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# Consequences of Reward and Nonreward Conditions: Runway Behavior, Neurotransmitters and Physiological Indicators of Stress

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EARLEY, C. J. AND B. E. LEONARD. *Consequences of reward and nonreward conditions: Runway behavior, neurotransmitters and physiological indicators of stress.* PHARMAC. BIOCHEM. BEHAV. 11(2) 215–219, 1979.—Rats were subjected to continuous reinforcement (CR), partial reinforcement (PR) or extinction (EX) schedules following food-motivated conditioning in a straight runway. On the final day of testing, the animals were removed from the runway after the fifth trial and were killed in order to determine the neurochemical consequences of differential reward. Corticosterone and adrenal ascorbic acid were also taken as indicators of immediate and long-term environmental stress, respectively. From the results it would appear that PR and EX caused a prolonged period of stress as indicated by the reduced ascorbic acid concentrations. However, only the PR group showed elevated concentrations of corticosterone, which would suggest that the behavioral conditions were still stressful to the PR, but not to the EX group at the time of killing. Changes in the septal concentrations of GABA and hippocampal 5-HT following PR and EX were attributed to the effects of nonreward conditions. Furthermore, the catecholaminergic-olfactory system may be necessary for appropriate extinction of food-motivated behavior, while the midbrain dopaminergic system may function to maintain motivation under conditions of variable reward.

Food-motivated behavior  Neurotransmitters  Corticosterone  Adrenal ascorbic acid  Nonreward

FROM his studies on the effects of self-stimulation and 6-hydroxydopamine (6-OHDA) on behavior in rats, Stein [25] postulated the existence of specific reward and punishment systems. The ascending noradrenergic system was considered to be involved in the mediation of reward, while the ascending serotonergic system was suggested to be involved in punishment. Since that time, lesion studies on the locus coerulus have implicated the ascending noradrenergic pathway in the acquisition of appetitive behavior [3]. However, 6-OHDA-induced depletion of forebrain, but not hindbrain, noradrenaline had no appreciable effect on the acquisition of food-motivated behavior [20]. This study suggests that the locus coerulus per se, rather than the ascending noradrenergic system, is involved in food reward. Furthermore, extinction of the appetitive response was impeded by 6-OHDA-induced depletion of forebrain noradrenaline [20] suggesting that the forebrain noradrenergic system functions under nonreward rather than reward conditions.

With respect to the serotonergic system, Tye and Coworkers [28] postulated a serotonergic punishment system involving response suppression. However, Miliaressis [21] has demonstrated that under self-stimulation conditions positive reward can be obtained by stimulation of serotonergic pathways. Thus the serotonergic system may mediate the effects of both punishment and reward. Dopamine has also been implicated in motivation [14,29] and in the mediation of reward [19].

The previous studies, in general, support the view that monoamines are involved in reward and punishment mechanisms, but it is unclear which neurotransmitter system underlies which type of behavior. Furthermore, while the limbic system is important in mediating the consequences of reward and punishment [17], the relationship between limbic functioning and the monoaminergic systems is still unresolved.

The aim of the present study was therefore to investigate the effects of different schedules of reinforcement on the monoaminergic system in discrete brain regions. As physiological indicators of behavioral treatment, corticosterone and adrenal ascorbic acid levels were determined. Since the involvement of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) in behavior has been virtually unexplored, the possible involvement of this amino acid in behavior was investigated in this study. GABA has been found to be involved in aspects of aggression and environmental stress [7].

## METHOD

### *Animals*

Forty-eight male Sprague-Dawley rats, initially weighing

250–300 g, were used. The animals were randomly assigned 4 per cage, each cage member representing one of 4 behavioral conditions (see Behavior). The animal room had an alternating light-dark cycle, with the light period extending from 0700–1700 hr. The animals were on ad lib water but were maintained on a 23 hr food-deprivation schedule for 2 weeks prior to training and throughout the experimental period. During the period of the experiment, the animals were allowed access to food for one hour commencing 15 min after completion of the day's testing.

*Apparatus*

The testing apparatus, based on the model of Gray [10], consisted of a 195 cm straight Plexiglas (opaque) runway 15 cm wide and 27.5 cm in height. It was divided by two hand-operated aluminum guillotine gates into a startbox (15.5 cm in length), an alleyway (162 cm in length) and a goalbox (15.5 cm in length). The alleyway was equipped with two photocells which were connected to an electric timer which gave a reading in 0.01 sec. One photocell was placed in the alleyway 12 cm from the startbox gate. The second photocell was placed in the alleyway 12 cm in front of the goalbox gate. The time to transverse the distance between the two photocells was taken as the dependent variable.

