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Amphetamine impairs the discriminative performance of rats with dorsal noradrenergic bundle lesions on a 5-choice serial reaction time task: New evidence for central dopaminergic-noradrenergic interactions

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Abstract. A series of experiments examined the effects of lesions of the dorsal noradrenergic bundle (DNAB), induced by 6-hydroxydopamine (6-OHDA), on the behavioural response to systemic and intra-accumbens amphetamine, using a rat analogue of Leonard's 5-choice serial reaction time task for humans. Although the 6-OHDA DNAB lesion produced a profound depletion of cortical noradrenaline (NA) (to around 5% of control levels) it did not impair any aspect of performance on this task. Both systemic and intra-accumbens amphetamine increased behavioural measures of impulsivity of responding, but neither impaired discriminative accuracy in the sham-operated control rats. However, the DNAB lesioned rats did show a discriminative impairment following both low doses of systemic amphetamine, and intra-accumbens amphetamine. The latter effect was antagonised by systemic administration of the specific dopaminergic (DA) antagonist alpha-flupenthixol. The DNAB lesion did not alter the effect of amphetamine on any other behavioural measure, including speed and impulsivity of responding. These results suggest that although DA and NA participate in qualitatively different behavioural processes, the effects of DNAB lesions on attentional processes depend on the level of DA activity within the nucleus accumbens.

Key words: *d*-Amphetamine – Attention – Discrimination – Dopamine-Noradrenaline interaction – Dorsal noradrenergic bundle – alpha-Flupenthixol – Nucleus accumbens – Rat

The proposal that lesions of the dorsal noradrenergic ascending bundle (DNAB) produce an impairment in selective attention (Mason and Iversen 1979) has recently been disputed (Pisa and Fibiger 1983). However, Carli et al. (1983) showed that rats with DNAB lesions may indeed show attentional deficits, but only under particular conditions. Specifically, they demonstrated that the accuracy of visual discrimination in a 5-choice serial reaction time task was impaired in DNAB-lesioned rats when a burst of loud white noise was presented just prior to the onset of the visual discriminanda. In contrast, the accuracy of sham-operated controls was not impaired. The white noise resulted in quicker responding and an increase in premature responses in both sham-operated and DNAB-lesioned rats. Thus, although the DNAB-lesioned rats showed a normal response to the noise in terms of measures of speed and impulsivity of responding, they showed an additional impairment in the accuracy of visual discrimination.

In previous studies, amphetamine has been shown to produce the same effects as white noise on speed and impulsivity of responding in unoperated rats on this task (see Robbins and Sahakian 1983). Therefore, if white noise and amphetamine produce similar behavioural effects by related psychological or neurochemical processes, it would be expected that amphetamine would also produce a discrimination impairment in DNAB-lesioned rats. This hypothesis was tested in Experiment 1 of the present study, which investigated the effects of systemically administered amphetamine on the performance of the same task employed by Carli et al. (1983) in rats with 6-hydroxydopamine (6-OHDA) lesions of the DNAB and sham-operated controls.

The behavioural effects of amphetamine are primarily mediated by its facilitatory action on central catecholaminergic neurotransmission (Groves and Tepper 1983). In particular, there is evidence that the rate-increasing and rate-reducing effects of the drug depend upon dopaminergic (DA) mechanisms in the nucleus accumbens (Kelly et al. 1975; Robbins et al. 1983). However, in addition to its stimulatory action on noradrenergic (NA) mechanisms, amphetamine also inhibits firing of NA neurones in the locus coeruleus via an alpha-2 adrenoceptor mechanism (Engberg and Svensson 1979). The functional result of these two opposing actions has been shown in the hippocampus to be a reduction in NA transmission following low doses of amphetamine (Huang and Maas 1981). Consequently, any performance decrement produced by amphetamine in DNAB-lesioned rats could result either from a further depression of NA transmission, or because the lesion impairs discrimination when DA systems are activated. These alternative hypotheses were assessed in two further studies. Firstly, the behavioural effects of amphetamine administered directly into the nucleus accumbens, a predominantly DA terminal region, in sham-operated and DNAB-lesioned rats were assessed, using the same behavioural paradigm as Experiment 1. The pharmacological specificity of these behavioural effects of intra-accumbens amphetamine was then tested by the use of a specific DA receptor antagonist, alpha-flupenthixol (Iversen 1985).

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Materials and methods

Subjects

The subjects were 30 (14 for Experiment 1 and 16 for Experiment 2) male hooded rats (Olac, Bicester, UK), housed in pairs under natural daylight. They were maintained throughout the experiment at 85% of their free feeding weight by restricting their daily intake of food to 15 g of laboratory chow per rat. Water was freely available.

Apparatus

One 25 × 25 cm aluminium chamber was used. The rear wall was curved, and set into this wall were nine 2.5 cm square holes, 4 cm deep and 2 cm above floor level. Each hole had an infra-red beam crossing the entrance vertically which illuminated a photo-electric cell. A 3 W bulb at the rear of each hole provided illumination for that hole. Each hole could be blocked by a metal cap. Alternate holes were blocked throughout the experiment. A diagram of the apparatus is given in Fig. 1 of Carli et al. (1983).

