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CUEING EFFECTS OF AMPHETAMINE AND LSD: ELICITATION BY DIRECT MICROINJECTION OF THE DRUGS INTO THE NUCLEUS ACCUMBENS

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Two groups of rats were trained to discriminate either d-amphetamine sulphate (AMPH; 1 mg/kg) or d-lysergic acid diethylamide bitartrate (LSD; 0.16 mg/kg). Microinjection of AMPH into the nucleus accumbens elicited a cueing effect which was similar to that of systemically administered AMPH in AMPH-trained animals (ED_{50} was 0.24 μg). Co-injection of (−)-sulpiride (50 or 100 ng) into the accumbens antagonized the effect of a fixed dose of AMPH (1 μg) which, alone, produced 76% of the systemic AMPH cue effect. Microinjections of AMPH (1-5 μg) into either the anterior dorsomedial or the anterior ventrolateral striatum failed to elicit the cueing effect of AMPH. In LSD-trained animals a dose of 1 μg LSD injected into the accumbens produced 84% of the systemic cueing effect of LSD. These results suggest that dopamine (DA) receptors in the nucleus accumbens are involved in AMPH discrimination. Furthermore, since both classical and atypical antipsychotic drugs block the AMPH cue, the results provide indirect evidence for involvement of mesolimbic DA in antipsychotic drug action.

Drug discrimination Nucleus accumbens Corpus striatum Amphetamine Dopamine LSD

1. Introduction

Drug discrimination (DD) procedures have been used in recent years to analyze successfully in vivo the mechanism of action of psychoactive compounds (Colpaert and Slangen, 1982). The recognition of DD as an important technique in behavioral pharmacology is largely due to the fact that the procedure is robust, sensitive, and pharmacologically specific. Briefly, in a DD experiment the 'internally' experienced effect of a drug is established as a discriminable signal (cue) for the experimental subject. Typically, this is accomplished by reinforcing the differential responding on one or the other of two levers in the presence or absence, respectively, of the drug effect. A particularly important aspect of DD is the relative inability of drug-induced motor and response deficits to influence the detection by the animal of pharmacologically (and behaviorally) relevant drug stimuli. The applicability of the method is indicated, for example, by the demonstration of reliable data obtained from animals with implanted electrodes or neuronal lesions (D'Mello, 1982; White et al., 1980; Hirschhorn et al., 1975).

The present experiments were designed to investigate the neuroanatomical basis for the discriminative stimulus effect elicited by a relatively low dose (1 mg/kg) of d-amphetamine sulphate (AMPH). This was of interest since the effect of this dose of AMPH is blocked by both classical and so-called 'atypical' antipsychotic drugs (Nielsen and Jepsen, 1985). Since a common action of both of these classes of drugs is to affect mesolimbic (A10) DA neurons (White and Wang, 1983; Chiodo and Bunney, 1983), this action may indi-

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cate that the stimulus effect of AMPH similarly involves A10 DA neurons. A10 DA cells project to several limbic structures (e.g. amygdala, nucleus accumbens and frontal cortex) as well as to some parts of the striatum (dorsomedial and ventrolateral regions) (see Kelley et al., 1982). Previous research has indicated a role for the nucleus accumbens in drug effects related to psychosis and addiction (e.g. drug self-administration and reinforcement) (Carr and White, 1983; Demirière et al., 1984; Monaco et al., 1981; Neill and Justice, 1981; Phillips et al., 1983; Prado-Alcalá and Wise, 1984; Roberts and Cook, 1983; Spyraki et al., 1982; Taylor and Robbins, 1984) as well as in highly integrated forms of normal behavior (e.g. changes arising from reinforcement and learning, and from stress-induced displacement activity) (Robbins and Everett, 1982; Robbins and Koob, 1980; Solomon and Staton, 1982). Based on these findings, the accumbens was selected as a candidate for a structure possibly involved in AMPH discrimination. In addition, we included two other DA-rich areas, namely the anterior ventrolateral striatum and the anterior dorsomedial striatum. The anatomical proximities of the striatal areas to the accumbens were also used to provide an anatomical and drug specificity control for diffusion of the drugs injected.

Previous research has shown that the AMPH cue is mediated by DA (Nielsen and Jepsen, 1985). (−)-Sulpiride ((−)-SUL) was therefore chosen as a suitable AMPH cue antagonist for intracerebral injection because SUL is a highly specific DA antagonist (Zahniser and Dubocovich, 1983; Arnt, 1985) and because the potential problem of diffusion following an intracerebral injection is minimal after low doses of (−)-SUL (Scheel-Krüger and Arnt, 1985), probably due to its low lipid solubility (Norman et al., 1979).

