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Involvement of Norepinephrine in Startle Arousal After Acute and Chronic *d*-Amphetamine Administration

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Abstract. Treatment with *d*-amphetamine produced a dose-dependent increase in startle amplitude in response to a buzzer. This increase appeared to be a reflection of a sensitization effect, i.e., enhanced responsivity as a function of repeated stimulus presentations. Treatment with α-methyl-p-tyrosine, which reduced whole brain concentrations of dopamine (DA) and norepinephrine (NE), or treatment with FLA-63, which reduced only NE, antagonized the effects of *d*-amphetamine on the startle reflex, suggesting a role of NE in this behavior. Startle amplitude was also reduced following chronic *d*-amphetamine treatment. The effect of *d*-amphetamine on startle was found to be independent of changes in drug-induced locomotor excitation. The data of the present investigation, together with earlier reports, suggests that tolerance occurs to those behaviors that involve a noradrenergic component.

Key words: *d*-Amphetamine – α-Methyl-p-tyrosine – FLA-63 – Norepinephrine – Startle reaction – Locomotor activity – Sensitization – Tolerance

Although several behavioral changes elicited by *d*-amphetamine are diminished following repeated drug administration (Brodie et al., 1970; Kokkinidis et al., 1976), other behavioral effects of *d*-amphetamine are either unaffected or enhanced with such treatment (Kokkinidis et al., 1976; Rech et al., 1975, Segal, 1975). On the basis of concurrent evaluation of several behaviors, it was recently suggested that tolerance may occur exclusively to those behaviors that are mediated by noradrenergic activity (Kokkinidis and Anisman, 1977; Kokkinidis et al., 1976). For example, amphetamine-induced stimulus perseveration, which has been shown to involve a noradrenergic component (Anisman and Kokkinidis, 1975), is attenuated by chronic drug treatment (Kokkinidis et al., 1976). On the other hand, behaviors that are mediated primarily by dopamine (e.g., locomotor activity and stereotypy [Carlsson, 1970; Creese and Iversen, 1975]), do not show tolerance (Kokkinidis and Anisman, 1977) and are in fact enhanced by protracted drug treatment (Segal, 1975). The fact that tolerance is observed to develop to the facilitative effects of amphetamine on self-stimulation of the medial forebrain bundle (Leith and Barrett, 1976), but not of the substantia nigra (Liebman and Segal, 1975), agrees with the notion that NE-mediated behaviors show tolerance, whereas behaviors subserved by DA do not.

Acute amphetamine administration has recently been reported to produce an enhanced startle reaction to auditory stimuli (Davis et al., 1975). On the basis of two sources of evidence it was suggested that this effect is mediated by dopamine activity. The first deals with the relative potency of the amphetamine isomers. Specifically, it is was suggested that since the *d*-isomer was four to five times more potent than the *l*-isomer in augmenting startle, dopaminergic mechanisms were involved in subserving the effects of the drug (Davis et al., 1975). However, in view of the contradictory biochemical findings concerning the effects of the isomers on reuptake of norepinephrine and dopamine (Coyle and Snyder, 1969; Thornburg and Moore, 1973a), it is premature to evaluate any behavioral or neurochemical relations on the basis of the potencies of *d*- and *l*-amphetamine (cf. Bunney et al., 1975; Kokkinidis and Anisman, 1978a). The second source of evidence implicating dopaminergic activity in subserving the acoustic startle response was based on the finding that the DA-receptor stimulant apomorphine

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enhanced startle amplitude, while the DA-receptor blocker haloperidol antagonized this effect (Davis and Aghajanian, 1976).

