Pharmacology Biochemistry & Behavior, Vol. 5, pp. 477–482.

Role of Noradrenergic and Dopaminergic Processes in Amphetamine Self-Administration[1]

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(Received 15 April 1976)

RISNER, M. E. AND B. E. JONES. *Role of noradrenergic and dopaminergic processes in amphetamine self-administration.* PHARMAC. BIOCHEM. BEHAV. 5(4) 477–482, 1976. – Dogs were trained to intravenously self-administer d-amphetamine (0.05 mg/kg/infusion) until a stable intake per 4 hr daily session was achieved. When the dogs were given noncontingent infusions of d-amphetamine in varying amounts (0% to 100% of the baseline intake) immediately prior to the session, they decreased their self-administration response rate appropriately so that total drug intake remained constant. However, there were no changes in subsequent responding for d-amphetamine following pretreatment with either the noradrenergic agonist methoxamine (0.5–2.0 mg/kg) or the noradrenergic antagonist phenoxybenzamine (1–8 mg/kg). Additionally, responding was not maintained when methoxamine (0.05 mg/kg/infusion) was substituted for d-amphetamine. In contrast, pretreatment with either the dopaminergic antagonist pimozide (5–40 μg/kg) or chlorpromazine (0.25–2.0 mg/kg) produced dose-dependent increases in the number of self-administered d-amphetamine infustions. These data suggest that noradrenergic neurotransmission is not responsible for d-amphetamine self-administration, but an intact dopaminergic system does appear to be important.

Self-administration Dog d-Amphetamine Methoxamine Phenoxybenzamine Pimozide Chlorpromazine

INTRAVENOUS infusions of d-amphetamine are self-administered when presented on a response-contingent basis. Monkey [5], rat [17], and dog [10,21] have all been used to demonstrate this phenomenon in the laboratory. Although the neurochemical substrates which mediate this and other central stimulatory actions of d-amphetamine are not known, there is much evidence that catecholamines are particularly involved [3]. Since d-amphetamine influences both the release and uptake of norepinephrine (NE), the role of this amine has been examined in several physiologic systems [11,27].

The experiments described below were designed to assess the role of NE neurotransmission in d-amphetamine self-administration. To a limited extent we also examined the role of dopaminergic (DA) systems in this behavior since recent evidence [4, 24, 32] suggests that many of the central actions of d-amphetamine are related to interactions with DA neurons. However, the relative importance of NE and DA in d-amphetamine's actions is a controversial issue [3].

It is known that laboratory animals exhibit stable self-administration behavior when given limited daily access to psychomotor stimulants [19, 20, 21]. Total drug intake per session remains relatively constant as the unit dose, i.e. mg/kg/infusion, is varied. For example, when the magnitude of the reinforcing unit dose is decreased, there is a compensatory increase in the number of self-administered infusions.

Changes in the response rate can also be produced by administering various drugs to animals which have a stable self-administration baseline. Generally, pretreatment with catecholamine synthesis inhibitors or receptor antagonists causes an increase in the frequency of self-administration. The increase is presumably an attempt to overcome the pharmacological attentuation of the neurochemical substrates responsible for self-administration behavior. For example, by reducing concentrations of NE and DA in tissue (including brain) with alpha-methyl-para-tyrosine, responding for methamphetamine [18] and cocaine [25] is increased. Chlorpromazine significantly increased the self-administration of several psychomotor stimulants by monkeys [29]. Although pretreatment with specific noradrenergic antagonists has not been shown to appreciably affect the frequency of stimulant self-administration [30,32], there is some evidence that d-amphetamine self-administration is altered following pretreatment with the DA antagonists haloperidol [4] and pimozide [32].