Food pellets (45 mg, C.S. Abel Ltd, Oxford, UK) were delivered to a tray at the front of the chamber, which could be accessed by pushing a hinged, Perspex panel. The distance from the panel to each hole at the rear of the box was 25 cm. The chamber was illuminated by a 3 W bulb located in the centre of the roof. The subjects were introduced to the box through a hinged Perspex flap at the front of the chamber. The whole chamber was housed in a dark, soundproof compartment with a ventilator fan providing low-level background noise. The apparatus was controlled, and the data collected on-line, by a Control Universal Cube system microcomputer, programmed in ONLI-BASIC.

Behavioural procedure

The start of each session was signalled by turning on the houselight and the free delivery of a single food pellet. The first trial started when the panel was opened to collect the food pellet. After a fixed delay (intertrial interval, ITI) the light at the rear of one of the five unblocked holes was illuminated for a short period. The light stimulus was presented in each of these holes an equal number of times during each complete session, and the order of presentation was randomised. While the stimulus was illuminated, and for a short period afterwards (limited hold), a response in the illuminated hole (correct response) resulted in the delivery of a food pellet. A response in any other hole (incorrect response) or a failure to make a response within the limited hold (omission) resulted in a period of time out which was signalled by turning off the houselight. Any response made in a hole during this period restarted the time out. The next trial was initiated by opening the panel, either to collect the food pellet or following the completion of the time out period. Additionally, a response made in a hole after a correct response or following the completion of time out before opening the panel resulted in a period of time out, as did a response made during the ITI. However, in the latter case, following the completion of time out, opening the panel restarted the current trial.

Each daily session consisted of 100 trials or 30 min of testing, whichever was completed sooner. At the end of the session, all the lights were extinguished and further responses were ineffective.

Training

In the first session of the test schedule the stimulus duration and the limited hold were both 60 s. These durations were then progressively reduced to 0.5 s and 5 s, respectively, during training. The ITI and time out were both 2 s for the first two sessions and were then increased to 5 s and 3 s, respectively, for all following sessions. The subjects were trained on this schedule until stable performance had been reached, with a mean of 80% correct and no more than 15% omissions (approximately 30 sessions). The subjects were then divided into two equal groups for surgery (DNAB lesion and sham control), matched for baseline performance.

Surgery

All rats were pretreated 30 min before surgery with an intraperitoneal (IP) injection of 50 mg/kg pargyline hydrochloride. Rats were anaesthetized with Equithesin (3.0 ml/kg) and secured in a stereotaxic instrument. Rats in the DNAB lesion group received bilateral infusions of 2 µl ascorbate (0.1 mg/ml) in 0.9% saline containing 2 µg/µl 6-OHDA (free base) through a 30 gauge stainless steel cannula connected by polythene tubing to a 10 µl microsyringe driven by a Harvard infusion pump over 4 min. Sham-operated controls received infusions of the neurotoxin vehicle alone. The cannula was left in position for at least 2 min prior to withdrawal. Stereotaxic co-ordinates for the DNAB lesion were; anterior-posterior, −6 mm from bregma; lateral, +/−1 mm from midline; vertical, −5 mm from dura, with the incisor bar fixed at 2.4 mm below the inter-aural line.

In Experiment 2, bilateral stainless steel guide cannulae (23 gauge) which gave access to the nucleus accumbens were implanted at the same time. The co-ordinates were; anterior − posterior, +3.4 mm from bregma; lateral, +/−1.7 mm from the midline; vertical, −6 mm from dura, with the incisor bar 5 mm above the inter-aural line.

All the animals were allowed a 14-day period for post-operative recovery prior to further behavioural testing.

Post-operative testing

Immediate post-surgical effects. In both experiments, following the post-operative recovery period, the rats were returned to the schedule and performance was allowed to restabilise over a period of 8 days. The performance over the following 3 days was used to assess the baseline.

Experiment 1

Systemic amphetamine (regimen 1). Over a period of 8 days, commencing immediately after the baseline had been assessed (25 days post-surgery), all rats received a sequence of IP injections of *d*-amphetamine sulphate, dissolved in 0.9% saline solution and administered in a volume of 0.1 ml/100 g body weight, 15 min prior to testing. The doses used were 0.4, 0.8, and 1.6 mg/kg (expressed as the salt), and the order of doses was based on a Latin Square design. Each drug day was preceded by a control day on which the saline vehicle was administered.

Systemic amphetamine (regimen 2). Twenty-four days after the completion of the first study of amphetamine (57 days post-surgery), during which the effects of alpha-flupenthixol were assessed (not to be reported here), a second series of amphetamine doses was administered. The procedure was identical to that of regimen *1*), but the doses used were 0.2, 0.4, and 0.6 mg/kg *d*-amphetamine sulphate.

