = 14$) or vehicle ($n = 6$). Infusions were made over a 1-min period and 2 min allowed to elapse for diffusion. One microliter was infused on each side of the brain at each site. Coordinates were, from bregma: (1) AP +1.0 mm, L +/− 0.8 mm, V −2.0 mm from dura; (2) AP +2.4 mm, L +/− 0.8, V −1.5 mm; (3) AP +2.4 mm, L +/− 0.8 mm, V −4.0 mm; (4) AP +3.0 mm, L +/− 0.8 mm, V −3.0 mm. The incisor bar was set at −2.3 mm below the interaural line (45).

CPu. Six rats received 2-μl infusions of 6-OHDA into each side of the CPu and four received sham lesions. Infusions were made over 2 min and the cannulae withdrawn after a 2-min diffusion period. Coordinates were: AP +2.0 mm, L +/− 3.5 mm, V −5.5 mm from dura (43).

A 14-day period was allowed to elapse for recovery from surgery before the start of experimental testing. Two of the CPu 6-OHDA rats had mild aphagia immediately after surgery and were fed palatable wet mash (Farlene baby food with added sucrose) for 5 days. Thereafter, they were returned to normal diet. All other rats regained preoperative body weight within a few days after surgery.

Apparatus

Tests for locomotor activity were conducted in a bank of 16 individual, wire photocell cages (40 × 25 × 18 cm). Each cage was fitted with two infrared photocell beams, 1 cm above the floor, spaced equally along the long access of the cage. Interruption of either beam resulted in a photocell count for that cage. Water was freely available in each photocell cage.

Behavioural Procedure

Rats were gradually reduced to 80% of their free-feeding weight (over a 4-day period) by restricted access to food in the home cage and maintained at this reduced weight for the duration of the experiment. All subjects were given daily 2-h tests for locomotor activity (between 1000 and 1400 h) and allocation to individual photocell cages on each day was on a pseudorandom schedule.

A 24-h periodicity of testing was used as peak locomotor activity in rats occurs on an approximately 24-h schedule (5) and testing at irregular intervals would therefore mask increases in locomotor activity due to the conditioning procedure. In addition, the anticipatory response to scheduled food delivery does not occur if the periods between meals are 10 or 29 h (8) but does occur if a 24-h cycle is used (7,8).

For the first 10 days of testing, rats were maintained at their reduced body weight by restricted home cage feeding at varying time intervals (2–6 h) after testing. This was to limit possible associations between activity testing and food presentation. The conditioning phase began on day 11. During this phase, the food supplements to maintain body weight were

presented in the photocell cages after the first 30 min of testing and no food was given in the home cage.

After day 30, each rat was challenged, on separate days, with either 1.5 mg/kg *d*-amphetamine sulphate (Sigma), 0.1 mg/kg apomorphine HCl (Sigma), or saline (0.9%). Food presentation was delayed until 1 h after drug administration to allow the interrupted measurement of drug-induced locomotor activity. Two no-injection days separated each drug administration. Amphetamine was prepared in saline and injected IP in a volume of 0.1 ml/100 g body weight. Apomorphine was prepared in 0.01% ascorbic acid in saline and injected SC in a volume of 0.05 ml/100 g body weight. All injections were made immediately prior to testing.

Neurochemical Analysis

Following completion of testing, rats were returned to ad lib feeding for 5 days and then sacrificed by cervical dislocation and decapitation. The brain was rapidly removed and placed in an ice-cold dissection block ventral surface uppermost. The PFC, NAC, and anterior (aCPu) and posterior CPu (pCPu) were dissected as previously described (14).

Tissue concentrations of noradrenaline (NE), DA, DOPAC, serotonin [5-hydroxytryptamine (5-HT)], and 5-hydroxyindole acetic acid (5-HIAA) were determined by high-performance liquid chromatography (HPLC) with electrochemical detection. Chromatographic separation was accomplished using a stainless steel column (15 × 0.46 cm i.d.) packed with C_{18} reversed-phase 5 μm Spherisorb ODS2 (Phase Separations Ltd., Clwyd, U.K.). This analytic column was fitted with a guard column (5 × 0.46 cm i.d.) also packed with 5 μm Spherisorb ODS2. The mobile phase consisted of 152 mM citric acid, 15 mM sodium acetate, 1.98 mM octane sulfonic acid, 80 mM EDTA, and 8% methanol and was adjusted to pH 3.6 with KOH. A dual piston pump (Waters Assoc., Milford, MA) delivered the mobile phase at 1.2 ml/min. Detection of the monoamines was achieved using a BAS (West Lafayette, IN) LC-4B electrochemical detector. The glassy carbon working electrode was set at an applied potential of 0.7 V vs. an Ag/AgCl reference electrode. Brain tissue samples were homogenised in 0.2 M perchloric acid, centrifuged, and the supernatant injected directly onto the HPLC column.