In the experiments described below, dogs were trained to respond for intravenous infusions of d-amphetamine until a stable drug intake per daily session was achieved. Several studies have shown that methoxamine acts as a direct alpha noradrenergic agonist in the spinal cord [11,27] and on the neurohumoral substrates responsible for EEG activation [7]. If d-amphetamine's primary mode of action in causing its self-administration involves activa-

[1] Portions of this paper were presented at the 59th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April 13–18, 1975.

tion of NE receptors then methoxamine should be self-administered. To further study the role of noradrenergic processes in d-amphetamine responding, dogs were pretreated with phenoxybenzamine, an effective and selective alpha noradrenergic antagonist in the CNS [11,27], then the rate of responding for d-amphetamine was measured. If NE neurotransmission is necessary for d-amphetamine self-administration then blockade of NE receptors should cause an increase in the frequency of self-administration. Similarly, dogs were pretreated with pimozide, a relatively selective blocker of dopaminergic systems, particularly at low doses [9]. Any increase in the number of self-administered d-amphetamine infusions would provide evidence that DA neurotransmission is important for d-amphetamine self-administration.

METHOD

The animals were 6 male and 6 female mongrel beagle dogs weighing between 7.7 and 13.8 kg. The surgical procedures and mechanical equipment have been previously described [21] and represent adaptations of those developed by Weeks [28], Yanagita *et al.* [31], and others.

Briefly, the dog test procedure included the following phases: (1) presurgery acclimation to the cage, harness, and spring-swivel attachment; (2) surgery, under sodium pentobarbital-induced anesthesia (30 mg/kg, IV), to fit the dog with an indwelling jugular catheter; (3) response-contingent saline infusions which served as a predrug control; and, (4) drug self-administration including an initial ad lib acquisition and training phase followed by limited access conditions. During the acquisition and training phase, response-contingent infusions of either cocaine HCl (0.15 mg/kg/infusion, 4 dogs; 0.20 mg/kg/infusion, 2 dogs), d-amphetamine H_2SO_4 (0.05 mg/kg/infusion, 5 dogs), or phenmetrazine HCl (0.20 mg/kg/infusion, 1 dog) were available 24 hr/day, 7 days/week. The drugs were dissolved in normal saline and given in a volume of 0.1 ml/kg at a rate of 1 ml/min. All unit doses were calculated on the basis of the salts.

Drug-seeking behavior was observed within 1–6 days after the drug solution became available [22]. After 1–6 weeks under the ad lib contingencies, access to drug infusions was reduced to a limited availability of four hours (1000–1400 daily). The 7 dogs previously taking cocaine or phenmetrazine were switched to d-amphetamine (0.05 mg/kg/infusion); the drug and unit dose were not changed for the 5 dogs previously trained with d-amphetamine. Under these conditions, drug intake (mg/kg/4 hr session) stabilized; variation in the number of infusions/4 hr session was generally 15% or less. The following series of experimental manipulations were performed.

Pretreatment with d-Amphetamine

Following acquisition of stable baseline responding, 7 dogs were selected for observation. The mean amount (mg/kg) of d-amphetamine self-administered during three consecutive sessions was determined. Immediately prior to the next daily session the dogs were intravenously administered 0, 33.3, 66.6, or 100.0% of the mean amount. At least one week elapsed before another treatment was administered. This mean baseline drug intake was recalculated weekly. Order of treatment presentation was random, and each treatment was tested once in each animal.

Pretreatment with Methoxamine

Two dogs, with stable d-amphetamine baseline response patterns, were pretreated with methoxamine in doses of 0.5, 1.0, or 2.0 mg/kg, IV, 30 min prior to the drug session. Each dose was given once to each dog; order of presentation was random. At least 3 days elapsed between successive methoxamine treatments.

Substitution of Methoxamine or Saline for d-Amphetamine

Five dogs, with stable rates of responding for d-amphetamine, were used to evaluate the reinforcing properties of methoxamine and saline. Either saline (0.1 ml/kg/infusion) or methoxamine (0.05 or 0.2 mg/kg/infusion) was substituted for d-amphetamine. At the end of the first substitution test the dogs were allowed to self-administer d-amphetamine again until presubstitution response rates were recovered, then a second substitution test was conducted. After five sessions the dogs were returned to d-amphetamine self-administration for baseline recovery, then a third substitution test was initiated. In this way all 5 dogs were given an opportunity to self-administer saline and both doses of methoxamine.

Pretreatment with Phenoxybenzamine

At weekly intervals 5 dogs were pretreated with either saline or phenoxybenzamine in doses of 1.0, 2.0, 4.0, or 8.0 mg/kg, IV, 30 min prior to the d-amphetamine session. Heat and agitation were required to dissolve the phenoxybenzamine in normal saline. The solution concentration was varied so that the pretreatment volume was always 1.0 ml/kg. Order of phenoxybenzamine dose was according to a Latin square sequence. Three or more consecutive d-amphetamine self-administration sessions served as the baseline period.