In order to explore the generality of the possible role that the nucleus accumbens might play in DD, we included in the present study animals which had been trained to discriminate lysergic acid diethylamide (LSD) from saline. LSD was chosen because it is an extensively characterized drug in DD research and because this research has shown that in contrast to AMPH discrimination, LSD discrimination primarily involves brain serotonin (Kuhn et al., 1978; White and Appel, 1982).

2. Materials and methods

2.1. Drug discrimination training

A total of 83 male Wistar rats (Panum Institute, Copenhagen) were deprived to 80-85% of their free-feeding initial weights (150-200 g) by restricting water intake to that received in 25 min daily experimental sessions (below). These sessions were conducted in eight chambers (Skinner boxes), which were each equipped with two response levers and a dipper that provided 0.1 ml deionized water reinforcements. Following i.p. injections of 1 mg/kg of d-amphetamine sulphate (AMPH; the 'training drug', dissolved in saline and administered in a volume of 1 ml/kg), one group of animals (N = 71) was placed 15 min later in individual chambers in which responding (pressing a lever) was reinforced only on a designated ('drug') lever. Following i.p. saline (control) injections, responding was reinforced only on the lever opposite to the drug lever. In order to control for olfactory cues, the assignment of drug and saline levers relative to the position (e.g. left/right) of the levers was counterbalanced within and between 'running' groups of eight animals. Further, responding on the incorrect lever (relative to the injection of AMPH or saline) never had any programmed consequences. Responding on the correct lever was reinforced following the completion of every 32 responses (fixed ratio (FR) 32 schedule). AMPH and saline training sessions were conducted in an irregular order but there were never more than three consecutive saline or AMPH training sessions.

A second group of animals (N = 12) was trained similarly (above) using LSD (0.16 mg/kg as the tartrate salt dissolved in saline, 1 ml/kg injection volume, i.p., t −15 min) as the training drug (instead of AMPH).

Stable high (90-95%) discrimination performance was acquired rapidly with both AMPH and LSD within 10-15 training sessions, as evidenced by the distribution of responses by the animals on

the two levers prior to the delivery of the first reinforcement (i.e. in the absence of any other cue than that provided by the presence or absence of the internally discriminable effect of the respective training drugs). Accordingly, discrimination accuracy (%) was calculated as 100 × the number of correct responses divided by the number of correct + incorrect responses prior to delivery of the first reinforcer. Training was continued until the discrimination performance was > 90% (for the group; > 75% for individual animals) for 5 days. Four animals showing unstable responding during acquisition were excluded.

2.2. *Intracerebral drug testing*

Following at least 33 consecutive training sessions, the animals were stereotoxically implanted (using a David Kopf apparatus) under pentobarbital (Nembutal®) anesthesia with guide cannulas (o.d. 0.7-0.75 mm) for bilateral microinjections into either the nucleus accumbens (Ant. 10.0, Lat. 1.6), the anterior ventrolateral striatum (Ant. 9.5, Lat. 2.8) or the anterior dorsomedial striatum (Ant. 8.9, Lat. 2.2). The guide cannulas terminated 3.75, 3 or 2 mm, respectively, above the injection sites (see fig. 1 for localization). Following 3-8 days of recovery from the implantations, the animals were then exposed to at least eight further training sessions (ending with a drug and a saline session, in that order) before two intracerebral test sessions were conducted. The abilities of the intracerebrally injected drugs to mimic the training drug cue were determined in the test sessions. These sessions were individually terminated once an animal had completed 32 responses on either lever (no reinforcement was delivered) or when 20 min had elapsed. The time required to complete the first 32 responses (i.e. 1. FR) was designated 'reaction time' and was used as an index of non-specific behavioral disruption by the test drug. If an animal did not complete 32 responses, reaction time was assigned a value of 1 200 s, the maximum session time. On the two test days, each animal only received one intracerebral injection on each test day. Thus, no animal received more than a total of two intracerebral test injections. The two test days were separated by a regular saline and drug training session (using systemic injections) as previously described.