The role of norepinephrine in mediating the startle reaction is not entirely clear. For example, there is some evidence that norepinephrine may exert an inhibitory influence on the startle reflex. Specifically, it was found that the noradrenergic receptor stimulant clonidine attenuated the startle amplitude of reserpinized animals (Fechter, 1974a). It is not entirely certain, however, whether the effects of clonidine on the startle response are the result of stimulation of central epinephrine or norepinephrine receptors (cf. Davis et al., 1977). In contradistinction to the data derived from the clonidine experiment, inhibition of noradrenergic reuptake produces an increase in startle amplitude (Davis et al., 1977), whereas lesions of the locus coeruleus depress the startle reaction (Geyer et al., 1976), suggesting that NE exerts an excitatory influence on the startle reaction. If, in fact, norepinephrine plays a role in the amphetamine-induced potentiation of startle amplitude, then dopamine-β-hydroxylase inhibition should successfully antagonize this behavioral effect. Moreover, it might be expected that tolerance would develop with protracted drug treatment, as is the case in other NE-mediated behaviors. But if the effect of amphetamine on the startle reaction is subserved primarily by dopaminergic activity, then tyrosine-hydroxylase inhibition should antagonize this effect, whereas dopamine-β-hydroxylase inhibition should be ineffective in this respect. Furthermore, the magnitude of the startle response should not diminish with repeated amphetamine treatment.

Experiment I

At the behavioral level, several possibilities may account for the facilitation of startle amplitude following amphetamine treatment (e.g., the drug influences startle threshold or alternatively interferes with habituation). Davis et al. (1975) have suggested that the observed augmentation of startle amplitude in the rat is the result of enhanced sensitization produced by drug treatment. Experiment I was carried out to determine whether *d*-amphetamine would augment startle amplitude and, further, to assess whether the extent of the increase would become progressively greater with successive stimulus presentations, as reported by Davis et al. (1975).

Materials and Methods

Subjects. A total of 50 male Swiss-Webster mice procured from the Bio-Breeding Laboratories, Ottawa, Ontario, served as subjects. They were housed in groups of three to five in polypropylene cages and were permitted free access to food and water. Mice were approximately 60 days of age and weighed 32–36 g at the time of testing.

Apparatus. The apparatus, modified from that described by Remington and Anisman (1976), consisted of a clear Plexiglas cylinder 0.60 cm thick, 20.0 cm in diameter, and 11.50 cm high. The cylinder was situated on an 8-W speaker measuring 20 cm in diameter, which in turn was covered by a 0.012-cm mylar sheath. The mylar was sealed between two O-rings attached to the metal frame of the speaker. Movement on the mylar sheath and the resulting fluctuation in air pressure between the taut sheath and speaker produced deflections in the speaker cone, which in turn varied the electromagnetic flux. The speaker was connected to a Beckman type RM dynograph (A-C coupler, type 9806A; Amplifier, type 482; Rectifier, type 9852A), which was calibrated so that a 30–40 g mouse walking on the mylar did not produce a deflection of the rectifier pen, but was sensitive to a startle reaction. Consequently, levels of locomotor activity did not influence the recording of the startle response. The startle stimulus was a 2-s, 105 dB noise produced from a buzzer (BU 24; 50–60 Hz; 4.6 A) situated in the centre of the clear Plexiglas roof. The apparatus was housed in an illuminated room with a background noise of 75 dB.

Procedure. Independent groups of mice ($N = 10$/cell) received an i.p. injection of either saline or *d*-amphetamine sulfate (1.0, 3.0, 5.0, 10.0 mg/kg salt weight). All drugs were injected in a volume of 10 ml/kg. Ten minutes following injection mice were placed in the apparatus and were allowed to explore freely for a 5-min period. Following the adaptation period mice were exposed to 10 buzzer presentations with an intertrial interval of 1 min. The amplitude of the startle response was recorded in mm on standard Beckman chart paper.