Pretreatment with Pimozide

A total of 5 animals were chosen for this experiment. When d-amphetamine self-administration was stable, the animals were intravenously given either the vehicle or pimozide, 30 min before the drug access session, in doses of 5, 10, 20 or 40 μg/kg. The pimozide was dissolved in 0.5% tartaric acid solution; heat and agitation were required. The solution concentration was held constant at 0.1 mg/ml. As in the preceding experiments, three or more d-amphetamine sessions served as the baseline control and at least 1 week separated successive administrations of pimozide. The pimozide doses were given on a random basis with the restriction that each animal be given each dose once.

Pretreatment with Chlorpromazine

Five dogs, with stable baseline response rates, were selected for observation. The dogs were pretreated with either saline or chlorpromazine in doses of 0.25, 0.50, 1.00 or 2.00 mg/kg, IV, 30 min before the d-amphetamine self-administration period. Each dose of chlorpromazine was given once to each dog; order of treatment presentation was determined by a Latin square design. Generally 1 week separated pretreatment sessions; d-amphetamine was available for at least 3 consecutive days before pretreatment. The chlorpromazine was dissolved in normal saline and given in a volume of 0.1 ml/kg.

RESULTS

The results of pretreating dogs with 0, 33.3, 66.7, or 100% of the amount of self-administered d-amphetamine are shown in Fig. 1. When the dogs were given 0% of their baseline intake there was no significant change ($p>0.05$) in the number of self-administered infusions on the test day. However, at pretreatment doses of 33.3, 66.7, and 100% there was a systematic, significant ($p<0.01$) decrease in the number of infusions per session. Total drug intake, calculated by summing the amount of drug given as a pretreatment plus the amount of drug self-administered during the 4 hr session, was significantly different from baseline intake ($p<0.05$) only when the pretreatment amount was 100%.

In contrast, dogs pretreated with methoxamine showed no significant changes in d-amphetamine intake. The response rate, response pattern, and locomotor activity were not appreciably altered following methoxamine pretreatment.

When saline was substituted for d-amphetamine there was a small nonsignificant increase in the self-administration rate, followed by a decrease (Fig. 2, upper panel). On Days 2 through 5 of the saline substitution test the dogs responded for an average of 9.4 saline infusions. Almost all of these infusions were taken during the first 15 min of the session. During the remainder of the 4 hr session the dogs generally sat quietly at the rear of the cage.