All intracerebrally injected drugs were dissolved in sterile vehicle and injected according to previously published methods (Scheel-Krüger and Arnt, 1985; Arnt, 1985). AMPH and LSD were dissolved in distilled water. (−)-SUL (Ravizza, Milan, Italy) was dissolved in 0.02 M acetic acid (5 mg in 5 ml) and diluted further with distilled water. Doses of 0.25-10 μg of AMPH, 1 μg of LSD and 50 and 100 ng of (−)-SUL were injected into each hemisphere. Sterile water was used as vehicle control; although (−)-SUL was dissolved in acetic acid (above), we did not attempt to determine the effect of acetic acid alone since (−)-SUL is a free base which neutralized the acid. The drugs were injected bilaterally over 30-40 s in a total volume of 1 μl (0.5 μl/hemisphere) via two Hamilton microsyringes (31 G needles, o.d. 0.25 mm) which were held in position for a further 30 s. The waking animals were hand-restrained during this procedure, following which saline (1 ml/kg) was given i.p. Test sessions began 5 min after intracerebral injections, except when noted otherwise (below). The intracerebral co-administration of (−)-SUL with AMPH (below) was achieved by mixing the drugs in the same injection bolus. The sequence of drug treatment was random, with the restriction that no animal received the same treatment twice.

The animals were killed upon completion of the experiments and the brains were fixed in formalin and cut in 80-100 μm sections for histological verification of the injection sites.

2.3. *Statistical analyses*

The data from the last saline and drug-training session prior to intracerebral drug testing were considered to provide a baseline for evaluating the effects of the test treatments.

The effects of the drugs upon discrimination accuracy and reaction time were analyzed by analysis of variance for a repeated measures design using the SAS general linear models programme (SAS Institute, Cary, NC, U.S.A.). Inasmuch as this procedure yielded significant overall F values, least significant difference intervals were then con-

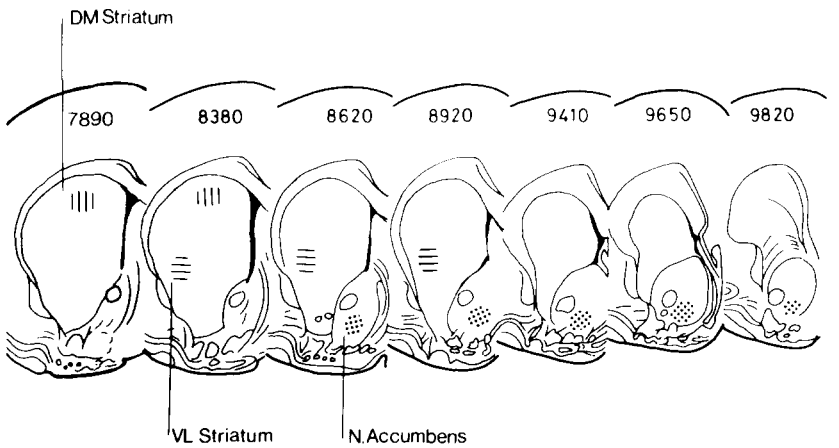

Fig. 1. Anatomical sections from the atlas of König and Klippel (1963) with locations for intracerebral test injections. Most of the accumbens injections were localized at the A-coordinate ~ 9.4-9.6. The numbers of animals tested in the subgroups were 46 (nucleus accumbens), 8 (anterior ventrolateral striatum) and 6 (anterior dorsomedial striatum). Each animal only received two intracerebral injections.

structed for post-hoc comparisons of treatment means. Dose-effect functions were analyzed by the SAS-PROBIT programme which generated ED_{50} values based upon log-probit relationships.

3. Results

Histological verification led to the exclusion of 13 animals because their injection sites were asymmetric or localized outside of the areas selected (fig. 1). Furthermore, six animals were excluded due to technical problems with the guide cannulas.

The test treatments induced significant overall changes in discrimination performance ($F(19,232) = 65.52$, $P < 0.001$) and in reaction time ($F(19,232) = 6.54$, $P < 0.001$). Specifically, it was found that, in the first series of test sessions, the restraining procedure necessary for performing the intracerebral injections itself produced a significant percentage of responding on the AMPH lever (table 1). However, the effect was short-lasting

TABLE 1

Effect of the restraining procedure used for injecting drugs intracerebrally (e.g. into the nucleus accumbens septi (NAS) upon discrimination accuracy and reaction time in animals trained to discriminate AMPH (1 mg/kg) from saline. Habituation to the restraint was accomplished by exposing the animals daily for three days to the injection procedure (although no injections were given). Discrimination accuracy is expressed as the percentage responses on the AMPH lever. Reaction time is the time to complete the first 32 responses (= 1st FR). Baseline data are from the last training sessions prior to intracerebral drug testing. Inj. int., injection interval. * $P < 0.05$ (ANOVA), ** $P < 0.01$ (indicated only when appropriate). [a] Compared to AMPH-baseline level; [b] compared to saline-baseline level.