Experiment 2

Intra-accumbens amphetamine. Over a 16-day period beginning immediately after the assessment of baseline performance (25 days post-surgery), each rat received a series of intra-accumbens injections of *d*-amphetamine sulphate. The bilateral injections were made using 30-gauge injection cannulae placed into the surgically-implanted guide cannulae, with the tip 1.2 mm below the end of the guide cannulae (−7.2 mm from dura). These were connected by polythene tubing to a 10 µl microsyringe mounted in a Harvard infusion pump. The infused volume was 1 µl over a 4-min period with an additional 2 min prior to the removal of the injection cannulae, during which time the animals were hand held. The rats were then returned to their home cage for 10 min before the test session commenced. Drug doses of 3, 10, and 30 µg *d*-amphetamine sulphate were employed. All the doses were calculated in terms of the salt and were dissolved in 0.9% saline, which was employed as vehicle (control) solution. The order of drug doses was based on a Latin Square design. The experiment was conducted on a 4-day cycle (baseline, drug injection, no test, baseline). Thus 3 days without drug preceded each injection.

Antagonism of intra-accumbens amphetamine by systemic alpha-flupenthixol. Immediately after the completion of the dose response study (42 days post-surgery), the combined effects of intra-accumbens amphetamine and systemic alpha-flupenthixol were studied. A dose of 0.3 mg/kg alpha-flupenthixol, dissolved in 0.9% saline and administered in a volume of 0.1 ml per 100 g body weight, was injected IP 30 min before the session. This was followed by a dose of 30 µg *d*-amphetamine sulphate injected into the nucleus accumbens (as described previously) 10 min before the session. Following a rest day and two control sessions, the effects of 0.3 mg/kg systemic alpha-flupenthixol and intra-accumbens saline were assessed.

Neurochemical assay and histology

At the end of the experiments, all the rats were killed under ether anaesthesia and their brains rapidly removed and dissected on ice into a strip of cortex, the hippocampus, and hypothalamus. Additionally, the nucleus accumbens was dissected from 11 of the rats in Experiment 2. All the dissections were made according to previously published methods and criteria (Robbins and Everitt 1982). The levels of NA were measured using high performance liquid chromatography with electrochemical detection, as described by Mefford (1981).

Five sections of brain containing the nucleus accumbens were placed into formalin and treated according to standard histological procedures (Wolf 1971) to determine the exact location of the injection site. The use of nucleus accumbens tissue for biochemical analysis prevented histological assessment of all the brains. However, during dissection, it was possible visually to verify the location of the injection cannulae tips in the nucleus accumbens.

Measures and statistical analysis

The main measures utilised in these experiments were:

Accuracy. The accuracy of performance was assessed using two variables. Percent correct (number of correct responses/number of correct responses + number of incorrect responses) and percent omissions (number of omissions/total number of trials).

The latency to respond, which is the time between the onset of the stimulus and the response, was analysed separately for correct and incorrect responses.

ITI responses. The number of responses in the holes during the ITI (premature responses) and the number of responses in the panel during the ITI were recorded.

All the data were analysed by analysis of variance (ANOVA), using GENSTAT (Rothamstead, Herts, UK), in a design including the factors Lesion (DNAB and SHAM) and Dose. When significant interactions were found, further analysis was made of the simple main effect. Specific comparisons were made using Student's *t* tests, with the alpha criterion set at $P < 0.025$ and the *df* for the appropriate error term derived from the analysis of variance.

Drugs

6-OHDA hydrobromide was purchased from Sigma Co. (Poole, Dorset, UK). Dexamphetamine sulphate was donated by Smith Kline & French (Welwyn Garden City, Herts, UK) and alpha-flupenthixol dihydrochloride was a donation from H. Lundbeck (Copenhagen, Denmark).

Results

Neurochemical and histological results

The effects of the DNAB lesion upon regional concentrations of NA for the rats used both in Experiments 1 and 2 are shown separately in Table 1. As can be seen, the neurotoxin reduced both cortical and hippocampal NA levels by around 90%, whilst reducing hypothalamic NA to 50% of control values. The DNAB lesion also reduced NA levels in the nucleus accumbens by 91% in the animals assayed from Experiment 2.

Histological analysis showed that the guide cannulae placements gave access to the nucleus accumbens. The infusion sites in the brains which were histologically analysed were approximately 1 mm below the tip of the guide cannulae, as shown in Fig. 1.

Behavioural results. Experiment 1. Effects of DNAB lesions on baseline performance

Accuracy. There was no effect of DNAB lesions on accuracy. Analysis of variance showed that there was no difference between the two groups in the percentage of correct re-

Table 1. Neurochemical effects of 6-OHDA lesions of the DNAB

	Cortex	Hippo-campus	Hypo-thalamus	Nucleus accumbens
Experiment 1				
DNAB ($n=7$)	0.017 ±0.004	0.004 ±0.003	1.165 ±0.059	
SHAM ($n=7$)	0.484 ±0.039	0.634 ±0.057	2.556 ±0.143	
% Depletion	96%**	99%**	55%*	
Experiment 2				
DNAB ($n=8$)	0.024 ±0.006	0.080 ±0.011	1.556 ±0.086	0.091[a] ±0.069
SHAM ($n=8$)	0.362 ±0.027	0.664 ±0.043	2.287 ±0.124	0.990[b] ±0.252
% Depletion	93%**	88%**	32%*	91%**

The values provided are mean levels of NA +/− SEM expressed as ng/mg concentration wet weight

* $P<0.01$; ** $P<0.001$ (Student's t test)

[a] $N=6$; [b] $N=5$

sponses (DNAB mean 78%, SHAM mean 81%) or omissions (DNAB mean 7.2%, SHAM mean 8.5%).