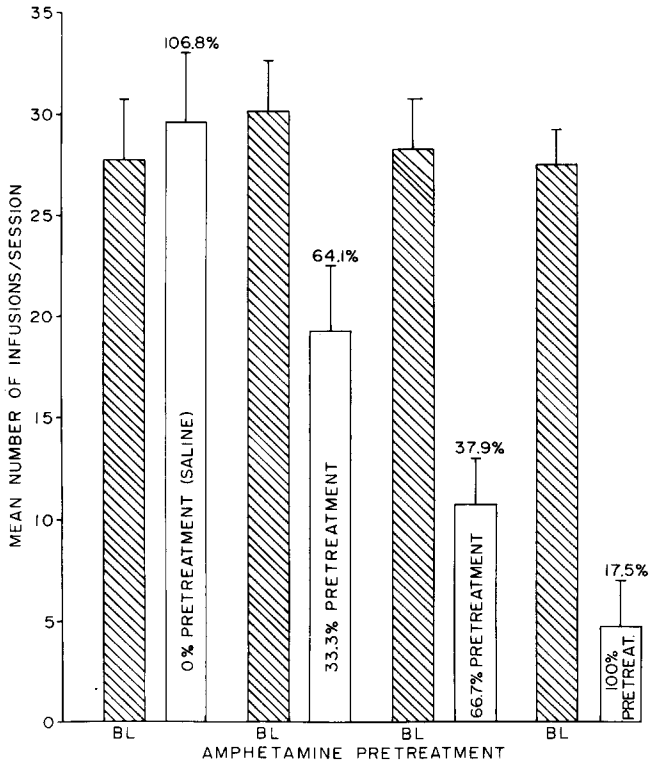

FIG. 1. The mean number of self-administered d-amphetamine infusions (0.05 mg/kg/infusion) as a function of d-amphetamine pretreatment (either 0%, 33.3%, 66.7%, or 100% of the baseline drug intake, IV, immediately prior to the session). Baseline (BL) values are based on the mean number of d-amphetamine infusions self-administered during the 3 sessions immediately prior to the test days. The same 7 dogs were examined under all of the pretreatment conditions. Vertical lines at the top of each bar represent standard errors of the means.

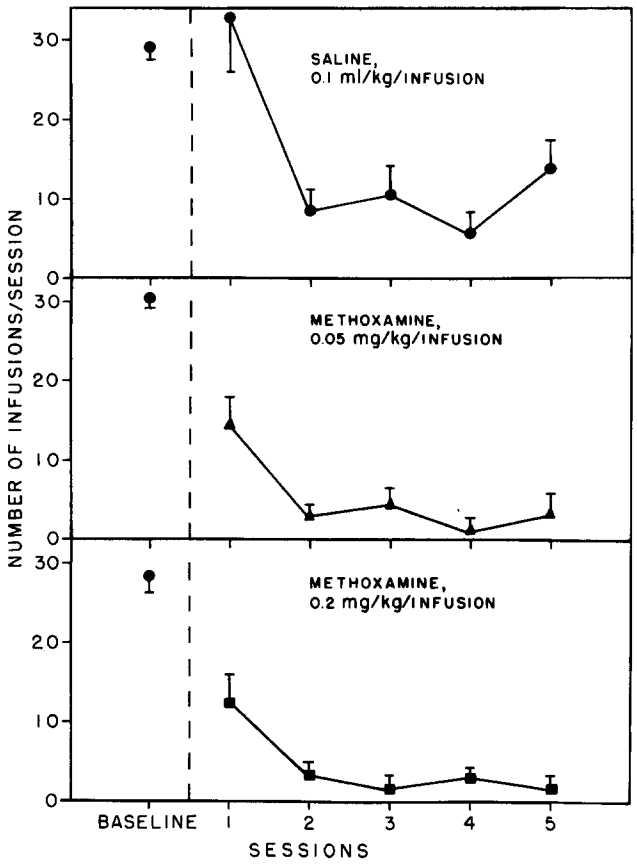

FIG. 2. The results of substituting either saline (0.1 ml/kg/infusions) or methoxamine (either 0.05 or 0.20 mg/kg/infusions) for d-amphetamine are shown. Neither saline nor methoxamine maintained responding. Baseline (BL) values represent the mean number of self-administered d-amphetamine infusions (0.05 mg/kg/infusion) for the 5 consecutive sessions immediately prior to the substitution tests. Each point depicts the mean of data from 5 dogs. Vertical lines represent standard errors of the means.

Extinction of responding also occurred when methoxamine was substituted for d-amphetamine (Fig. 2, middle and lower panels). The mean number of self-administered infusions, at both unit doses, was significantly less than the number of saline infusions on Day 1 ($p<0.01$) and during the entire 5 day substitution test ($p<0.01$).

Pretreatment with phenoxybenzamine in doses of 1, 2, 4, and 8 mg/kg had no effect on d-amphetamine-reinforced responding. As shown in Fig. 3, the change in the number of self-administered infusions per session was 4% or less; a value comparable to the variation between successive baseline sessions.

In Fig. 4 the effects of pimozide pretreatment on d-amphetamine self-administration are depicted. At doses of 5, 10, 20, and 40 μg/kg there were significant ($p<0.01$) dose dependent increases in the number of infusions per session. Doses higher than 40 μg/kg produced excessive gnawing behavior [23] and reduced the number of pedal-press responses. However, there were no observable effects of pimozide alone, at lower doses.

