Operant Performance Following Tail-Pinch in the Rat: Effects of d-Amphetamine

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Abstract

To extend the investigation of tail-pinch induced behavioral changes, rats performing on a differential reinforcement of low rates of 10 sec (DRL10), a fixed-interval of 60 sec (FI60), and a fixed-ratio of 20 (FR20) schedules were exposed to a paper clip applied to the tail. While a 10 min tail-pinch conducted 1 hr before operant sessions significantly altered the DRL10 behavior, this stressor had little effect on either FI60 or FR20 responding. Marked DRL10 behavior performance changes following tail-pinch included increases in the number of lever presses, decreases in the number of the reinforcers, and disruption in the frequency distribution of inter-response times (IRT). These DRL10 operant deficits were diminished when the subject received a tail-pinch pretreatment followed by d-amphetamine treatment (0.2 and 2.0 mg/kg). In combination with biochemical data from others, the present results suggest that catecholamine systems are involved in modulation of DRL10 behavior following tail-pinch.

Key Words: stress, DRL10, FI60, FR20, catecholamine, inter-response time

Introduction

Tail-pinch as a mild form of stress elicits a wide array of reflexive behavior, including oral stereotypy, feeding, aggression, and maternal behavior (5, 14, 27). To the best of our knowledge, no previous work has investigated the effects of tail-pinch on operant behavior. Arousal in animal subject is believed to shift during or following tail-pinch, along with the subject's motivational state. These two factors are important in determining the expression of behavior established under operant conditioning. The present work employed three types of reinforcement schedules to study how tail-pinch affects operant behavior, the differential reinforcement of low rates (DRL), the fixed-interval (FI) and the fixed-ratio (FR) schedules. Operant behaviors maintained on these three schedules of reinforcement are different in both quantitative and qualitative aspects (reviewed by 25, 30). The FI schedule was chosen because steady baseline behavior in individual subject can be easily maintained throughout single experimental session. The DRL schedule of reinforcement is a useful procedure for measuring response control or behavioral inhibition, because the animal under a DRL schedule is required to space its responses for some minimum interval of time. In contrast to FI or DRL, which implement time-based contingencies, the FR schedule differentially reinforces subjects for high rates of responding. We assumed that these distinct types of operant responding could differentially responsive to stress manipulations.

A large body of research has examined the effects of stressors on cortical catecholamine (CA) neurotransmission, and it is generally agreed that synthesis and utilization of adrenergic and dopaminergic systems are altered under stressful conditions (reviewed by 1). However, the pattern of CA alteration following stressor presentation has not been uniformly consistent, and may vary depending upon the nature of the stressor employed. Recent work using microdialysis demonstrated that the releases of dopamine (DA) and noradrenaline were differentially regulated across three areas of the mesotelencephalic DA systems after the application of tail-pinch as a mild stressor (7). Moreover, an

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increase in cortical DA metabolism induced following tail-pinch (e.g. DOPAC) was demonstrated using the *in vivo* voltammetry technique (8). The second objective of the present study was to extend our understanding of the relevance of these neurochemical findings to operant behavior changes by determining whether a CA-ergic agonist altered the effects of tail-pinch pretreatment on rats tested in operant behavior. As mainly producing the agonistic effects on CA systems (26), d-amphetamine was chosen in an attempt to facilitate the detection of potential changes in CA released after tail-pinch.

Materials and Methods

Subjects

The subjects were male Wistar rats, averaging approximately 250 g of body weight upon receipt (the Breeding Center of Experimental Animals, National Taiwan University Hospital, Taipei). After 10 days of adaptation with food and water ad libitum, the rats were maintained on a water deprivation regimen such that 5 min access to tap water in the home cage occurred no sooner than 30 min after the end of each daily experimental session. The rats were monitored and kept at 85 percent of their pre-experimental body weight. Food pellets were continuously available in each home cage. Training and/or test sessions were administered daily at the same time (10:00 to 15:00) each day during the light portion of the vivarium's 12/12 hr light-dark cycle.