Speed. There was no effect of Lesion on the latency to make either a correct response (DNAB mean 0.38 s, SHAM mean 0.36 s) or an incorrect response (DNAB mean 1.43 s, SHAM mean 1.39 s).

ITI responses. There was no effect of the DNAB lesion on the number of premature responses (DNAB mean 12.3, SHAM mean 14.1) or the number of panel pushes during the ITI (DNAB mean 33.7, SHAM mean 30.9).

Effects of systemic amphetamine (regimen 1)

Accuracy. Although there was no overall effect of Dose on the accuracy of discrimination, analysis of variance revealed a Lesion × Dose interaction ($F=2.971$, df 3,36, $P<0.05$). Further analysis revealed that DNAB-lesioned rats were less accurate than sham-operated controls after 0.4 mg/kg amphetamine, and that there was no significant effect of dose in the sham-operated controls, as shown in Fig. 2a. Amphetamine increased the number of omissions from a mean of 7.2% following saline injection to a mean of 14.9% following 1.6 mg/kg amphetamine ($F=2.952$, df 3,36, $P<0.05$) but there was no effect of Lesion.

Speed. There was no effect of Lesion on the latency to make either a correct or incorrect response. Although there was no significant effect of Dose on the latency to make a correct response, amphetamine did tend to enhance speed of responding at the lowest dose (saline mean 0.38 s, 0.4 mg/kg amphetamine mean 0.33 s) but not the higher doses (0.8 mg/kg amphetamine mean 0.37 s, 1.6 mg/kg mean 0.38 s). Amphetamine did not affect the latency to make an incorrect response.

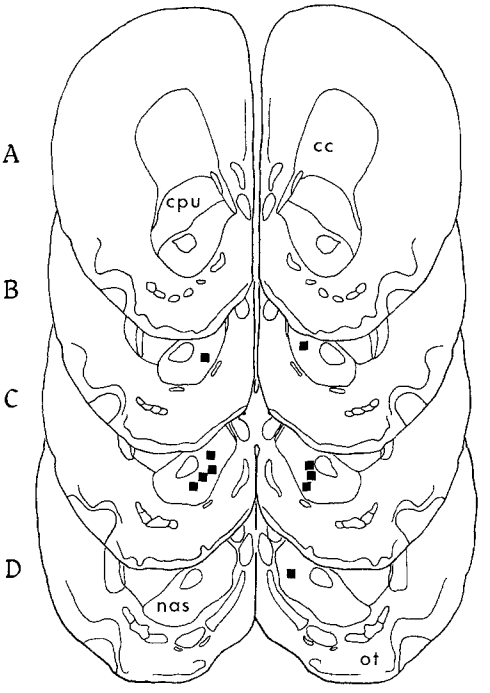

Fig. 1. Brain sections modified from Pellegrino and Cushman (1976) indicating individual rat bilateral injection tips from the five rats who were histologically analysed (Experiment 2). The distances (in mm) of each section from bregma is: $A=3.8$, $B=3.6$, $C=3.4$, $D=3.2$. Abbreviations are as follows: *CC* corpus callosum; *CPU* caudate nucleus and putamen; *NAS* nucleus accumbens septi; *OT* olfactory tubercle

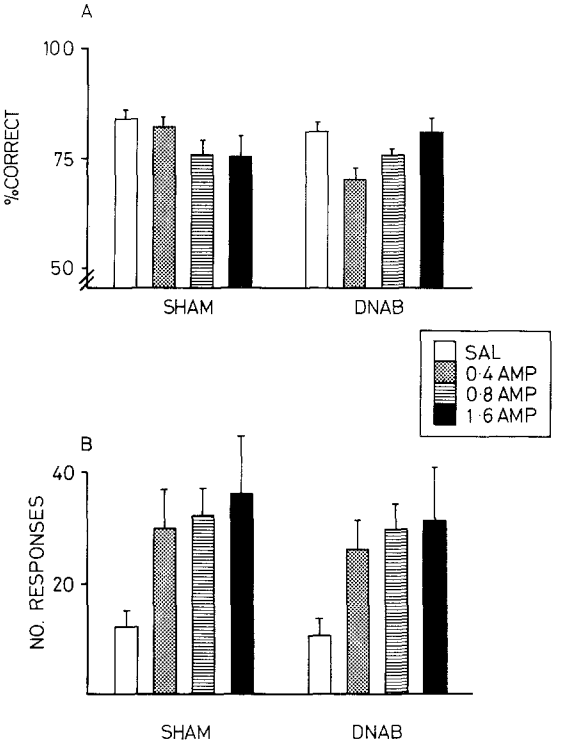

Fig. 2A, B. Effects of 6-OHDA DNAB lesions on the response to amphetamine doses in mg/kg for discriminative accuracy (**A**) and premature responding (**B**) in Experiment 1 (regimen 1). Data are presented as mean +1 SEM