Treatment	Inj. int. (min)	AMPH responses (%)	Reaction time (s)	N
AMPH 1 mg/kg i.p. (baseline)	15	91.0 ± 2.5	61 ± 11	65
Saline i.p. (baseline)	15	4.6 ± 1.5	30 ± 4	65
Restraint + NAS water − habituation	5	47.3 ± 18 **a,b	89 ± 15	6
Restraint + NAS water − habituation	23.5	1.0 ± 0.6	33 ± 5	6
Restraint − habituation	5	31.0 ± 13 **a,*b	86 ± 8	6
Restraint + NAS water + habituation	5	7.9 ± 3.5	72 ± 10	7
Restraint + habituation	5	5.3 ± 1.2	53 ± 8	9

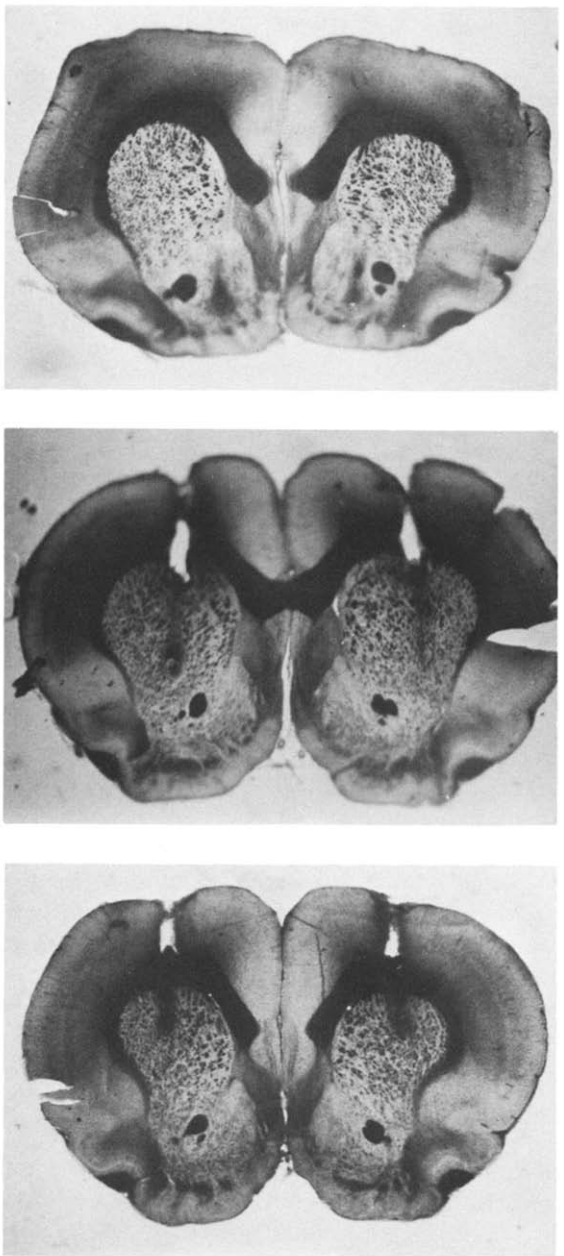

Fig. 2. Examples of injection sites from animals receiving AMPH into the nucleus accumbens (upper section), the anterior ventrolateral striatum (middle section), or the anterior dorsomedial striatum (lower section).

since it had disappeared when tested after 23.5 min. The animals in which the restraint effect was observed were not used in further pharmacological experiments (below). Three days of habituation training abolished the restraint effect observed in non-habituated animals. Following these initial findings, all subsequent testing was performed in habituated animals.

When 0.25, 1, 5 or 10 μg of AMPH was injected into the accumbens (see fig. 2 for a histological example), a clear dose-dependent elicitation of the systemically established AMPH cue was obtained (fig. 3). The ED_{50} of AMPH was 0.24 μg. In contrast, AMPH (1 or 5 μg) injected into the two striatal areas failed to elicit the cueing effect of AMPH (i.e. saline-lever responding occurred). In further experiments, a fixed dose of 1 μg of AMPH was co-injected with 50 or 100 ng of (−)-SUL into the accumbens. As can be seen (fig. 3), (−)-SUL dose dependently antagonized the effect of intracerebrally administered AMPH (1 μg).