Apparatus

Operant responses were measured in two chambers located in a room separate from the animal colony. These two operant chambers were serviced by a microcomputer. The interior dimension of each chamber was 20 cm by 25 cm by 30 cm. Aluminum panels formed the front and back walls, and clear plexiglas comprised the remaining sides and top. Stainless steel bars (diameter 5 mm) were set 11 mm apart to provide flooring. Each chamber was equipped with a lever placed 4 cm above the floor and positioned 4 cm from the right corner of the front panel. A liquid dispenser was set outside of the front of the chamber. The reinforcer (water) delivery mechanism contained 0.2 ml water for each presentation. The water was delivered into a receiving dish located on the center of the front panel and 4 cm above the floor. The chamber was illuminated by a small light bulb located 10 cm above the floor and positioned 5 cm from the left corner of the front panel. The chamber was enclosed in a plywood box with a fan to provide the necessary ventilation and masking noise. The contingency for each schedule of reinforcement was programmed and compiled via a commercial kit, Medstate Notation (MED Associate Inc., East Fairfield VT, USA).

Procedure

Rats were initially shaped to press the lever on a continuous reinforcement schedule. Afterwards, subjects were divided into three groups and further trained to respond on a DRL schedule of 10 sec (DRL10; n=16), an FI schedule of 60 sec (FI60; n=20), or a FR schedule of 20 (FR20; n=8) for reinforcement contingency. In DRL10, a reinforcer was delivered contingent upon a lever press if at least 10 sec had elapsed since the previous press. Each lever press, reinforced or not, reset the delay timer. The FI60 schedule reinforced the first lever press given after 60 sec had elapsed since the preceding reinforcer. Lever presses made during each 60 sec interval were without reinforcing consequences. In FR20, the subject was reinforced for every accumulated twenty lever presses. Each daily session was 15 min in duration for all three types of operant responding. The criterion for definition of a stable baseline was less than 10% variation in the response rate under each schedule for three consecutive sessions. Following stable operant performance, each subject was exposed to the tail-pinch manipulation. Conducted 1 hr before the commencement of each operant session, a sponge-padded paper clip (2.3 cm x 0.5 cm) was applied for 10 min to a position 2 cm from the tip of the tail.

Due to the lack of tail-pinch effect on FI60 and FR20 behavior (see results), the second part of this study investigated the effects of d-amphetamine on tail-pinch induced changes only under DRL10. Another group of naive rats (n=24) were trained to respond on the aforementioned DRL10 schedule of reinforcement. These subjects were then divided into three subgroups, each (n=8) assigned to receive a different dose of d-amphetamine (0, 0.2, and 2.0 mg/kg). D-amphetamine HCl (Sigma Chemical Co., St. Louis, MO, USA.) was dissolved in normal saline. Drug solutions were freshly prepared just before administration at the specified dosages expressed as the salt. Intraperitoneal (IP) injections were conducted 15 min prior to the beginning of operant session. The injection volume was kept in 1 ml per 1 kg of body weight. The subjects were then run on the DRL10 schedule for 7 sessions without any experimental treatment after the determination of the dose effects for d-amphetamine. Subsequently, each subject received an aforementioned tail-pinch treatment followed by the same dose injection of d-amphetamine given before.

Table 1. Numbers of Responses and Reinforcers in 15 min Under DRL10 (n=16), FI60 (n=20), and FR20 (n=8) Schedules after Tail-pinch Pretreatment.

	DRL 60	FI 60	FR20
No. of Responses			
baseline	104.8±5.0	271.4±24.9	1359.6± 92.4
pinch	121.8±5.5**	266.3±26.7	1087.2±175.5
No. of Reinforcers			
baseline	30.3±1.5	13.8±0.2	66.1±4.4
pinch	25.0±1.0**	13.9±0.1	52.9±8.5

**p<0.01, indicate significant differences between baseline and pinch from a paired t-test.
Data are presented as the mean ± SEM of the pinch-free baseline and the pinch treatment respectively.

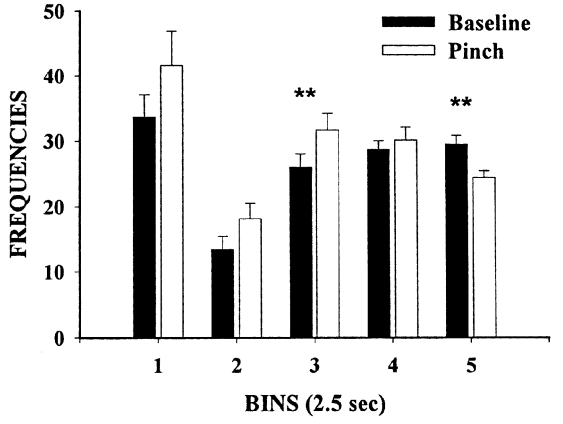

Fig. 1. Frequency distribution of inter-response times (IRT) over baseline control (black bar) and tail-pinch (white bar) sessions running on the DRL10 schedule of reinforcement. Each bar represents the mean frequency (+ 1 s.e.m.) of responses which occurred with an IRT time less than or equal to the interval indicated on the abscissa. Reinforced responses are illustrated under IRTs greater than 10 sec. **p<0.01, indicate significant differences from control state as revealed by the paired t-test.