Results and Discussion

The mean startle amplitude over 10 buzzer presentations for each drug dosage is depicted in Fig. 1. Analysis of variance of the startle scores yielded significant main effects for Drug Dosage, $F(4,45) = 8.81$, $P < 0.001$, and for Buzzer Presentation, $F(9,405) = 2.72$, $P < 0.005$. Consistent with previous findings (Davis et al., 1975), Newman-Keuls multiple comparisons ($\alpha = 0.05$) revealed that the three higher dosages of *d*-amphetamine (3.0, 5.0, and 10.0 mg/kg) enhanced startle amplitude relative to saline-treated mice. However, startle augmentation with repeated stimulus presentations (i.e., sensitization) was not observed. Davis et al. (1975) have shown that the magnitude of the startle reflex, as well as the sensitization effect following amphetamine treatment may depend on the drug-test interval and the number of stimulus presentations. Accordingly, in Experiment II, testing commenced immediately after amphetamine administration in order to determine whether the magnitude of the startle reaction in amphetamine-treated mice would be altered relative to that seen in Experiment I. Moreover, the course of the amphetamine excitation was evaluated to determine whether startle amplitude would increase with successive stimulus presentations as observed by Davis et al. (1975).

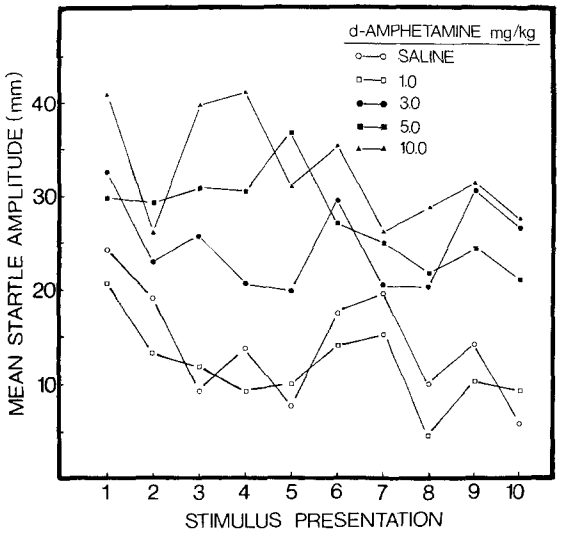

Fig. 1. Mean startle amplitude (± SEM) as a function of drug treatment (saline or 1.0, 3.0, 5.0, and 10.0 mg/kg of *d*-amphetamine)

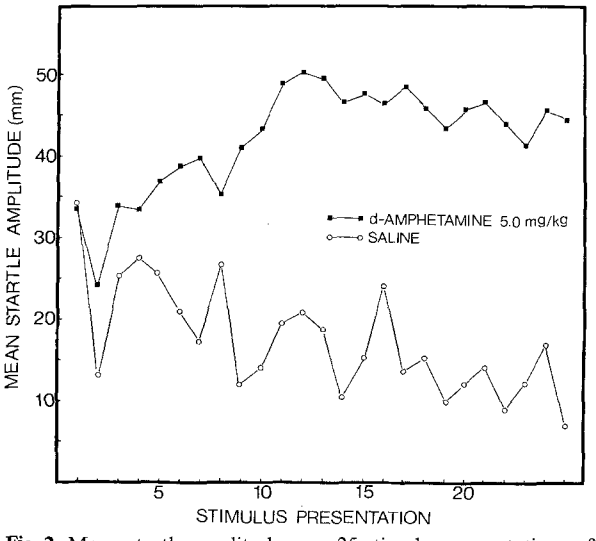

Fig. 2. Mean startle amplitude over 25 stimulus presentations after injection of either saline or 5.0 mg/kg of *d*-amphetamine. Mice tested immediately after injection

Experiment II

Materials and Methods

Sixteen naive male Swiss Webster mice served as subjects. The apparatus and procedural specifications were identical to those described in Experiment I, with the exception that testing was initiated immediately after injection of either saline or *d*-amphetamine sulfate (5.0 mg/kg) ($N = 8$/cell), and the number of buzzer presentations was increased from 10 to 25.