Data Analysis

For the neurochemical data, the concentration of each compound of interest in a particular brain region was analysed separately by analysis of variance [ANOVA; (67)] with one between-subject factor, lesion group. The sham-operated groups were combined as they did not significantly differ. Where appropriate, the data were subjected to a logarithmic transformation to achieve homogeneity of variance (67). The DOPAC/DA ratio and the 5-HIAA/5-HT ratio were also calculated as they are thought to provide an index of neurotransmitter utilisation and have been used in previous studies of forebrain monoamine function and preparatory behaviour (e.g. 4,25).

There were differences between the various sham lesion groups in their spontaneous locomotor activity scores, probably due to their being tested on different days, although each sham group was tested with its appropriate lesion group. Therefore, to be able directly to compare the effects of the different lesion group, the total locomotor activity scores for the initial 30-min period on each day were expressed as a percentage of the activity scores for their respective sham groups and subjected to ANOVA with one repeated measure, days.

The lesion procedures used in this experiment produced large and relatively stable changes in spontaneous locomotor activity compared to their respective controls. Therefore, to assess adequately the effects of the conditioning procedure on these different baseline scores the locomotor activity during the conditioning phase was subjected to analysis of covariance, with the covariate being the mean photocell counts for the 2 days immediately prior to the start of the conditioning phase. A separate ANOVA was conducted of the mean locomotor activity scores for blocks of 5 days with one between-subjects factor, lesion, and one within-subject factor, block. Appropriate posthoc comparisons were made using Newman-Keuls analysis.

The photocell counts for the first hour after injection of 1.5 mg/kg *d*-amphetamine were analysed by two separate procedures, either ANOVA of the photocell counts with 1 between-subject factor, lesion, and 1 within-subject factor, drug (either saline or amphetamine), or ANOVA of the percentage change in activity scores. Similar analyses were conducted for the response to 0.1 mg/kg apomorphine; again, the photocell counts for the first hour after injection were analysed.

RESULTS

Neurochemical Analysis

The results of the neurochemical analysis are presented in Table 1. Each of the lesion procedures used in this experiment produced profound and relatively specific patterns of neurotransmitter depletion.

DA. PFC or NAC (NACP and NACT) infusions of 6-OHDA both produced a large DA depletion (greater than 85%) within the PFC, $F(4, 38) = 37.28$, $p < 0.001$. CPu infusions of 6-OHDA had no effect on the concentration of DA in the PFC. Only the NACP and NACT groups had significant DA depletions in the NAC, $F(4, 38) = 70.88$, $p < 0.001$. Posthoc comparisons indicated that the two NAC lesion groups differed in the amount of dopamine remaining ($p < 0.05$). The NACT group had a mean DA depletion of 90%, whereas the NACP group had a mean depletion of 67%.

There were also significant lesion effects on the concentration of DA in the anterior CPu, $F(4, 38) = 21.80$, $p < 0.001$. The CPu lesion and the NACT and NACP lesions depleted DA in this region by 43, 56, and 29%, respectively. Posthoc comparisons indicated that the two NAC lesions differed in the concentration of DA remaining ($p < 0.05$), but neither of these groups significantly differed from the CPu lesion group.

As indicated in Table 1, only the CPu lesion significantly depleted DA in the posterior CPu (−76%), $F(4, 38) = 10.32$, $p < 0.001$.

DOPAC/DA ratio. In the PFC, the concentration of DOPAC could not be consistently measured in either the PFC group or the two NAC lesion groups and therefore the DOPAC/DA ratio could not be calculated. However, there was a significant decrease in the DOPAC/DA ratio in the PFC from CPu-lesioned rats, $F(1, 18) = 6.25$, $p = 0.022$. In contrast, there were significant increases in this ratio in both the anterior, $F(4, 38) = 3.14$, $p = 0.025$, and posterior CPu, $F(4, 38) = 8.02$, $p < 0.001$, in the CPu lesion group. The DOPAC/DA ratio was also 20% greater in the NAC in the NACT group; however, this did not quite reach significance, $F(4, 38) = 2.42$, $p = 0.065$.