Statistics

The appropriate t-test (two-tailed) or analysis of variance (ANOVA) was used to determine the statistical significance with a criterion of $p < 0.05$. Along with each ANOVA, separate t-tests (paired comparisons) were performed to characterize the difference between baseline control and tail-pinch treatment (31).

Results

Table 1 illustrates the effects of tail-pinch pretreatment on the numbers of responses emitted and reinforcers obtained during operant responding under DRL10, FI60, and FR20. Tail-pinch pretreatment significantly affected operant performance on the DRL10 schedule by increasing the frequency of lever presses and decreasing the number of reinforcers, $t(15)=3.228$, $p<0.001$ and $t(15)=4.889$, $p<0.001$, respectively. In contrast to DRL behavior, neither the response frequencies nor the numbers of obtained reinforcers in the FI60 and FR20 groups were significantly altered with tail-pinch pretreatment.

Figure 1 shows the effects of tail-pinch pretreatment on the frequency distribution of inter-response times (IRT) under the DRL10. A two-way ANOVA yielded statistically significant effects of tail-pinch, $F(1, 15)=13.9$, $p<0.001$, bins, $F(4, 60)=10.39$, $p<0.001$, and a significant interaction, $F(4, 60)=3.466$, $p<0.05$. That the normal bimodal distribution of IRT frequencies was significantly shifted to the left by tail-pinch pretreatment was further confirmed by separate t-tests. The tail-pinch pretreatment significantly increased the median IRTs of 5.1-7.5 sec and decreased the long IRTs of 10 sec or greater, $t(15)=3.688$, $p<0.01$ and $t(15)=3.816$, $p<0.01$, respectively. Among the other three IRT bins, tail-pinch pretreatment increased the first one and decreased the second one to a level marginally significance, $t(15)=1.977$, $p=0.067$ and $t(15)=2.042$, $p=0.059$, respectively. Unlike DRL10 responding, the distribution of IRT's under FI60 was not significantly affected by tail-pinch pretreatment (data not shown).

From the second part of this study, Figure 2 presents the effects of d-amphetamine on the number of responses and the number of reinforcers under DRL10 in the absence or presence of tail-pinch pretreatment. In regard to the number of responses (Figure 2A), a two-way ANOVA revealed a dose effect at a marginal significance level, $F(2,21)=3.177$, $p=0.062$. Neither the pinch effect nor the dose-by-pinch interaction was significant. However, separate t-tests conducted for each group showed that