Results and Discussion

Figure 2 shows the mean startle amplitude as a function of drug treatment. Analysis of variance of the startle data yielded a significant interaction between Drug Treatment and Buzzer Presentation, $F(24,336) = 3.08$, $P < 0.001$. Subsequent Newman-Keuls multiple comparisons ($\alpha = 0.05$) of the simple main effects involved in this interaction revealed that the startle amplitude among mice treated with *d*-amphetamine was significantly enhanced relative to that of the saline controls. Consistent with the data reported by Davis et al. (1975) the amphetamine-induced potentiation of startle was not evident following the first buzzer presentation, but became apparent only after several stimulus presentations (see Fig. 2). The finding that the startle response was potentiated with repeated stimulus presentations when testing occured immediately after drug injection, but not when testing was carried out 15 min after injection (see Experiment I), appears to argue against an explanation based on drug-induced sensitization. When the magnitude of the startle amplitude is considered at comparable postdrug injection intervals in Experiments I and II, however, it becomes apparent that the effects of amphetamine on startle interact with prior exposure to the startle stimuli. Specifically, it will be noted that upon the first tone presentation in Experiment I (i.e., 15 min after drug administration), the startle amplitude among mice which received 5 mg/kg of amphetamine was 20.8% greater than that seen among saline-treated animals. At a comparable postdrug injection interval in Experiment II (i.e., on the 15th stimulus presentation), amphetamine enhanced the startle amplitude by 196.7% relative to saline-treated mice. These data agree with the findings of Davis et al. (1975) and suggest that the amphetamine response is greater following prior exposure to loud startle stimuli (sensitization).

Experiment III

The purpose of Experiment III was to evaluate further the role played by norepinephrine and dopamine in modulating the effects of amphetamine on the startle. It was previously observed that inhibition of the rate-limiting enzyme tyrosine hydroxylase by α-methyl-p-tyrosine (α-MpT) effectively antagonized the effects of amphetamine on the acoustic startle reflex (Davis et al., 1975). If noradrenergic activity is involved in the amphetamine-induced potentiation of startle amplitude, then inhibition of dopamine-β-hydroxylase activity should similarly attenuate the effects of the drug on the startle reflex.

Materials and Methods

Subjects and Apparatus. A total of 108 male Swiss-Webster mice procured from the Bio-Breeding laboratories served as subjects. All

Table 1. Whole brain levels of monoamines 3 h after administration of saline, α-MpT (250 mg/kg), or FLA-63 (40 mg/kg)

Treatment	DA		NE		5-HT	
	Concentration μg/g ± SEM	% Control concentration ± SEM	Concentration μg/g ± SEM	% Control concentration ± SEM	Concentration μg/g ± SEM	% Control concentration ± SEM
Saline	1.756 ± 0.132	–	0.778 ± 0.128	–	0.219 ± 0.018	–
α-MpT	0.938 ± 0.133*	53.52 ± 7.61	0.419 ± 0.041*	53.47 ± 5.73	0.209 ± 0.021	95.43 ± 9.52
FLA-63	2.067 ± 0.179	116.78 ± 10.20	0.432 ± 0.058*	55.09 ± 7.30	0.220 ± 0.019	100.51 ± 8.55

* Significantly different from saline values, $P < 0.05$

subject and apparatus specifications were identical to those described in Experiment I.

Procedure. Mice received an i.p. injection of either saline, α-methyl-p-tyrosine methyl ester (α-MpT; 250 mg/kg in a 25 mg/ml solution of saline), or bis-(4-methyl-l-homopiperazinylthiocarbonyl) disulphide (FLA-63; 40 mg/kg in a 4 mg/ml solution). FLA-63 was put into the solution by adding the drug to warm saline that contained several crystals of acetic acid amide (acetamide). The mixture was stirred until the drug was in solution. Three hours after initial treatment, mice in each of these groups were subdivided ($N = 18$/cell) such that one-half of the animals received an i.p. injection of *d*-amphetamine sulfate (5.0 mg/kg), while the remaining animals received saline. As in Experiment I, mice were placed in the startle apparatus 10 min following the amphetamine injection and were allowed to explore freely for a 5-min period. Testing was initiated immediately following the adaptation period.