TABLE 1

EFFECT OF FOREBRAIN INFUSIONS OF 6-OHDA ON BRAIN TISSUE CONCENTRATIONS OF MONOAMINES AND METABOLITE/MONOAMINE RATIOS

	Brain Region			
Lesion Group	PFC	NAC	aCPu	pCPu
DA				
Sham (n = 21)	0.086 ± 0.009	9.872 ± 0.380	12.380 ± 0.348	11.887 ± 0.356
PFC (n = 14)	0.006 ± 0.003*	8.645 ± 0.360	11.981 ± 0.691	12.051 ± 0.741
NACP (n = 5)	0.010 ± 0.004*	3.238 ± 0.586*	8.816 ± 0.480†	11.193 ± 0.497
NACT (n = 8)	0.003 ± 0.002‡	0.971 ± 0.181‡	5.411 ± 0.625*	10.278 ± 0.747
CPu (n = 6)	0.110 ± 0.007	9.291 ± 0.518	7.065 ± 1.356*	2.836 ± 1.121*
DOPAC/DA ratio				
Sham (n = 21)	0.195 ± 0.026	0.172 ± 0.005	0.087 ± 0.003	0.070 ± 0.002
PFC (n = 14)	–	0.155 ± 0.011	0.084 ± 0.003	0.076 ± 0.006
NACP (n = 5)	–	0.176 ± 0.027	0.075 ± 0.008	0.062 ± 0.003
NACT (n = 8)	–	0.205 ± 0.013	0.102 ± 0.018	0.066 ± 0.004
CPu (n = 6)	0.062 ± 0.006†	0.174 ± 0.010	0.115 ± 0.011†	0.118 ± 0.018†
5-HT				
Sham (n = 21)	0.725 ± 0.044	0.707 ± 0.058	0.345 ± 0.019	0.540 ± 0.033
PFC (n = 14)	0.396 ± 0.031†	0.808 ± 0.081	0.389 ± 0.022	0.547 ± 0.047
NACP (n = 5)	0.690 ± 0.043	0.691 ± 0.118	0.276 ± 0.031	0.459 ± 0.041
NACT (n = 8)	0.811 ± 0.035	1.070 ± 0.093*	0.391 ± 0.031†	0.526 ± 0.044
CPu (n = 6)	0.840 ± 0.047	0.921 ± 0.107	0.451 ± 0.034	0.642 ± 0.052
5-HIAA/5-HT				
Sham (n = 21)	0.359 ± 0.023	1.093 ± 0.022	1.174 ± 0.068	0.971 ± 0.095
PFC (n = 14)	0.496 ± 0.036†	0.978 ± 0.128	1.147 ± 0.060	1.067 ± 0.088
NACP (n = 5)	0.336 ± 0.063	1.018 ± 0.104	1.578 ± 0.263	1.122 ± 0.070
NACT (n = 8)	0.325 ± 0.036	0.969 ± 0.143	1.172 ± 0.079	0.862 ± 0.085
CPu (n = 6)	0.375 ± 0.036	1.020 ± 0.085	1.221 ± 0.223	0.879 ± 0.085
NE				
Sham (n = 21)	0.397 ± 0.029	0.272 ± 0.036	ND	ND
PFC (n = 14)	0.019 ± 0.007‡	0.271 ± 0.036	ND	ND
NACP (n = 5)	0.037 ± 0.008‡	0.134 ± 0.040	ND	ND
NACT (n = 8)	ND‡	0.137 ± 0.089†	ND	ND
CPu (n = 6)	0.304 ± 0.043	0.442 ± 0.080	ND	ND

Data are expressed as mean concentration ± SEM (ng/mg wet weight tissue). The DOPAC/DA and the 5-HIAA/5-HT ratios are also presented. ND, not detectable; PFC, medial prefrontal cortex; NAC, nucleus accumbens; aCPu, anterior caudate putamen; pCPu, posterior caudate putamen.

*$p < 0.01$.

†$p < 0.05$.

‡$p < 0.001$.

5-HT. Following 6-OHDA lesions of the forebrain, there were also significant alterations in the 5-HT content of the brain regions assayed. 6-OHDA lesions of the PFC reduced 5-HT levels in the PFC by 45%, $F(4, 38) = 16.08, p < 0.001$. On the other hand, the large 6-OHDA lesions of the NAC (NACT) produced a significant 60% increase in the 5-HT content of the NAC, $F(4, 38) = 2.90, p = 0.035$, an effect not apparent with the smaller lesions (NACP). Similarly, the CPu infusions also produced a significant increase in the 5-HT content of the anterior CPu, $F(4, 38) = 3.80, p = 0.011$. No changes in 5-HT concentration were evident in the posterior CPu.