Figure 5 depicts the effects of chlorpromazine on subsequent self-administration of d-amphetamine. There was a significant ($p<0.01$) dose-dependent increase in the

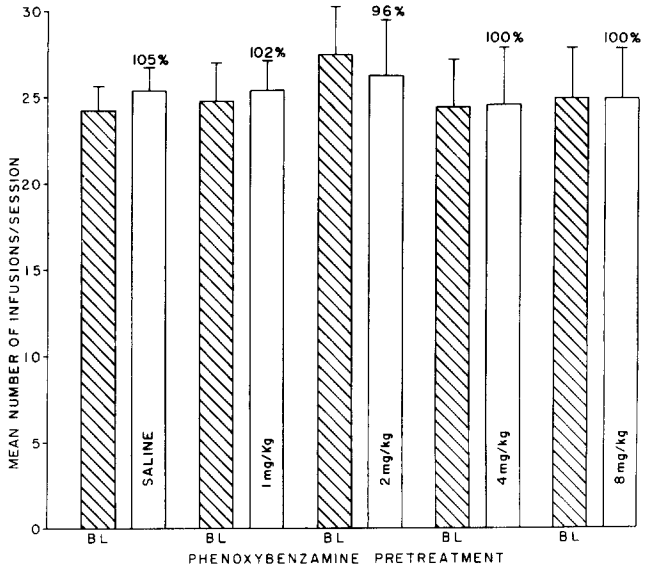

FIG. 3. The mean number of self-administered d-amphetamine infusions (0.05 mg/kg/infusion) as a function of either saline or phenoxybenzamine pretreatment (1.0, 2.0, 4.0, or 8.0 mg/kg, IV, 30 min prior to the session). Baseline (BL) values are based on the mean number of d-amphetamine infusions self-administered during the 3 sessions immediately prior to the test days. The same 5 dogs were examined under all of the pretreatment conditions. Vertical lines at the top of each bar represent standard errors of the means.

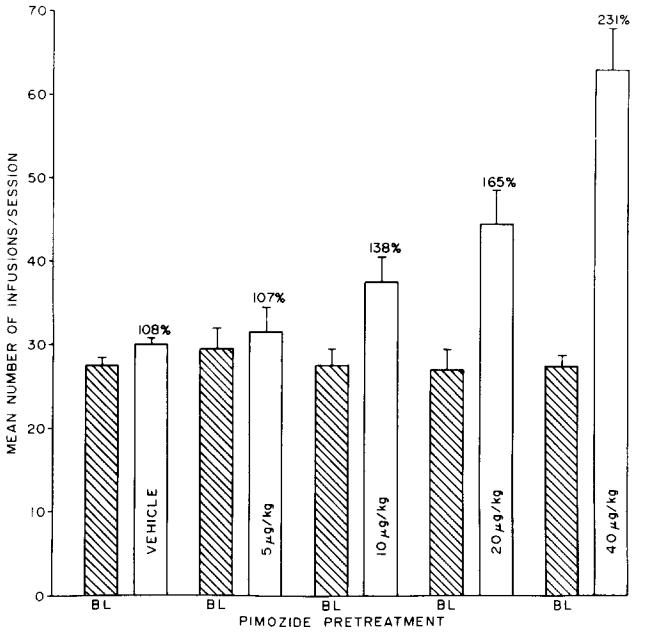

FIG. 4. The mean number of self-administered d-amphetamine infusions (0.05 mg/kg/infusion) as a function of either vehicle or pimozide pretreatment (5, 10, 20, or 40 µg/kg, IV, 30 min prior to the session. Baseline (BL) values are based on the mean number of d-amphetamine infusions self-administered during the 3 sessions immediately prior to the test days. The same 5 dogs were examined under all of the pretreatment conditions. Vertical lines at the top of each bar represent standard errors of the means.