In addition to the behavioral experiment, 18 mice received an injection of either α-MpT (250 mg/kg) or FLA-63 (40 mg/kg) or their respective vehicles. Three hours after drug administration the mice were decapitated. The brains were quickly removed and stored in liquid nitrogen until fluorometric assays were carried out using a modification of the hydroxyindole method (Laverty and Taylor, 1968; Maickel at al., 1968).

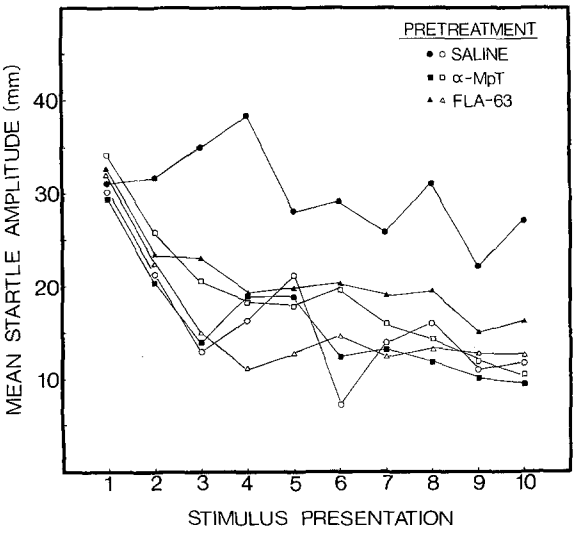

Fig. 3. Mean startle amplitude over 10 stimulus presentations as a function of drug pretreatment (250 mg/kg of α-MpT, 40 mg/kg of FLA-63, or saline) and test treatment (saline or 5.0 mg/kg of *d*-amphetamine 3 h after pretreatment)

Results and Discussion

Analysis of variance of the biochemical assay data revealed that α-MpT (250 mg/kg) and FLA-63 (40 mg/kg) significantly decreased norepinephrine levels relative to the saline controls, $F(2,15) = 5.84$, $P < 0.01$, whereas only α-MpT reduced dopamine levels $F(2,15) = 13.97$, $P < 0.001$. Whole brain levels of serotonin were not affected by pretreatment with either α-MpT or FLA-63 (see Table 1).

Analysis of variance of the startle scores revealed a significant main effect for stimulus presentation, $F(9,918) = 15.49$, $P < 0.001$, as well as a significant Drug Pretreatment × Amphetamine Treatment interaction, $F(2,102) = 4.82$, $P < 0.01$. In agreement with the results of Experiment I, Newman-Keuls multiple comparisons ($\alpha = 0.05$) indicated that startle amplitude among mice pretreated and tested with saline decreased as a function of repeated stimulus exposure (see Fig. 3). Treatment with *d*-amphetamine enhanced the startle response at all but the first buzzer presentation. Pretreatment with α-MpT 3 h prior to testing had no effect on startle when mice were tested with saline, but virtually eliminated the augmentation of the startle reflex elicited by *d*-amphetamine. Comparable results were observed when animals were pretreated with FLA-63 (Fig. 3). If, in fact, the role of norepinephrine in mediating the startle response is inhibitory (Fechter, 1974a, b), whereas the function of dopamine is one of excitation (Davis and Aghajanian, 1976; Davis et al., 1974), then pretreatment with FLA-63 should have augmented startle and potentiated the effects of amphetamine. The fact that both α-MpT and FLA-63 antagonized the amphetamine effects on the startle reflex indicates that newly synthesized norepinephrine is important in producing the amphetamine-induced augmentation of the acoustic startle reflex.