5-HIAA/5-HT ratio. Associated with the significant decrease in 5-HT content of the PFC in the PFC lesion group, there was a significant 38% increase in the 5-HIAA/5-HT ratio, $F(4, 38) = 3.41, p = 0.018$. No changes were evident in the NAC, $F(4, 37) = 0.25$, n.s., anterior CPu, $F(4, 38) = 2.23$, n.s., or posterior CPu, $F(4, 35), = 0.88$, n.s., in any lesion group.

NE. Infusions of 6-OHDA into the PFC also produced a 95% depletion of NE in the PFC, $F(4, 38) = 57.74, p < 0.001$. NACP and NACT infusions of 6-OHDA also significantly depleted NE in the PFC, by 91 and 100%, respectively. Infusions of 6-OHDA also significant altered NAC NE, $F(4, 38) = 3.52, p = 0.015$. NE in the NAC was lower in the NACP (51%) and NACT (50%) groups compared with the sham-lesioned group, although this did not reach significance. There were, however, significant reductions in NAC NE in the NACP and NACT lesion groups compared with the CPu group ($p < 0.05$). There was no reduction in NAC NE in the PFC lesion group. NE was not routinely measurable in either the anterior or posterior CPu.

Spontaneous Locomotor Activity

As indicated in Fig. 1, the lesion parameters used in this experiment produced large and relatively stable effects on spontaneous locomotor activity. The two NAC lesion groups

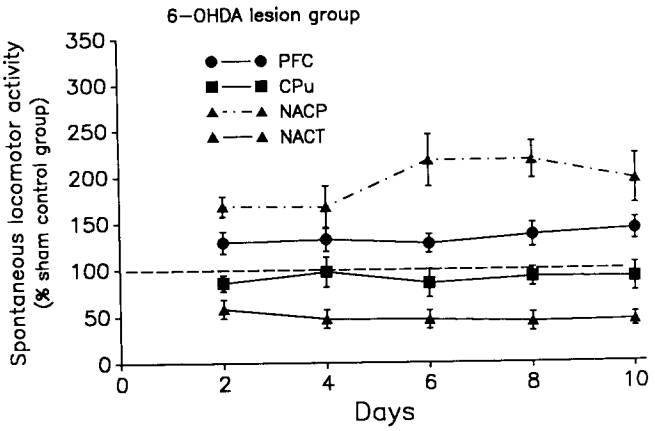

FIG. 1. Effect of forebrain 6-hydroxydopamine (6-OHDA) lesions on spontaneous locomotor activity. Data are expressed as percent locomotor activity for the respective sham-operated groups. For clarity of presentation, each point represents the mean score of 2 days. The vertical bars represent the SEM. PFC, medial prefrontal cortex (n = 14); CPu, caudate putamen (n = 6); NACP, partial nucleus accumbens lesions [mean dopamine (DA) depletion 67%; n = 5]; NACT, large nucleus accumbens lesions (mean DA depletion 90%; n = 8).

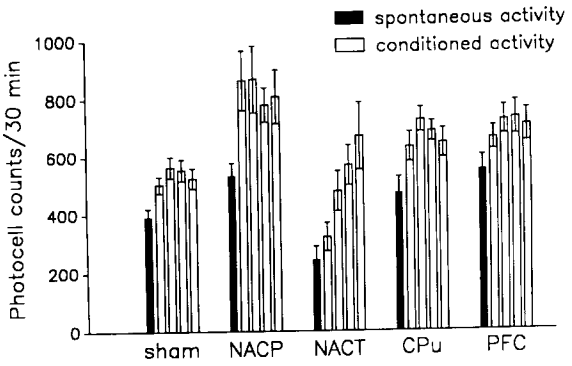

FIG. 2. Effect of forebrain 6-hydroxydopamine lesions on locomotor activity conditioned to food presentation. The mean photocell counts (blocks of 5 days) for the first 30 min of testing prior to feeding are presented. The solid bars represent the mean locomotor activity for the 5-day period immediately prior to conditioning. The open bars represent the mean locomotor activity for each 5-day period following conditioning. The vertical bars represent the SEM. See Fig. 1 for definitions of abbreviations.

showed opposite effects compared to their respective sham-operated controls. Whereas the NACT group was significantly less active, $F(1, 12) = 15.93, p < 0.01$, the NACP group was considerably more active than controls, $F(1, 8) = 31.67, p < 0.001$. The PFC lesion group was also more active than the appropriate sham-lesioned group, $F(1, 18) = 9.22, p < 0.01$, although not to the same extent as the NACP animals (Fig. 1). In contrast, the CPu lesions produced no significant alteration of spontaneous locomotor activity, $F(1, 8) = 2.82$, n.s.