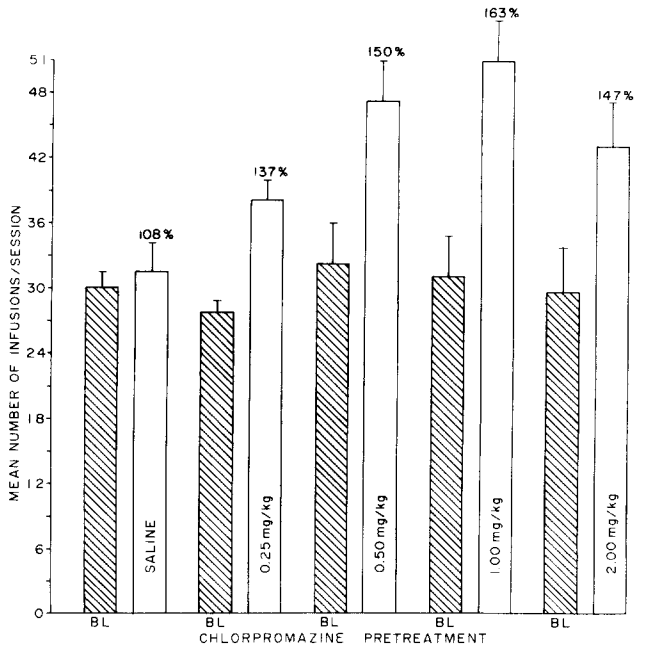

FIG. 5. The mean number of self-administered d-amphetamine infusions (0.05 mg/kg/infusion) as a function of either saline or chlorpromazine pretreatment (0.25, 0.50, 1.0, or 2.0 mg/kg, IV, 30 min prior to the session). Basline (BL) values are based on the mean number of d-amphetamine infusions self-administered during the 3 sessions immediately prior to the test days. The same 5 dogs were examined under all of the pretreatment conditions. Vertical lines at the top of each bar represent standard errors of the means.

number of self-administered infusions. Responding for d-amphetamine increased 37, 50, and 63% when the dogs were given 0.25, 0.50, and 1.0 mg/kg, chlorpromazine, respectively. There was also a significant increase (47%, $p<0.01$) in responding for d-amphetamine infusions when the chlorpromazine dose was 2.0 mg/kg. Although the increase was lower than that seen with the preceding doses, it did not significantly deviate from the linear regression line.

DISCUSSION

It has been previously demonstrated that dogs maintain a relatively constant d-amphetamine intake when access to intravenous infusions of the d-amphetamine solution is limited to one 4 hr session per day [21]. Additionally, there is a systematic, inverse relationship between unit dose (i.e., mg/kg/infusion) and number of self-administered infusions. When the unit dose is increased there is a concomitant reduction in response rate; likewise, when the unit dose is lowered there is a predictable increase in the rate of responding. Consequently, total drug intake exhibits only minor variation. In the present study, dogs were given noncontingent infusions of d-amphetamine in different amounts (0% to 100% of the baseline intake) immediately prior to their regular self-administration session. All of the animals decreased their self-administration response rate appropriately so that total drug intake did not increase appreciably. The stable regulation of drug intake seen when either the unit dose is varied or noncontingent infusions are given provides evidence of the dog's ability to measure drug effect and respond accordingly.

The results of three experiments described in the present paper question the hypothesis that noradrenergic processes alone are responsible for d-amphetamine self-administration. (1) Intake of d-amphetamine was not altered in dogs pretreated with the α-noradrenergic agonist methoxamine; however, d-amphetamine intake was significantly decreased following pretreatment with d-amphetamine. (2) Additionally, methoxamine would not maintain responding when it was substituted for d-amphetamine. Instead, all of the dogs ceased responding during the methoxamine substitution test. The inability of methoxamine to serve as a reinforcer may be partially due to an aversive property which hastened the extinction process as compared to saline. In this regard, emesis was observed when some of the dogs received methoxamine infusions. (3) When the dogs were pretreated with the noradrenergic antagonist phenoxybenzamine, in doses ranging from 1.0–8.0 mg/kg, there were no significant changes in subsequent responding for d-amphetamine. This result implies that noradrenergic activation is not necessary for d-amphetamine to serve as a reinforcer. Similar findings were reported by Yokel and Wise [32] who observed that d-amphetamine self-administration by rat did not increase following pretreatment with phentolamine. Additionally, d-amphetamine's ability to produce state-dependent control of discriminative behavior in the rat was unaffected by noradrenergic receptor blockade [24].

One can raise the question whether methoxamine is a centrally active α-noradrenergic agonist and whether phenoxybenzamine has central α-noradrenergic antagonist properties. That methoxamine crosses the bloodbrain barrier and produces CNS effects is demonstrated by several observations. The electroencephalogram of chicks [6], rabbits, cats, and dogs [7] is activated by methoxamine. Flexor reflex activity in the chronic spinal dog is facilitated by methoxamine at doses as low as 0.1 mg/kg [12]. Furthermore, Vaupel and Martin [27] found that methoxamine facilitated both the monosynaptic and polysynaptic reflex potentials of the acute spinal cat, thereby providing evidence that methoxamine can stimulate central noradrenergic systems.