Finally, a single dose of LSD (1 μg), when injected into the accumbens, substituted completely for the systemically estabished LSD cue; the intraaccumbens test dose produced 84 ± 8% LSD lever responses (N = 6). This level was not significantly different from that following the training dose of LSD (0.16 mg/kg i.p.: 98.6 ± 1% LSD level responses (last training session prior to testing)) although the reaction time (272 ± 116 s) was increased significantly ($P < 0.05$) when compared to the level following the injection of water into the accumbens (72 ± 10 s, N = 7).

4. Discussion

The fact that AMPH injected into the nucleus accumbens was found to produce a cueing effect which was similar to that of systemically administered AMPH suggests that the accumbens may be an important site for AMPH discrimination. The specificity of the involvement of the accumbens was indicated by the inability of AMPH injected into two sites of the anterior striatum to induce the systemically acquired AMPH cue. In addition, this lack of effect of intrastriatal AMPH also indicates that diffusion of AMPH from the accumbens into other brain areas was probably not the basis for the intraaccumbens AMPH cue generalization.

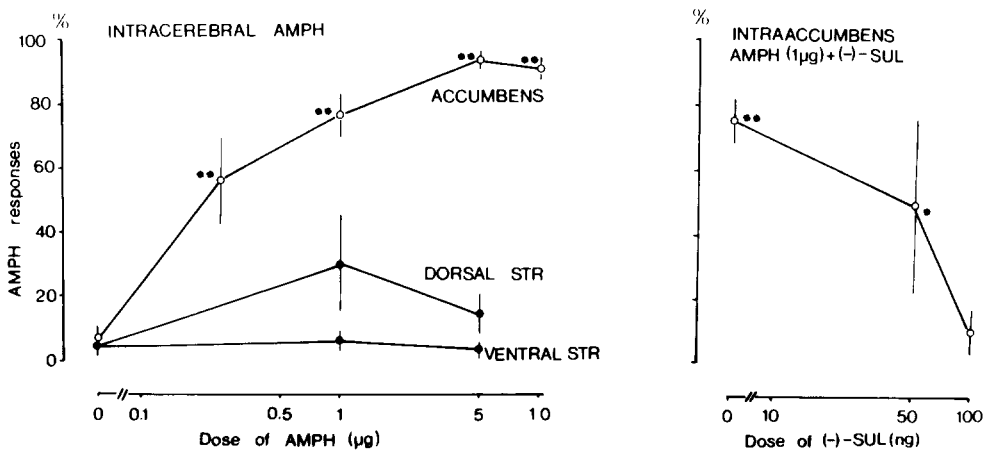

Fig. 3. Left section. Ability of AMPH injected into either the nucleus accumbens, the anterior dorsomedial striatum, or the anterior ventrolateral striatum, to mimic the stimulus effect of systemically administered AMPH (1 mg/kg i.p., t −15 min). Values denote means ± S.E.M. of data from 6-7 animals per dose. The effect of water (accumbens-injected animals) or the effect of no injection (striatal groups), i.e. handling and restraint alone is indicated at the dose = 0. Only the highest doses of AMPH (5 and 10 μg), when injected into the accumbens, increased reaction time significantly (to 493 ± 227 s, N = 6, $P < 0.01$, and 382 ± 173 s, $P < 0.01$, N = 7, respectively) when compared to the level following water injected into this area (72 ± 10 s, N = 7; ANOVA). When injected into the striatal areas, only the dose of 1 μg of AMPH in the dorsal striatum increased reaction time significantly (to 246 ± 113 s, N = 6, $P < 0.05$) when compared to baseline (53 ± 8 s, N = 9). Right section. Dose-dependent ability of intraaccumbens-injected (−)-sulpiride (−)-(SUL) to antagonize the discriminable similarity of intraaccumbens-injected AMPH (1 μg) to systemically administered AMPH (1 mg/kg i.p., t −15 min). (−)-SUL was mixed with the fixed dose of 1 μg of AMPH and the drugs were co-injected into the accumbens. None of the treatments altered reaction time significantly from that following the injection of water into the accumbens. * $P < 0.05$, ** $P < 0.01$ (% of responses on the AMPH lever compared to the level follwing water in the accumbens; ANOVA).