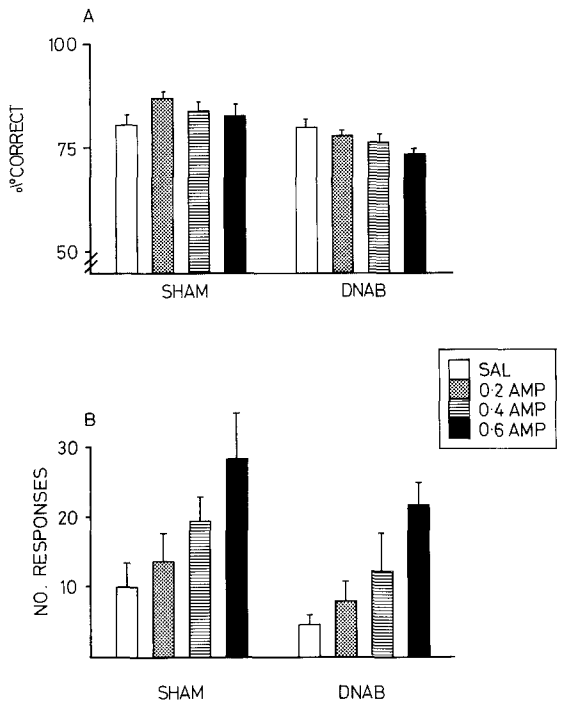

Fig. 3A, B. Effects of 6-OHDA DNAB lesions on the response to amphetamine (doses in mg/kg) in Experiment 1 (regimen 2). **A** mean +1 SEM percent correct, **B** mean +1 SEM number of premature responses at each dose for both the DNAB-lesioned rats and the sham-operated controls

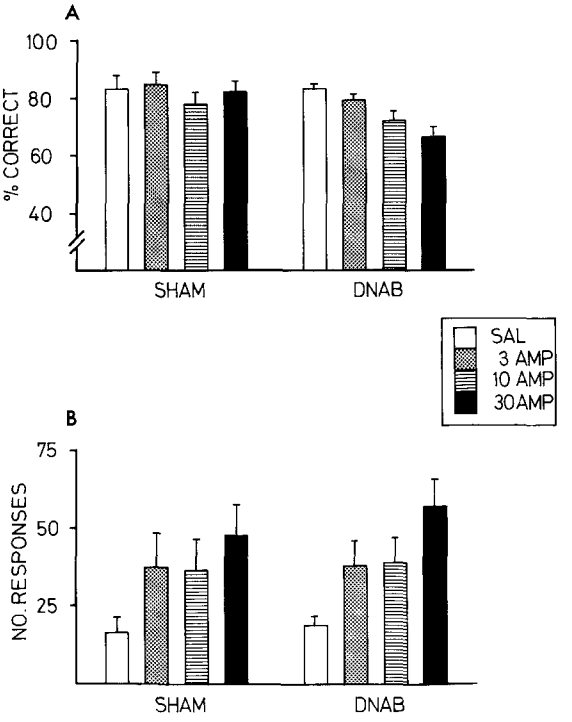

Fig. 4A, B. Effects of 6-OHDA DNAB lesions on the response to intra-accumbens amphetamine (doses in μg). **A** discriminative accuracy (per cent correct), **B** impulsivity of responding (premature responses). Data are presented as mean +1 SEM

ITI responses. Amphetamine caused a dose-dependent increase in the number of premature responses, as shown in Fig. 2b ($F=6.456$, *df* 3,36, $P<0.005$) but this was unaffected by Lesion. The number of panel pushes during the ITI was also increased by amphetamine (saline mean 9.4, 1.6 mg/kg amphetamine mean 37.4; $F=7.627$, *df* 3,36, $P<0.001$), but there was no additional effect of Lesion.

Effects of systemic amphetamine (regimen 2)

Accuracy. As shown in Fig. 3a, the performance of DNAB-lesioned rats became less accurate following all doses of amphetamine, but the performance of sham-operated controls was unaffected at all doses (Lesion × Dose interaction $F=2.969$, *df* 3,36, $P<0.05$). Omissions were not affected by either Lesion or Dose.

Speed. The latency to make a correct response was shortened significantly by amphetamine ($F=11.699$, *df* 3,36, $P<0.001$) from a control mean of 0.38 s to 0.30 s following 0.6 mg/kg amphetamine, but was unaffected by Lesion. The latency to make an incorrect response was unaltered by both Dose and Lesion.

ITI responses. Analysis of variance showed that premature responses were increased by amphetamine, as shown in Fig. 3b ($F=11.153$, *df* 3,36, $P<0.001$), but there was no additional effect of Lesion. Responses at the panel during the ITI were also unaffected by Lesion but were increased by the drug ($F=9.737$, *df* 3,36, $P<0.005$) from a control mean of 14.6 to 36.9 following 0.6 mg/kg amphetamine.