There were no significant interactions between days and lesion either for the CPu groups, $F(9, 72) = 0.82$, n.s., the PFC groups, $F(9, 162) = 0.65$, n.s., or the NACT groups, $F(9, 108) = 0.80$, n.s. However, there was a significant lesion $\times$ days interaction for the NACP groups, $F(9, 72) = 2.86$, $p < 0.01$, although this merely reflected a slight increase in locomotor activity compared with sham controls in the middle of this 10-day period.

Conditioned Locomotor Activity

Analysis of the conditioned locomotor activity scores covaried against the mean spontaneous activity scores for days 9 and 10 indicated a main effect of lesion, $F(4, 48) = 3.37, p = 0.016$. Posthoc comparisons indicated that the NACP group had higher activity scores overall compared with sham-lesioned animals. No other comparisons were significant. A significant lesion $\times$ days interaction, $F(76, 913) = 0.94, p < 0.001$, was also apparent. This interaction was due to the differing effects of the two NAC lesion procedures. Whereas the NACP group immediately showed a greater increase in photocell counts compared with the shams, the NACT group showed the same relative increase to controls in the first few days and an increase in the last few days. 6-OHDA lesions of the CPu or PFC did not significantly affect locomotor activity conditioned to food presentation.

For clarity, Fig. 2 shows the conditioned activity data presented as the mean of blocks of 5 days. As can be seen, the conditioning procedure produced an increase in locomotor activity in all groups of rats. Analysis of this data confirmed a significant effect of lesion, $F(4, 49) = 4.80, p = 0.002$, and a significant lesion $\times$ block interaction, $F(3, 147) = 6.25, p < 0.001$. Posthoc comparisons indicated that the NACP group was significantly more active than sham-lesioned rats during the first block ($p < 0.05$) and the NACT group was more active during the last block of 5 days ($p < 0.01$).

Pharmacological Challenges

d-*Amphetamine 1.5 mg/kg.* The locomotor response to amphetamine was differentially affected by the forebrain 6-OHDA lesions, $F(4, 40) = 4.00, p < 0.01$. As indicated in Fig. 3, both NAC lesion procedures produced marked attenuation of amphetamine-stimulated locomotor activity, which was approximately the same magnitude in the NACP and NACT groups. Neither the CPu nor the PFC lesion groups showed a significantly altered response.

These effects were confirmed by the analysis of the percentage change in activity scores, with a significant main effect of lesion, $F(4, 40) = 4.86, p < 0.01$ (Fig. 3, bottom). Posthoc Newman-Keuls comparisons indicated that the NACP group differed from the PFC, CPu, and sham groups ($p < 0.01$ in each case) and that the NACP and NACT groups did not differ.

Apomorphine 0.1 mg/kg. ANOVA indicated a significant interaction between lesion and drug condition, $F(4, 40) = 4.96, p < 0.01$. As expected with this sedative dose of apomorphine (41,56), sham-operated controls showed a reduction in photocell counts (Fig. 4).

This pharmacological challenge revealed a clear difference between the two NAC-lesioned groups. Whereas NACP rats showed an similar reduction in activity to that in control animals, locomotor activity in the NACT group significantly increased. This finding was confirmed by the analysis of the percentage increase in photocell counts, $F(4, 40) = 4.23, p < 0.01$. The NACT group had the highest percentage increase in activity scores following 0.1 mg/kg apomorphine (Fig. 4, bottom). Posthoc Newman-Keuls comparisons indicated that the NACT group differed from all other groups ($p < 0.01$) and that the NACP group showed a different response to the CPu group ($p < 0.05$).