Experiment IV

The results of Experiment III indicate that norepinephrine is involved in mediating the effects of amphetamine on the acoustic startle response, but the dosages necessary to potentiate startle also increased locomotor activity. Moreover, there exists an abundance of data concerning the importance of dopaminergic activity in mediating the effects of amphetamine on locomotor activity (Creese and Iversen, 1975). Furthermore, tyrosine-hydroxylase inhibition consistently has been shown to antagonize the locomotor effects of amphetamine, whereas dopamine-β-hydroxylase inhibition is without effect in this respect (Carlsson, 1970). Thus, it is possible that the enhanced startle produced by amphetamine, as well as the reversal of the amphetamine-induced potentiation of startle amplitude following pretreatment with α-MpT, reflects the effects of these drugs on locomotor activity.

With respect to the antagonism of the amphetamine-induced potentiation of startle by FLA-63, it is not unlikely that the behavioral effects of the dopamine-β-hydroxylase inhibitor are mediated peripherally and are due to nonspecific irritant properties of the drug (Thornburg and Moore, 1973b). Accordingly, Experiment IV was designed to determine if the effects of α-MpT and FLA-63 on amphetamine-induced locomotor excitation would parallel the effects observed in the startle task. If, in fact, FLA-63 does not affect locomotor activity, irritant properties of the drug probably do not influence startle.

Materials and Methods

Subjects and Apparatus. A total of 56 male Swiss-Webster mice purchased from the Bio-Breeding laboratories served as subjects. The activity boxes were made up of circular black anodized aluminum chambers 30 cm in diameter and 30 cm high. Six infrared photoelectric relay units, placed 0.50 cm above the grid floor, were situated 7.85 cm apart about the perimeter of the cylinders, forming a 3×3 matrix. If the mouse broke a beam, then this beam could not be activated again until a second beam was broken, thus preventing the recording of such movements as head bobbing or tail thrashing.

Procedure. As in Experiment III, mice were trated with saline, α-MpT (250 mg/kg), or FLA-63 (40 mg/kg). Three hours following pretreatment the mice received a second injection, so that one-half of the animals ($N = 9$/cell) received saline, while the remaining animals received *d*-amphetamine sulfate (5.0 mg/kg). Ten minutes following the second injection the mice were placed in one of six activity chambers and allowed to explore freely for 5 min. Immediately following the 5-min adaptation period, activity (photocell counts) was recorded and printed every 2 min over a 10-min period.

Results and Discussion

Analysis of variance of the photocell crossings yielded a significant Drug Pretreatment $\times$ Test Drug Treatment interaction, $F(2,48) = 6.37$, $P < 0.005$. The mean photocell crossings for each group over the 10-min test period is depicted in Fig. 4. Subsequent Newman-Keuls multiple comparisons ($\alpha = 0.05$), revealed that among saline-pretreated mice *d*-amphetamine increased locomotor activity. In the absence of treatment with *d*-amphetamine, FLA-63 reduced the number of photocell crossings, but because of the large within-group variance this reduction did not reach statistical significance. Since the amphetamine effects on locomotor activity were unaffected by pretreatment with the dopamine-β-hydroxylase inhibitor, it is unlikely that the nonspecific irritant property of the drug was a factor in the observed reversal of amphetamine-induced potentiation of the startle. Of course, startle response may be more sensitive to the toxic effects of FLA-63.

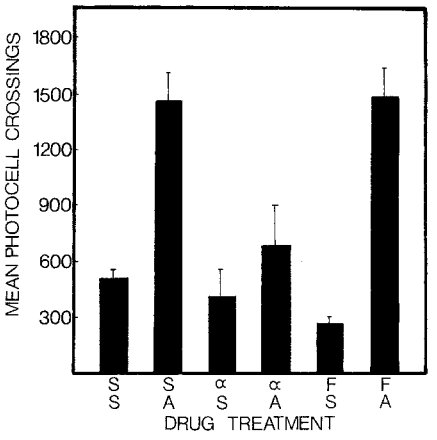

Fig. 4. Mean photocell crossings ($\pm$ SEM) as a function of drug pretreatment (250 mg/kg of α-MpT, 40 mg/kg of FLA-63, or saline) and test treatment (saline or 5.0 mg/kg of *d*-amphetamine 3 h after pretreatment)