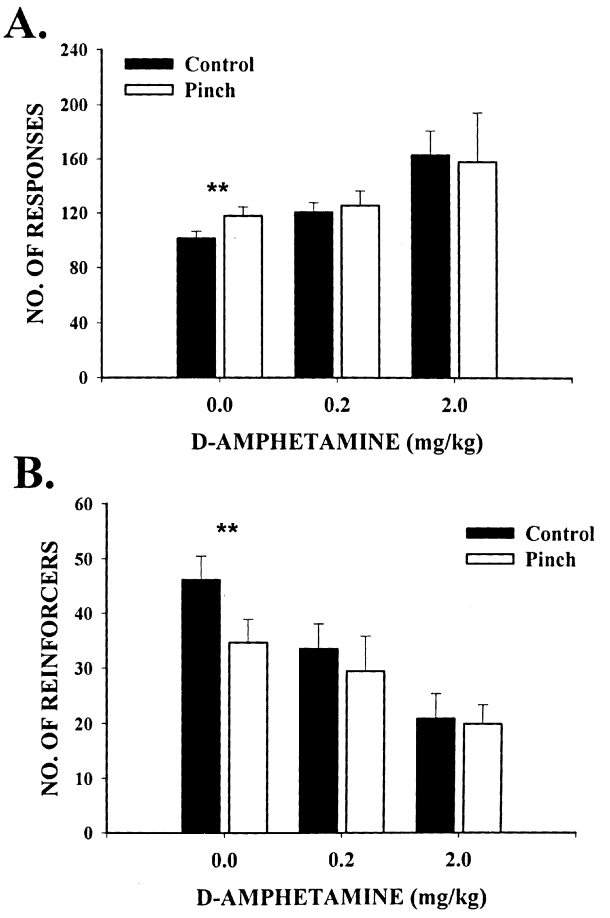

Fig. 2. Comparison of the effects of tail-pinch on the number of responses (A) and the number of reinforcers (B) under DRL10 in three groups (n=8 each) treated with different doses of d-amphetamine. The black bars represent three groups receiving amphetamine or vehicle only, whereas the white bars represent these three groups subsequently re-tested by amphetamine administration with tail-pinch pretreatment. Mean scores + 1 s.e.m. are represented. **p<0.01, indicate significant difference from control state as revealed by a paired t-test

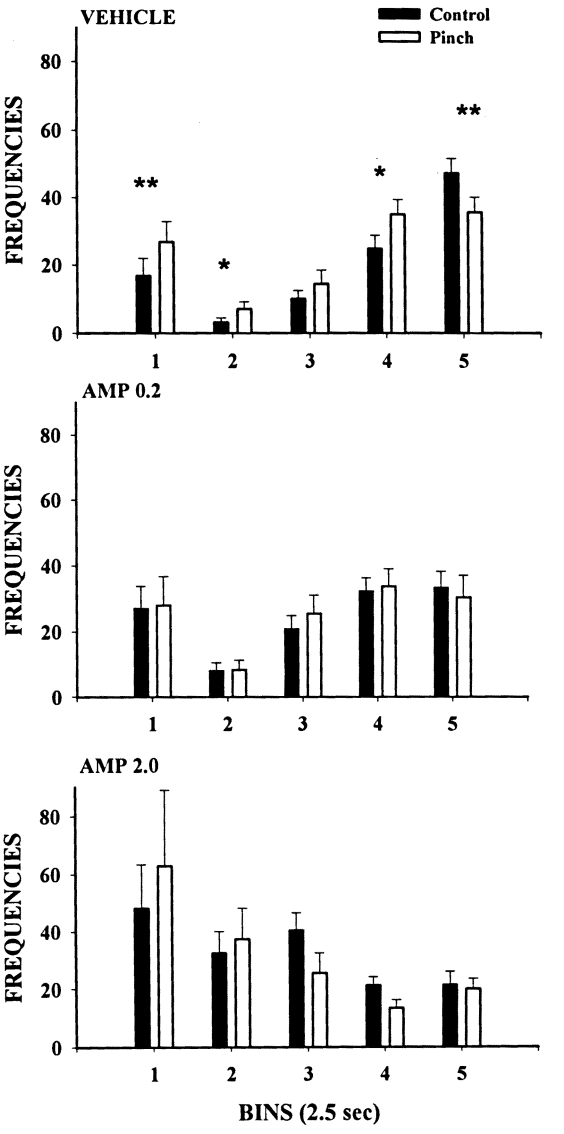

Fig. 3. Frequency distributions of inter-response times (IRT) for the baseline (black bar) and tail-pinch (white bar) sessions maintained on the DRL10 schedule of reinforcement as compared across three groups (n=8 each) treated in separated with 0.0 mg/kg (top panel; shown as Vehicle), 0.2 mg/kg (middle panel), and 2.0 mg/kg (bottom panel) doses of d-amphetamine. Each bar represents the mean frequency (+ 1 s.e.m.) of responses which occurred with an IRT time less than or equal to the interval indicated on the abscissa. Reinforced responses are illustrated as IRTs greater than 10 sec (right-most paired bars). *p<0.05 and **p<0.01, indicate significant differences from the control state as revealed by paired t-tests.

more lever presses were made following tail-pinch under the vehicle control condition, $t(7)=5.328$, $p< 0.01$. This difference between the absence and presence of tail-pinch pretreatment vanished at the 0.2 or 2.0 mg/kg doses of d-amphetamine. In Figure 2B, the ANOVA yielded a significant dose effect, $F(2,21)=6.722$, $p<0.01$. The main effect of pinch was marginally significant, $F(1,21)=3.227$, $p=0.087$; whereas the dose-by-pinch interaction was not significant. Revealed from separate t-tests, tail-pinch significantly decreased the number of reinforcers delivered to the group treated with saline vehicle, $t(7) =4.012$, $p<0.01$. No significant tail-pinch effect was evident on the number of reinforcers under DRL10 behavior for either the 0.2 mg/kg or 2.0 mg/kg groups ($p>0.05$).