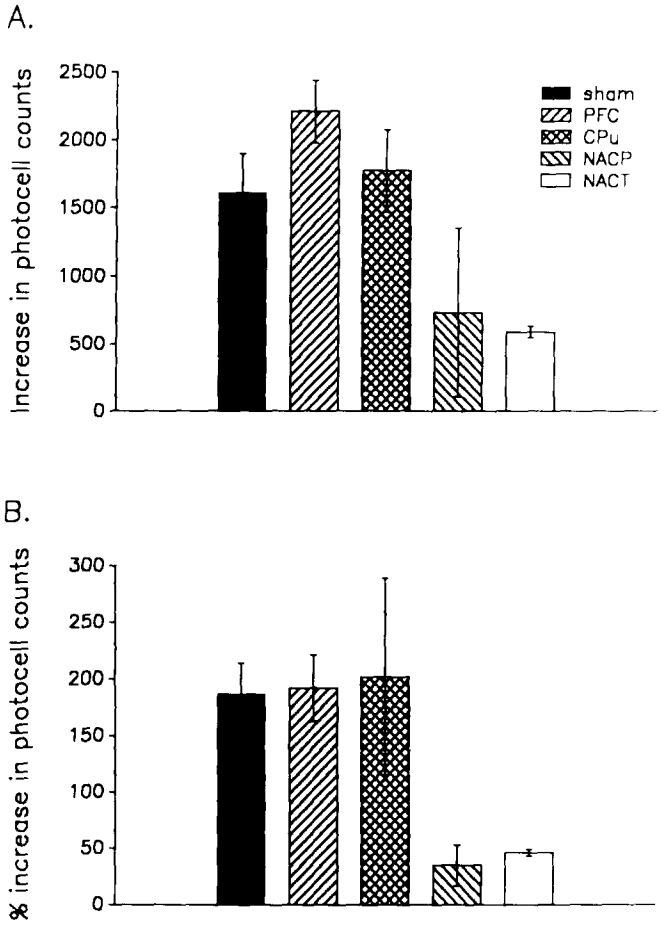

FIG. 3. Effect of forebrain 6-hydroxydopamine lesions on the locomotor response to an injection of 1.5 mg/kg *d*-amphetamine sulfate IP. The vertical bars represent the SEM. (A). Data expressed as the increase in photocell counts/h compared to saline injection. (B). Data expressed as the percentage increase in photocell counts/h compared to saline injection. See Fig. 1 for definitions of abbreviations.

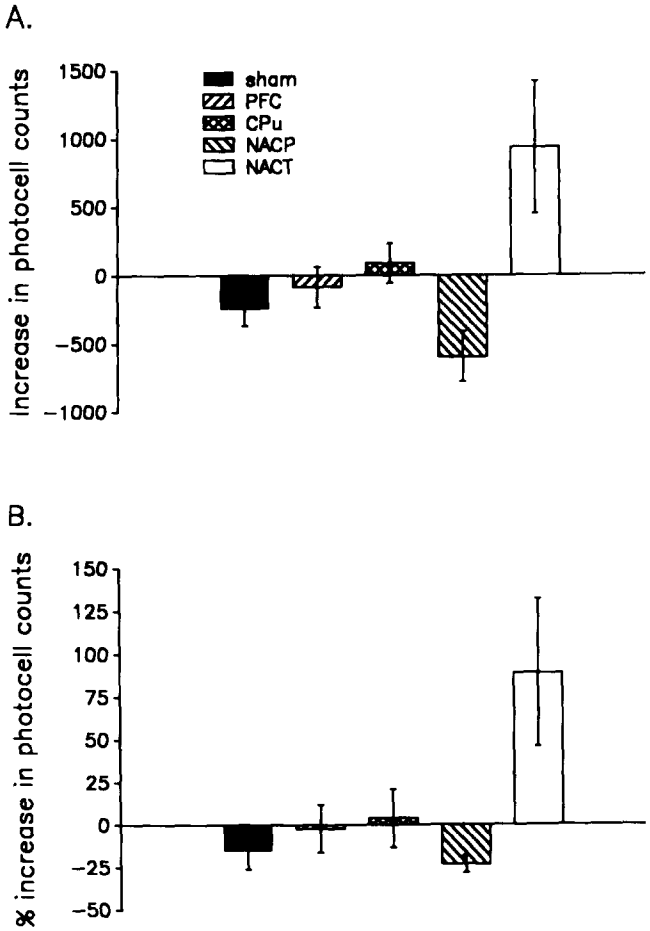

FIG. 4. Effect of forebrain 6-hydroxydopamine infusions on the locomotor response to an injection of 0.1 mg/kg apomorphine HCl SC. The vertical bars represent the SEM. (A) Data expressed as the increase in photocell counts/h compared to saline injection. (B) Data expressed as the percentage increase in photocell counts/h compared to saline injection. See Fig. 1 for definitions of abbreviations.

DISCUSSION

These results have demonstrated that mesocortical, mesolimbic, and mesostriatal DA depletion differentially influence spontaneous, drug-induced, and conditioned locomotor activity.