Behavioural results. Experiment 2. Effects of DNAB lesions on baseline performance

As in Experiment 1, there was no effect of the lesion on any behavioural measure (data not reported).

Effects of intra-accumbens amphetamine

Accuracy. As shown in Fig. 4, amphetamine injected into the nucleus accumbens impaired the accuracy of DNAB-lesioned, but not sham-operated control rats (Lesion × Dose interaction $F=3.662$, *df* 3,42, $P<0.05$). Thus the DNAB-lesioned rats were less accurate than the sham-operated controls after all doses of the drug, but not saline. The lesion did not affect omissions, which were, however, increased by amphetamine ($F=4.288$, *df* 3,42, $P<0.05$) from a control mean of 7.2%–14.8% following 30 μg amphetamine.

Speed. The latency to make a correct response was lengthened by intra-accumbens amphetamine ($F=5.054$, *df* 3.42, $P<0.01$) from a control mean of 0.35–0.48 s following 30 μg amphetamine, but was unaffected by Lesion. Analysis of variance also showed a significant effect of Dose on the latency to make an incorrect response ($F=3.057$, *df* 3,42, $P<0.05$). Further analysis showed that after 3 and 10 μg intra-accumbens amphetamine, the rats were slower to make an incorrect response, but this effect was not pres-

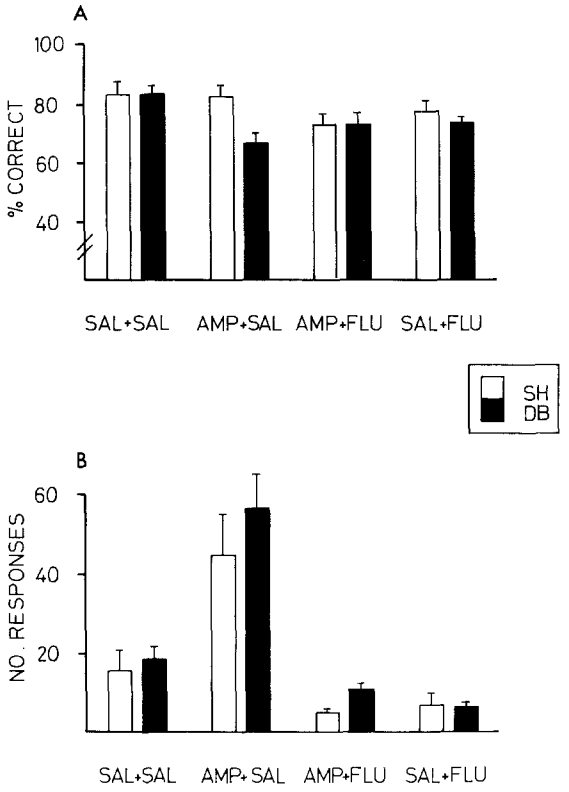

Fig. 5A, B. The effects of 6-OHDA DNAB lesions on discriminative accuracy (**A**) and premature responding (**B**) following: (1) intra-accumbens saline and systemic saline; (2) intra-accumbens amphetamine and systemic saline; (3) intra-accumbens amphetamine and systemic alpha-flupenthixol; (4) systemic alpha-flupenthixol and intra-accumbens saline. The data are presented as mean +1 SEM

ent following 30 μg intra-accumbens amphetamine. There was no additional effect of Lesion.

ITI responses. Intra-accumbens amphetamine produced a dose-dependent increase in the number of premature responses, as shown in Fig. 4b ($F=6.571$, df 3,42, $P<0.01$), but the DNAB lesion did not affect this measure. The drug also enhanced the number of panel pushes during the ITI ($F=3.726$, df 3.42, $P<0.05$), but there was no effect of Lesion.

Effects of intra-accumbens amphetamine and systemic alpha-flupenthixol

Accuracy. Fig. 5a shows the combined effects of intra-accumbens amphetamine and systemic alpha-flupenthixol on the accuracy of discrimination. Analysis of variance revealed a significant 3-way interaction (Lesion × Amphetamine × alpha-Flupenthixol, $F=7.697$, df 1,14, $P<0.05$). Further analysis showed that without systemic alpha-flupenthixol, amphetamine impaired the accuracy of the DNAB-lesioned rats but had no effect on the performance of the sham-operated controls (Lesion × Amphetamine interaction, $F=4.831$, df 1,14, $P<0.05$). However, following systemic alpha-flupenthixol, neither Amphetamine nor Lesion affected the accuracy of performance. Analysis of the simple interaction between amphetamine and alpha-flupenthixol separately for the two groups revealed a significant Amphetamine × alpha-Flupenthixol interaction in the DNAB-lesioned group ($F=14.299$, df 1,14, $P<0.01$) but no significant main effect of either drug or a significant interaction in the sham-operated controls. Omissions were increased by both amphetamine (control mean 7.8%, amphetamine mean 18.9%, $F=19.195$, df 1,14, $P<0.001$) and alpha-flupenthixol (control mean 8.8%, alpha-flupenthixol mean 17.8%, $F=16.442$, df 1,14, $P<0.001$) but there was no interaction between the drugs, or with the lesion.