In contrast to FLA-63, pretreatment with α-MpT produced a marked attenuation of amphetamine-induced locomotor excitation (see Fig. 4). The finding that α-MpT antagonized the amphetamine effects on locomotor activity, whereas FLA-63 was without effect in this respect, demonstrates the importance of dopamine in mediating locomotor activity. The fact that both α-MpT and FLA-63 were effective in reducing the amphetamine effects on startle amplitude in Experiment III, but that only α-MpT antagonized the locomotor stimulating properties of the drug, suggests the relative independence of these amphetamine-induced behaviors.

Experiment V

The results of Experiments III and IV demonstrate that the effects of amphetamine on the startle reflex probably are not related to drug-induced changes in

locomotor activity. Moreover, whereas locomotor activity is probably dopamine-mediated, the startle reflex involves a noradrenergic component. Recent work from this laboratory (Kokkinidis and Anisman, 1978a, b; Kokkinidis et al., 1976), has shown that other amphetamine-induced behaviors (e.g., stimulus perseveration) that apparently also involve norepinephrine (Anisman and Kokkinidis, 1975), undergo tolerance following repeated drug administration. The purpose of Experiment V was to determine whether tolerance would also develop to the amphetamine effects on the startle response using a chronic drug schedule that was previously successful in producing tolerance to stimulus perseveration (see Kokkinidis and Anisman, 1977).

Materials and Methods

A total of 40 male Swiss-Webster mice procured from the Bio-Breeding laboratories served as subjects. Mice were housed individually from the time of arrival and throughout the experiment. All other subject and apparatus specifications were identical to that described in Experiment I. Mice were randomly assigned to two groups and received daily i.p. injections of either saline (10 ml/kg) or *d*-amphetamine sulfate (10.0 mg/kg) for five consecutive days (chronic phase). On test day (Day 6) the mice were subdivided ($N = 10$/cell) so that one-half of the animals were treated with *d*-amphetamine (5.0 mg/kg) while the remaining mice received an equivalent volume of saline. As in Experiment I, 10 min after injection the mice were placed in the apparatus and allowed a 5-min adaptation period. As previously described, testing was initiated following the adaptation period.

Results and Discussion

The mean startle amplitude as a function of stimulus presentation and drug treatments is shown in Fig. 5. Analysis of variance of the startle data yielded a significant Drug Treatment (chronic phase) × Test Day Drug Treatment × Stimulus Presentation interaction, $F(9,324) = 2.14$, $P < 0.05$. In agreement with the results of the previous experiments, Newman-Keuls multiple comparisons revealed that startle amplitude among mice pretreated and tested with saline declined with repeated stimulus exposure, whereas treatment with *d*-amphetamine on the test day augmented startle amplitude. Chronic treatment with *d*-amphetamine resulted in a diminution of the startle augmentation. As shown in Fig. 5, the reduction in startle amplitude was most apparent between the second and seventh stimulus presentations ($P < 0.05$). Interestingly, chronic treatment with *d*-amphetamine produced a somewhat larger startle reaction on the first buzzer presentation (Fig. 5), but this difference did not reach statistical significance. It is noteworthy that these findings agree with those involving the effects of reserpine on the startle response. Specifically, the influence of reserpine