Phenoxybenzamine's ability to gain access into the CNS was demonstrated by Masuoko *et al.* [14] using whole-body autoradiography, and Cicero *et al.* [2] using radioactively labelled compounds. Evidence that phenoxybenzamine blocks central noradrenergic processes is provided by the observation that it antagonized methoxamine's enhancement of the monosynaptic reflex potentials of the acute spinal cat [27] and reduced the clonidine-induced increase in the flexor reflex activity of the acute spinal rat [1].

Based on the studies described above, it appears that d-amphetamine self-administration is not based on NE neurotransmission. There are, however, several other central actions of d-amphetamine which are affected by phenoxybenzamine-induced NE antagonism. Phenoxybenzamine inhibits the analeptic effects of d-amphetamine on the rabbit electroencephalogram [16]; reduces the facilitatory effects of d-amphetamine on the flexor reflex in the chronic spinal dog [11]; and reduces the lethal effects of d-amphetamine [15] which are presumably mediated centrally [33].

The increased responding for d-amphetamine following pretreatment with pimozide (in doses ranging from 5–40 μg/kg) provides evidence that dopaminergic systems play an important role in mediating d-amphetamine self-administration. Yokel and Wise [32] have also found that pimozide treatment produced a dose-dependent increase in d-amphetamine self-administration by rat. Since pimozide typically produces behavioral depression [9], the increased responding for d-amphetamine following pimozide pretreatment may indicate that the reinforcing aspects of d-amphetamine were being attenuated, thus higher intake of d-amphetamine was required to maintain the desired drug effect. Pimozide appears to be a relatively selective DA blocker, particularly at low doses [9]; however, its selectivity has not been definitively examined. It antagonizes apomorphine-induced stereotypy and emesis in dogs [23], and blocks other dopaminergically based actions of d-amphetamine [9]. Attenuation of d-amphetamine effects by pimozide cannot be attributed to an increase in d-amphetamine metabolism or decreased penetration into the brain [26]. Clinically, d-amphetamine euphoria is decreased following pretreatment with pimozide, thus implicating dopaminergic processes in this subjective response [8].

When the dogs were pretreated with chlorpromazine in doses ranging from 0.25–2.0 mg/kg there was an increase in the number of d-amphetamine infusions administered during the session. Since chlorpromazine has diverse actions, including blockade of DA receptors, the increased self-administration of d-amphetamine consistent with the hypothesis that DA neurotransmission is important for d-amphetamine reinforcement. Wilson and Schuster [29] reported that chlorpromazine pretreatment produced increased responding for intravenous infusions of several psychomotor stimulants including cocaine, methylphenidate, and phenmetrazine.

Chlorpromazine generally produces a decrease in the response rate if other reinforcers are used, probably as a result of behavioral depression. To substantiate this point we trained dogs to pedal-press for drinking water during a daily 4 hr session. At an amount of 5 ml per response the dogs responded approximately 30 times per session. Following acquisition of stable baseline responding the dogs were given chlorpromazine in doses comparable to those which produced an increase in drug self-administration. There was a dose-dependent decrease in responding for water.

Martin *et al.* [13] compared the effects of several psychomotor stimulants, including d-amphetamine on 11 different physiologic, subjective and behavioral indices in man. They concluded that the euphorigenic effects of the drugs they studied were not due to activation of NE receptors. Based on the results of the experiments described above, we likewise conclude that intravenous self-administration of d-amphetamine is not based on activation of NE receptors; however, there appears to be an important role for DA systems in this behavior.

ACKNOWLEDGEMENTS

Pimozide was obtained from McNeil Laboratories through Mrs. M. L. Ralston. Chlorpromazine and phenoxybenzamine were supplied from Smith, Kline, and French Laboratories with the aid of Dr. Henry Anlage.

The authors would like to thank Dr. W. R. Martin for reviewing earlier versions of the manuscript.

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