Figure 3 presents the effects of tail-pinch pretreatment on the IRT frequency distributions for DRL10 under various doses of d-amphetamine. A two-way ANOVA for the pinch condition by IRT bin with repeated measures was conducted for each dose treatment. Regarding the vehicle group, shown in the top panel of Figure 3, ANOVA revealed significant main effects for both pinch and bin, $F(1,7)=29.054$, $p <0.01$ and $F(4,28)=12.519$, $p<0.001$, respectively.

Also, a significant interaction of pinch-by-bin was found in the vehicle treated group, $F(4,28)=9.225$, $p<0.001$. Further analyses using paired t-test indicated significant differences between the control and tail-pinch states appeared on bins 1, 2, 4, and 5, $t(7)=4.116$, $p<0.01$, $t(7)=2.535$, $p<0.05$, $t(7)=2.74$, $p<0.05$, and $t(7)=4.092$, $p<0.01$, respectively. Shown in the middle panel of Figure 3, ANOVA for the group treated with d-amphetamine of 0.2 mg/kg only revealed a significant main effect of IRT bin, $F(4,28)=4.32$, $p<0.01$. None of the tests of ANOVA applied on the group treated with 2.0 mg/kg d-amphetamine was significant as shown by data presented in the bottom panel of Figure 3.

Discussion

The present study clearly shows that the acute effects of mild stressor induced by tail-pinch can alter the operant behavior maintained on the DRL10 schedule of reinforcement. While tail-pinch disrupted behavioral performance in the DRL10 rat, this stressor had little effect on either the FI60 or the FR20 subject. These differential effects of tail-pinch can be attributed to the different reinforcement contingencies required for DRL and the other two types of operant behavior. To the best of our knowledge, this finding of tail-pinch induced deficits in DRL behavior has not been reported previously. Nevertheless, a recent work investigated the effects of thermal stress on multiple DRL-FR behavior (29). Responding on the DRL18 component was significantly affected by cold stress, while that of FR10 remained unchanged. Regardless of the difference in the types of stressors employed, the current findings of increased numbers of responses, the decreased numbers of reinforcers, and the shifted IRT frequency distribution were in accord with those reported by Thomas et al. (29). A more recent work studied whether FR-maintained operant behavior in food-deprived rats was affected by an acute 3 hr restraint stress (32). Their results, compatible to the present findings for FR, showed that rats' operant responding on the FR15 schedule was similar to the subjects tested in a 30 min session after the 3 hr restraint manipulation. However, the FR15 behavior was abolished (reduced to zero rate) when these subjects were re-tested after the exposure of 3 hr restraint plus water immersion stress. The latter stress can be too large to compare with the mild stress like tail-pinch applied in the present work. Thus, it seems that FR-maintained behavior is resistant to the effects of a mild stressor. Together, these results support the idea that sensitivity for stressor-provoked behavioral disturbance may be greater on the DRL schedule than under other operant schedules (i.e., FI and FR).

In addition to its low-rate responding, DRL behavior is normally characterized by temporal adjustment and response withholding (13, 20). Thus, it is likely that the application of tail-pinch in the present work impaired DRL10 responding via the disruption of temporal regulation and the loss of behavioral inhibition. The IRT distribution was markedly shifted to the left by tail-pinch pretreatment as shown in Figure 1. A trend of increasing frequency was seen for the burst responses made on the bin 1. These frequency increases on the non-reinforced bins can be interpreted as the loss of behavioral inhibition control, while the IRT variability produced by tail-pinch pretreatment reflects the disruption of temporal regulation. In terms of temporal regulation, one might argue why the tail-pinch pretreatment affected DRL10 but not FI60. Although both types of operant responding are related to temporal parameter (i.e., sec in the present study), the requirements of reinforcement contingencies for both are quite different from each other (11). DRL behavior is normally performed with a higher cognitive representation of the critical temporal adjustment than FI behavior. The latter is partly compensated by the synchronizing effect of the periodic reinforcer delivery, whereas the former is not. Accordingly, the distinctive operant characteristics between DRL10 and FI60 explain the differential effects of both schedule-controlled behaviors affected by tail-pinch pretreatment. It should be noted that the tail-pinch was conducted for 10 min in the 1 hr prior to the commencement of the operant session. That the operant measurement was not conducted during the tail-pinch manipulation should exclude the potential confounding effect of painful or aversive stimulation induced by the stressor.