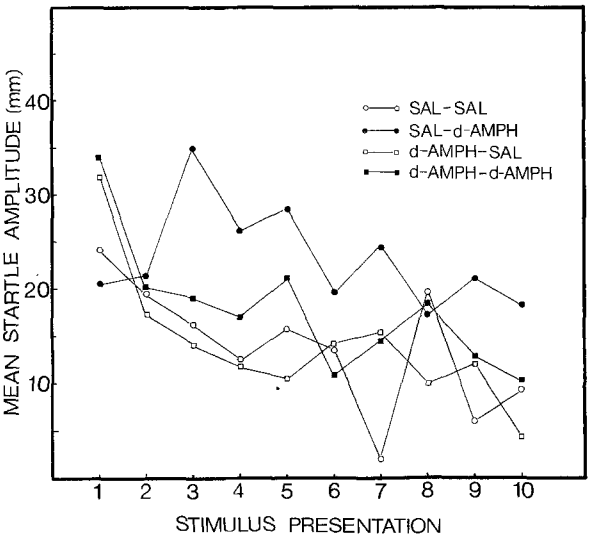

Fig. 5. Mean startle amplitude over 10 stimulus presentations as a function of 5 daily injections of either saline of *d*-amphetamine (10.0 mg/kg) and drug treatment on test day (5.0 mg/kg of *d*-amphetamine or saline)

on the startle amplitude was greatest upon initial exposure to the stimulus (Fechter, 1974a). Moreover, similar findings have been reported with respect to the effects of 6-hydroxydopamine on startle amplitude (Sorensen and Davis, 1975).

General Discussion

Presentation of an auditory stimulus (buzzer) produced a startle reaction among naive mice, the amplitude of which declined with repeated stimulus presentations. As previously reported (Davis et al., 1975), treatment with *d*-amphetamine potentiated the startle amplitude. The extent of the increase did not depend only on the drug-test interval, but interacted with the number of stimulus presentations. Specifically, the magnitude of the startle reaction was greater 15 min than 1 min after drug administration. In addition, at the 15-min drug-test interval those mice that received a series of buzzer presentations exhibited a larger startle reaction relative to saline controls than those mice that received their first buzzer presentation at this time interval. As such, these data agree with those of Davis et al. (1975) suggesting that the drug-induced potentiation of startle represents, at least in part, a sensitization effect.

Unlike the effects of *d*-amphetamine on locomotor activity, which apparently involves the release of dopamine (Carlsson, 1970; Creese and Iversen, 1975), amphetamine-induced potentiation of startle may well be a consequence of the effects of the drug on norepinephrine release and reuptake. To be more explicit, following pretreatment with FLA-63, which depleted

NE but did not affect whole brain DA, the enhanced startle produced by amphetamine was antagonized. Since FLA-63 did not influence amphetamine-induced locomotor activity and also does not influence the stereotypic behaviors engendered by amphetamine (Carlsson, 1970; Wallach, 1974), it cannot be argued that the reducton of startle was due to the emergence of competing behaviors (e.g., stereotypy).

Although the data of the present investigation suggest that NE is involved in startle reactivity, this does not exclude a role for DA in the elicitation of this behavior (Davis and Aghajanian, 1976). It is, however, important to determine whether both catecholamines conjointly mediate startle (cf. Kehne and Sorenson, 1978) or, alternatively, whether an optimal, or at least an adequate, motor excitation involving DA is necessary in order that startle arousal mediated by NE becomes manifest. Further, it is necessary to determine whether discrete DA and NE pathways contribute to different aspects of the startle reflex and its maintenance.

As in the case of other amphetamine behaviors involving a noradrenergic component (see introduction), the augmentation of startle amplitude was limited following chronic amphetamine treatment. It might be argued that the decline in startle amplitude was a consequence of the emergence of competing behaviors (e.g., stereotypy) following chronic drug treatment. This, however, does not appear to be the case since treatment with dosages of *d*-amphetamine that engender more pronounced stereotypy (10 mg/kg in Experiment I) did not diminish startle amplitude. Since tolerance has as yet not been reported to occur to behaviors mediated primarily by DA, we should at least provisionally consider the possibility that tolerance occurs primarily to behaviors involving NE activity. Furthermore, if stimulus factors influence startle amplitude, in common with stimulus perseveration and other behaviors that show tolerance (cf. Davis, 1974; Kokkinidis and Anisman, 1977), tolerance might be a reflection of a 'breakdown' of selective attention otherwise elicited by amphetamine.

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