Speed. There was a significant interaction between alpha-flupenthixol and amphetamine on the latency to make a correct response ($F=11.275$, df 1,14, $P<0.01$). Intra-accumbens amphetamine alone increased the latency to make a correct response from 0.35 s to 0.51 s, as did alpha-flupenthixol alone, but the two effects were not additive (alpha-flupenthixol alone mean 0.53 s, amphetamine and alpha-flupenthixol mean 0.48 s). There was no additional effect of the lesion. Analysis of variance also revealed an Amphetamine × alpha-Flupenthixol interaction on the latency to make an incorrect response ($F=22.064$, df 1,14, $P<0.001$). Further analysis revealed that whilst intra-accumbens amphetamine alone did not affect the latency to make an incorrect response, following alpha-flupenthixol, amphetamine decreased the mean latency from 2.13 s to 1.40 s.

ITI responses. As shown in Fig. 5b, alpha-flupenthixol antagonised the amphetamine-induced increase in premature responses ($F=21.989$, df 1,14, $P<0.001$), but there was no interaction with Lesion. Analysis of variance revealed a Lesion × Amphetamine interaction for the number of ITI panel pushes. DNAB-lesioned rats showed an increase in panel pushing following amphetamine (control mean 37.5, amphetamine mean 53.4) but the sham-operated controls decreased panel pushing following amphetamine (control mean 43.9, amphetamine mean 34.6). alpha-Flupenthixol did not affect the number of panel pushes during the ITI.

Discussion

These experiments have shown that low doses of systemic amphetamine and direct infusions of amphetamine into the nucleus accumbens produce an impairment in the ability of DNAB-lesioned rats to perform a 5-choice serial reaction time task accurately. However, 6-OHDA induced lesions of the DNAB failed to alter any of the other behavioural responses to amphetamine measured. Additionally, neither the DNAB lesion nor amphetamine alone had any effect on accuracy of discrimination, even though systemic amphetamine increased impulsivity and (less reliably) the speed of responding. We believe these results are important because they suggest a novel hypothesis concerning functional interactions between central DA and NA systems. However, alternative interpretations of the data will also be discussed.

Neural and behavioural mechanisms underlying the effects of systemic amphetamine

The enhanced speed and impulsivity of responding produced by systemic injections of amphetamine replicates and extends the unpublished findings of Carli et al. (see Robbins

and Sahakian 1983) and is also qualitatively similar to the changes in performance produced by white noise (Carli et al. 1983). However, although intra-accumbens infusions of amphetamine also produced graded, dose-related increases in impulsivity of responding as measured by premature responses, the speed of responding was reduced, as shown by the increased latency to make a correct response. These contrasting effects of systemic and intra-accumbens amphetamine on the latency to make a correct response cannot be explained by the rate dependent action of amphetamine, since the baseline latencies were comparable across the two experiments. This result suggests that although the nucleus accumbens may mediate the increased impulsivity of responding caused by systemic amphetamine, it is unlikely that it also mediates the reduction in latency to make a correct response. However, since the behavioural effects of amphetamine infusions into other DA terminal regions were not studied, their involvement in the behavioural actions of systemic amphetamine cannot be assessed.

In contrast to several other reports which have shown that systemic amphetamine can reduce discriminative accuracy (e.g. Weight et al. 1980; Ksir and Slifer 1982; Koek and Slangen 1983), there was no effect of amphetamine on discrimination in this task. Lyon and Robbins (1975) proposed that amphetamine would only impair discriminative performance as a consequence of the response constraints imposed by hyperactive and stereotyped behavioural patterns, but that any such effect of amphetamine on discriminative performance would be reduced by a high level of stimulus control. The present results broadly agree with these predictions, but also show that more impulsive or faster responding does not necessarily entail an impairment in either discrimination or selective attention in unlesioned rats.

Effects of DNAB lesions on amphetamine affected discrimination performance

The most striking feature of the amphetamine-induced discrimination impairment shown by the DNAB-lesioned rats is its behavioural specificity, as shown by the lack of effect of the lesion on any other behavioural response to amphetamine measured. Although the impairment in accuracy is quantitatively small, it is reliable, being present in all three studies. Taken together, the lack of effect of the DNAB lesion on baseline performance and the behavioural specificity of the amphetamine-induced discrimination impairment tend to rule out most of the general performance or motivational factors which could potentially explain this result. Consequently, the data are most consistent with the view that the amphetamine-induced performance decrement reflects an impairment of attentional processes in the DNAB-lesioned rats, as proposed by Carli et al. (1983) to explain the impairment produced by white noise in DNAB-lesioned rats.

There are three mechanisms which might underlie this discrimination impairment. Firstly, lesions of the DNAB might affect the response to amphetamine indirectly by affecting the dopaminergic mechanisms that mediate behavioural responses to the drug. Secondly, the impairment could result from the action of amphetamine on NA, rather than DA mechanisms. Finally, the impairment might occur because NA is important for maintaining stimulus control of behaviour when impulsivity of responding is enhanced.