In addition, the present study compared the effects of tail-pinch on DRL10 behavior under d-amphetamine treatment. Psychostimulant drugs (including amphetamine) have been known for their capacity to affect operant behavior, but the effects depended upon the dose administered and upon the baseline rate of responding (25). The present dose range is lower than the doses that produce stereotyped behavior. The present finding that d-amphetamine altered DRL10 performance is consistent with previous work (12, 23). Amphetamine significantly disrupted the efficacy of DRL behavior by increasing the number of responses and decreasing reinforcements. These operant changes induced by amphetamine were also consistent with those reported from previous work employing the DRL task with a longer parameter of 18 sec or 60 sec (6, 17, 22). In terms of temporal regulation, amphetamine has been suggested to increase the speed of an internal clock used by rats in time discrimination tasks (18, 19, 21).

It is then possible that the temporal regulation for DRL10 behavioral performance was impaired on the basis of internal clock speed altered by amphetamine. This inference is supported by that the frequencies of shorter IRTs (bins 1 to 3 in Figure 3) that were increased by amphetamine in a dose-related fashion. Both tail-pinch manipulation and amphetamine administration, when conducted by itself, produced quantitatively the same effects on response and reinforcement frequency on DRL behavior. These results may be attributed to the activation of the mesocorticolimbic dopaminergic systems. Several studies using microdialysis techniques demonstrated that the extracellular concentrations of DA in the striatum and the nucleus accumbens were significantly increased shortly (10-15 min) after the peripheral administration of d-amphetamine in doses similar to those used in the present study (9, 10, 15, 16, 24). On the other hand, pretreatment of 15 min tail-pinch increased CA extracellular levels in various degrees in the striatum, the nucleus accumbens, and the medial prefrontal cortex (7). Furthermore, the time course of DA extracellular concentrations monitored after a 30 min tail-pinch indicates that the stress-increased DA levels can last at least 75 min in the striatal areas (15, 16). Moreover, the CA systems in the prefrontal cortex were activated after a 20 min tail-pinch by showing the increases of DA and noradrenaline release (28). Thus, the enhanced CA release in the forebrain may be the common factor produced by either tail-pinch pretreatment or amphetamine challenge to disrupt DRL behavioral performance.

When d-amphetamine was given with a pretreatment of tail-pinch, the DRL10 behavioral deficits as observed in the vehicle control group were diminished at both doses tested in the present study. Without producing behavioral deficits in a further degree, the effects of tail-pinch combined with d-amphetamine treatment on DRL10 responding were not additive from either treatment given alone. However, the DRL10 behavioral deficits after tail-pinch was only set close to that of d-amphetamine given alone, but not the baseline level. This was generally true over two dependent variables of DRL10 responding measured in the present work (see Figure 2). In consideration of the sequence of conducting tail-pinch and amphetamine treatments in the present study, tail-pinch induced disruption on DRL10 behavior could be partially reversed by amphetamine. A series of early works demonstrated that inescapable shock reliably impaired subsequent escape performance, and this escape deficit could be eliminated by drugs (e.g. L-DOPA) that increased CA activity (2, 3, 4). Although these data provide a compatible evidence for the stress-induced behavioral deficits reversed by CA-ergic agonism, the reversal effects of d-amphetamine on the tail-pinch induced disruption on DRL10 behavior were subtle in the present work. Alternatively, it could be argued that the effects of tail-pinch were masked by amphetamine treatment. In this case, tail-pinch induced DRL impairment was merely de-sensitized by d-amphetamine to somewhat extents rather than completely reversed back to the baseline levels. These data suggest that the neurochemical activity of CA produced by d-amphetamine may play an influential role for this behavioral outcome.

In conclusion, current data show that the acute effects of mild stress induced by tail-pinch can alter operant behavior maintained on the DRL10, but not the FI60 or the FR20 schedule of reinforcement. These deficits of DRL10 behavior induced by tail-pinch were diminished when the subject was given d-amphetamine treatment. In consideration with extant biochemical data from others, it is suggested that CA neurotransmission systems are involved in the modulation of DRL10 behavior following tail-pinch.

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