It is noteworthy that the cueing effect of systemic LSD could also be elicited by intraaccumbens injection of the training drug (i.e. LSD). This situation suggests that the accumbens may play a role not only in LSD and AMPH discrimination by in DD in general. In this respect, it has been observed previously that various rewarding effects could be achieved via distinct pharmacological mechanisms within the accumbens (e.g. opiate or DAergic; Phillips et al., 1983; Prado-Alcalá and Wise, 1984). However, it has been methodologically difficult in the past to separate the effects of reinforcing events, such as brain stimulation or drug self-administration, from effects occurring simultaneously on response or motor control. A promising procedure in this respect is the conditioned place-preference procedure which, similarly to DD, establishes a relationship between a spatial cue (i.e. placement of the animal in one or the other side of an experimental chamber) and the stimulus effect of a 'training' compound (e.g. Spyraki et al., 1982). This procedure has the important advantage of the relative independence of the spatial choice (e.g. lever) controlled by the absence or presence of the training drug effect, from response-rate effects occurring at the same time. Although the place-preference procedure yields a low drug/saline effect ratio, it has been possible to demonstrate that intraaccumbens AMPH produced place-preference whereas, in contrast, intracaudate AMPH failed to elicit such an effect (Carr and White, 1983; Spyraki et al., 1982). It is noteworthy that the present data not only confirm the place-preference data but demonstrate further that the discriminable effect following intraaccumbens AMPH was *similar* to that produced by systemic AMPH administration. The importance of this finding is obviously that the accumbens may mediate at least those aspects of the actions of AMPH that are related to the 'net' experienced effect of the drug (e.g. euphoria, psychomotor excitation, etc.).

The finding that the specific DA antagonist, (−)-SUL, antagonized the intraaccumbens-elicited

AMPH cue suggests that DA receptors in this area mediate the cueing effect of AMPH. The specificity of this antagonism was demonstrated by the lack of effect of (−)-SUL upon reaction time suggesting again that there was probably no diffusion of drug outside the accumbens. Taken together, these results provide evidence that the cueing effect of AMPH involves mesolimbic DA systems. The results further confirm previous suggestions of a role for mesolimbic DA in the discriminative and reinforcing effects of AMPH (see Introduction for references).

Previous research on the pharmacology of the LSD cue has shown that it may primarily involve 5-HT_2 receptor agonism (Nielsen et al., 1985). Therefore, it is possible that the present finding that intraaccumbens LSD generalized to the systemic LSD cue similarly may involve 5-HT_2 receptors, since high levels of these receptors are found in the accumbens (Nakada et al., 1984).

The present finding of a lack of cueing effect following intrastriatal AMPH is interesting because the A9 DA system (projecting to the caudate-putamen complex) and the A10 system have been differentially linked to various behavioral effects of AMPH. Thus, the A9 system may preferentially mediate the stereotyped motor behavior seen after higher doses of AMPH (> 3 mg/kg), while it is believed that A10 neurons are involved in low dose locomotor stimulation and in the reinforcing effects of AMPH and related drugs (e.g. cocaine) (see Introduction for references). Most recently, it was demonstrated that radiolabelled 2-deoxyglucose (2-DG) utilization, a marker of brain metabolic activity, showed parallel differentially activity patterns following different doses of AMPH: low doses of AMPH preferentially increased accumbens 2-DG utilization, while higher doses of AMPH predominantly increased 2-DG utilization in extrapyramidal areas (Porrino et al., 1984). Thus, the present findings with AMPH extend the differential behavioral roles of accumbens and striatal DA in the effects of AMPH to include the discriminative effects of the drug at a low dose. Further, it is of interest to note that apomorphine, which does not substitute for a low-dose AMPH cue (Nielsen and Jepsen, 1985), fails to activate accumbens 2-DG utilization (after 1 mg/kg; Grome and McCulloch, 1983), although extrapyramidal DA areas (e.g. globus pallidus) are activated.

The observation that restraint 'stress' produced a partial AMPH-like stimulus effect also implicates limbic DA tracts in AMPH discrimination since these pathways are particularly activated during periods of stress (Thierry et al., 1976). Alternatively, it is possible that the stress effect could be explained by non-specific disruption of the discrimination by the handling stress.

Finally, the present results are of relevance for the understanding of the actions of antipsychotic drugs. Antipsychotic drugs of the classical type (which induce extrapyramidal side-effects) act at least at both A9 and A10 DA neurons (Chiodo and Bunney, 1983; White and Wang, 1983), while atypical antipsychotic drugs (which have a reduced ability to induce extrapyramidal symptoms) may preferentially affect A10 DA neurons. Therefore, since both classical and atypical antipsychotic compounds block the AMPH cue (Nielsen and Jepsen, 1985), the present findings represent indirect evidence for the involvement of mesolimbic DA pathways (e.g. A10-accumbens) in the mechanism of action of antipsychotic compounds.

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