The two different NAC lesion procedures produced marked but opposite effects on spontaneous locomotor activity, whereas CPu lesions had no effect. The large NAC DA depletions of 90% (NACT group) reduced spontaneous locomotor activity, while smaller depletions of 67% (NACP group), produced hyperactivity. 6-OHDA lesions of the mesolimbic DA pathway have previously been reported to produce either increases (40), decreases (22,26,39), or no change (68) in spontaneous locomotor activity and it is apparent that the degree of lesion is critically important. Opposite effects of different sized mesolimbic DA lesions have been reported previously, particularly for 6-OHDA lesions of the VTA. Koob et al. (40) demonstrated that "relatively small" lesions of the VTA (defined by the amount of 6-OHDA infused), which reduced NAC DA by 86%, resulted in a marked elevation in spontaneous locomotor activity, whereas "large" lesions (97% depletion) did not significantly alter locomotor activity (40).

Locomotor activity following NAC infusions of 6-OHDA has been reported to be similarly dependent upon lesion size. For example, large lesions either have no effect (31,60) or decrease locomotor activity (26,30,35,39) whereas smaller lesions either produce transient effects (13,20,32) or increase locomotor activity [(17), p. 513]. The present results, to our knowledge, are the first demonstration of both hypoactivity and hyperactivity following 6-OHDA lesions of the NAC in the same study. The effect of the degree of NAC DA depletion on locomotor activity is perhaps larger than has been previously reported. However, the method of measuring activity (60), the part of the day/night cycle when the measurements are made (42), and the time period after lesion (13,68) are all important determinants of the locomotor effects of mesolimbic DA lesions. In addition, unlike in most other studies except, for example, Koob et al. (39), subjects in the present experiment were tested food deprived, a procedure known to elevate the susceptibility to exhibit increased locomotor activ-

ity in normal animals (12). Insensitivity to changes in deprivation state (44) or reduced responsiveness to behaviourally activating stimuli (51) following mesolimbic DA depletion may have contributed to the magnitude of the reduction in spontaneous locomotor activity in the NACT group.

The neural mechanism underlying this difference in locomotor activity between the two NAC lesion groups is unknown. Not only was the degree of NAC DA depletion much less in the NACP group, the DA depletion in the anterior CPu was also smaller in this group. This latter result is unlikely to be a contributory factor as CPu 6-OHDA lesions themselves did not significantly alter spontaneous locomotor activity. Increases in locomotor activity following small 6-OHDA lesions of the VTA can be blocked by additional 6-OHDA lesions of the NAC (40), encouraging the view that compensatory changes in NAC DA function contribute to the increased locomotor activity. However, in the present experiment there was actually a tendency for the NACT group to have the highest NAC DOPAC/DA ratio, possibly indicating greater DA utilization. Furthermore, whereas both NAC lesions blocked amphetamine-induced locomotor activity only the NACT group showed locomotor activation following a low dose of apomorphine (35,37), an effect that has been interpreted as indicating postsynaptic NAC DA receptor supersensitivity (35,58,59).

It should also be mentioned that NAC DA function has been considered capable of rapid recovery from 6-OHDA lesions (20,32,35), which may have precluded finding the neurochemical basis for this difference in the NACP and NACT groups. Although this apparent rapid recovery from 6-OHDA lesions can, to a certain extent, be demonstrated behaviourally (13,37,66) it has proved remarkably difficult to identify its neurochemical correlates (36,68). No recovery was evident from the present behavioural data as spontaneous activity scores in the two NAC groups did not show any alteration compared with controls for the 10 days of testing (up to 28 days postoperatively).

PFC 5-HT, apparently uniquely sensitive to 6-OHDA (17,29), was also depleted by infusions of 6-OHDA directly into the PFC, but not by NAC infusions, and therefore cannot explain the difference between the NACP- and NACT-lesioned rats. A further difference between the NACT and NACP groups is that the NACT group had a significant elevation of 5-HT in the NAC that was not present in the NACP group. This result supports the view that spontaneous locomotor activity may be influenced by the balance between DA and 5-HT activity in the NAC (15) and adds further credence to the hypothesis that the effects of mesolimbic DA lesions are dependent upon a complex relationship between several neurotransmitters and brain areas.

It has also been suggested that locomotor activity is influenced by the balance between PFC NE and DA (16,42). However, this also cannot account for the difference between the NAC groups in the present experiment as the two lesions produced comparable effects on both NE and DA in the PFC and also on NE in the NAC.