Considering the first hypothesis, it has been proposed by Antelman and Caggiula (1977) from several lines of pharmacological evidence that NA indirectly modulates the activity of DA systems. Consequently, NA depletion should enhance those behavioural effects of amphetamine mediated by DA stimulation. However, specific studies on the effects of central NA depletion on amphetamine-induced behaviour have failed to provide conclusive support for this hypothesis. Specifically, central NA depletion has been reported to: (a) have no effect on amphetamine-induced locomotor activity and stereotypy (Creese and Iversen 1975; Roberts et al. 1975); (b) enhance amphetamine induced stereotypy, as shown by a specific increase in licking (Braestrup 1977) and amphetamine-induced perseveration in an 8-arm maze (Bruto et al. 1984) and (c) reduce amphetamine-induced stereotypy (Kostowski et al. 1977) and locomotor activity (Ogren et al. 1983; Archer et al. 1986).

Our results also fail to support this hypothesis for two reasons. Firstly, there was no evidence that the DNAB lesion actually enhanced the behavioural responses to amphetamine mediated by DA, since neither impulsivity of responding (see Figs. 2b, 3b, and 4b) nor speed of responding were greater in the DNAB-lesioned group than controls. Secondly, since amphetamine itself did not produce a discrimination impairment over a wide range of doses, it is difficult to explain the impairment shown specifically by the DNAB group in terms of a shifted dose response curve.

In relation to the second hypothesis, it has recently been shown that considerable neurochemical compensation occurs following 6-OHDA lesions of the DNAB (e.g. Acheson et al. 1980; U'Prichard et al. 1980; Harik et al. 1981). It is thus possible that the DNAB-lesioned rats are only able to perform accurately under control conditions due to the action of the remaining NA on supersensitive postsynaptic adrenergic receptors. Consequently, if low doses of amphetamine further reduce NA activity, the DNAB-lesioned rats show a discrimination impairment which is, however, independent of the drug's facilitatory action on DA.

This hypothesis is supported by the fact that in Experiment 1 (regimen 1) only low doses of systemic amphetamine impaired the discriminative accuracy of DNAB-lesioned rats, thus apparently correlating with the inhibitory action of amphetamine on NA mechanisms at low doses (Huang and Maas 1981). However, there are two lines of evidence against this interpretation. Firstly, intra-accumbens amphetamine is most unlikely directly to inhibit the NA neurones within the locus coeruleus, even taking into account the possibility of diffusion from the infusion site. However, at all doses studied, intra-accumbens amphetamine did impair the discriminative accuracy of DNAB-lesioned rats. Secondly, this impairment was antagonised by systemic alpha-flupenthixol, a specific DA receptor antagonist.

Because central infusions of drugs cause non-specific damage to tissue around the infusion site, it was necessary to restrict the number of infusions given to each animal. Consequently, only one dose of intra-accumbens amphetamine and systemic alpha-flupenthixol were studied together. Within the limitations imposed by a single dose study, this result suggests the involvement of DA receptors.

The results are perhaps most consistent with the hypothesis that NA is important for maintaining stimulus control of behaviour when impulsivity of responding is enhanced. Consistent with this view is the reduction in discriminative accuracy induced by intra-accumbens amphetamine in the

DNAB-lesioned rats and their unimpaired performance when the impulsivity-enhancing action of intra-accumbens amphetamine was antagonised (see Fig. 5a). The only result not consistent with this hypothesis is the lack of discrimination impairment following the higher peripheral doses of amphetamine. It is worth emphasising that the DNAB-lesioned rats were significantly more accurate following 0.8 and 1.6 mg/kg amphetamine than following 0.4 mg/kg amphetamine. Thus, the lack of effect seen at the higher doses was not caused by the sham-operated group becoming progressively less accurate. Although at high doses the stimulatory actions of amphetamine are not restricted to catecholamines, it seems unlikely that stimulation of a non-catecholamine mechanism is the explanation for the lack of effect seen in the DNAB-lesioned rats, since all the doses utilised were relatively low. The most parsimonious explanation may be in terms of the stimulatory action of amphetamine on NA at these doses, as 6-OHDA-induced lesions of the DNAB do not result in total loss of forebrain NA. Thus, an enhanced synaptic accumulation of NA at the remaining terminals, acting upon supersensitive receptors (Dalton et al. 1985), may be sufficient to compensate for the lesion.

The implication of these results is that systemic amphetamine does not normally cause an impairment in discriminative performance because it simultaneously stimulates both NA and DA mechanisms. Whilst the stimulation of DA mechanisms increases both the rate and speed of responding, the stimulation of NA mechanisms maintains stimulus control of behaviour.

In conclusion, these data show that there is a very close relationship between NA and DA in the control of behaviour. In contrast to the proposal of Antelman and Caggiula (1977) that central NA exerts an indirect modulation on DA systems, these data show that DA mechanisms within the nucleus accumbens, and the DNAB, may mediate qualitatively different behavioural processes. Whilst DA within the nucleus accumbens is probably involved in the activation of responses, leading to an enhanced probability of responding, the DNAB appears to be crucial for maintaining stimulus control over behaviour when DA within the nucleus accumbens is activated.

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