In confirmation of previous studies (16,47), PFC 6-OHDA lesions increased spontaneous locomotor activity. However, elevations in locomotor activity following PFC DA depletion are not consistently reported (32) and, although Tassin et al. (62) reported an inverse relationship between PFC DA and locomotor activity, these elevations may depend upon more subtle neurotransmitter relationships (16,61).

Some studies have also reported that PFC DA depletion increases indices of DA activity in subcortical structures (47) and can also influence NAC DA receptor function (48). However, the present results failed to confirm this effect. For example, in confirmation of other reports (17) the PFC group in this experiment did not show an altered response to apomorphine.

It is apparent that to understand the role of the PFC and NAC in spontaneous locomotor activity further comprehensive studies are required.

The present experimental design has also allowed for the relatively pure measurement of food-related preparatory behaviour. The results are confounded with neither specific response requirements, as the delivery of food is unconditional, nor alterations in consummatory behaviour, as locomotor activity is measured prior to delivery of food. All rats showed an increase in locomotor activity following the conditioning procedure. Not only did infusions of 6-OHDA into the NAC produce the largest effects on spontaneous locomotor activity, but they were also the only lesion parameters that significantly influenced the anticipatory response to food presentation (preparatory behaviour). Whereas the NACP group showed an immediate greater increase in activity compared with controls, the NACT group showed no difference from controls in their initial response, followed by an enhancement toward the end of testing.

The lack of initial effect of the almost total DA-depleting lesions of the NAC on the conditioned response is consistent with the effects of NAC DA depletion in other related situations. For example, rats with mesolimbic DA depletion do not show the normal increases in activity associated with pronounced food deprivation (44), an effect shown to be due not to intrinsic effects of deprivation per se (12) but to increased sensitivity to environmental stimuli (5,53). In addition, NAC 6-OHDA lesions, which produced an 85% depletion of NAC DA, failed to influence responding with conditioned reinforcers [CRs; (64)] and rats with a mean NAC DA depletion of 75% did not show an altered conditioned place preference for amphetamine, although some manipulation of the data did reveal a tendency for the larger lesions to have the greatest effect (55). Thus, it would seem that responding to stimuli associated with reward is not dependent upon intact DA terminals in the NAC. However, the magnitude of any potentiation of these responses is apparently influenced by DAergic processes in the NAC. For example, responding for CRs is elevated by systemic (50) or intraaccumbens (27,63) *d*-amphetamine, effects that can be blocked by NAC DA depletion (50,64).

It is possible that the enhanced response in the NACT group in the latter stages of testing reflects neural recovery processes described earlier. A striking feature is that this "recovery" started at precisely the time the conditioning procedure was introduced and it is possible that if it does represent recovery, and not just a delayed response, it was precipitated by the change in status of external stimuli. The implication of this interpretation is that DAergic activity within the NAC mediates conditioned responses to incentive stimuli. However, after testing for conditioned activity the NACT group still showed the usual altered pattern of responses to psychomotor stimulants following large 6-OHDA lesions of the NAC, that is, a blockade of the locomotor-stimulating effects of *d*-amphetamine and an increase in locomotor activity following a low dose of apomorphine (37).

Both conditioned activity and the effects of CRs are dependent upon processing of information by limbic structures such as the amygdala (11) and hippocampus (19), which project

to the NAC/ventral striatum (33,34). Whereas appropriate responding to stimuli may be determined by limbic regions, DA transmission in the NAC may serve to alter the magnitude of behavioural output.

Also evident from the present results is that although PFC 6-OHDA lesions increased spontaneous locomotor activity they had no discernible effect on the response to psychomotor stimulants [cf. (17)] or on conditioned locomotor activity. The modulation of NAC DA (47) or locomotor activity (16,61) by PFC DA does not therefore seem to alter behavioural responses that depend upon the processing of motivationally significant information.

In contrast to 6-OHDA lesions of the NAC, CPu DA depletion failed to influence the locomotor response to stimuli predictive of food reward but did produce transitory aphagia immediately postoperatively, underlining the possible role of CPu DA in consummatory rather than preparatory behaviour.

In summary, these results demonstrate differential effects of discrete forebrain 6-OHDA lesions on spontaneous, drug-induced, and conditioned locomotor activity. The extent of DA depletion of the NAC critically determined the effect of NAC 6-OHDA lesions on both spontaneous locomotor activity and locomotor activity conditioned to food presentation. These results further implicate NAC DA in the behavioural response to incentive stimuli or in a general preparatory state.

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