*Behavior*

The training and testing period commenced at 0800 hr. The 48 animals were divided into two groups of 24 animals each and tested successively on the same day. These two groups, and the order in which the two were tested, were held constant. The behavioral treatments were noncontingent control (NC), continuous reinforcement (CR), partial reinforcement (CR) and extinction (EX). Except for the NC group, the animals underwent 4 days of training and 16 days of testing in the runway according to the procedures of Gray [10]. The animals were given 8 trials/day during the 16 days of testing. For the first 8 days, all the animals (excluding the NC group) were maintained under continuous reinforcement conditions. During the last 8 days, the CR group continued under the continuous reinforcement schedule while the PR group was placed on a partial reinforcement schedule (50%). The EX group received 4 further days of continuous reinforcement but was then given nonreward trials for the last 4 days.

Each trial consisted of placing the rat in the startbox raising the gate and then lowering the gate of the goalbox once the animal had entered. After leaving the rat for 30–40 sec in the goalbox it was removed and placed in a holding cage, and the next animal was introduced into the runway. The animals were returned to the home cage after about 3 min in the holding cage. One animal from each behavioral group was present in any one cage, giving 4 animals per cage. Each member of a cage group was differentiated by a dye marking and an order of testing was established for each animal. Selection was performed in accordance to a randomized block design. The order of testing was then rotated across trials and across days. This was done in order to control for any order-of-testing factors (e.g. odor cues in alleyway). Subjects in the NC group were treated in exactly the same manner as those in the other 3 groups, except that they did not experience the runway, but instead were placed directly into the holding cage and given a food pellet. During the testing of any given set of cage mates, the animal from the NC group was permitted to run freely across the adjoining cage tops until being placed into holding cage. This procedure permitted compatible levels of "activity" between the NC animals and the animals from other treatment groups.

*Biochemistry*

On Day 17, the animals were given 5 standard trials according to their previously assigned schedule. The fifth trial was also a nonreward trial for the PR group. After the fifth trial, the animal was removed from the runway (or from the holding cage if it was an NC animal) and passed outside of the testing room where it was killed by decapitation. The time lapse between handing the animal outside the door and decapitation was less than 10 sec. All efforts were taken to ensure it was done in an unstressful manner. The blood was collected upon decapitation and the adrenals removed and placed in pre-weighed tubes containing oxalic acid. The heads were placed in a microwave oven (2.5 kw) within 30 sec of decapitation and exposed to microwave radiation for 1.5 sec. Microradiation stops all enzymatic processes permitting dissection to be carried out at room temperature.

Serum corticosterone, taken as a measure of short term or immediate environmental stress, was determined by the methods of Glick, von Redlich and Levine [9]. Adrenal ascorbic acid, taken as an indicator of long term environmental stress, was determined as described by Demetriou [6]. The brains were dissected, according to the methods of Popov *et al.* [23], into brain stem (pons-medulla), midbrain (mesencephalon), septal area, amygdaloid cortex, hippocampus, and the olfactory system (bulbs and tuberculum). The isolation procedures and the spectrofluorimetric determinations of noradrenaline, dopamine, 5-hydroxytryptamine [8] and γ-aminobutyric acid [7] have been described previously.

*Statistical Procedures*

Analysis of variance was used to assess the behavioral data; Student's $t$-test (two-tailed) was used in interpreting the biochemical results; the $\alpha$ level was set at $p<0.05$. The data presented in the results represents those aspects of the experiment which were found to be reproducible in two subsequent independent replications.

## RESULTS

*Behavior*

The behavior of the animals under different schedules of reinforcement is presented in Fig. 1. The behavior of the CR group was compared with the Day 1–8 behavior of the PR or the Day 1–12 behavior of the EX group. This was to ensure that the behavior of the PR and EX groups was similar to the CR group prior to changes in reinforcement schedules. Analysis of variance (treatment group × days) revealed no overall differences between groups.

The last 4 days of behavior were subjected to analysis in order to ascertain the behavioral status of the three groups prior to biochemical assessment. A comparison of the CR and PR groups revealed no treatment, time, or treatment × time effects. However, the EX group in comparison with the CR group did display significant treatment, $F(1,22)=9.20$, $p<0.01$, and time, $F(3,66)=3.96$, $p<0.025$, effects. This is indicative of the reduction in behavior accompanying EX.

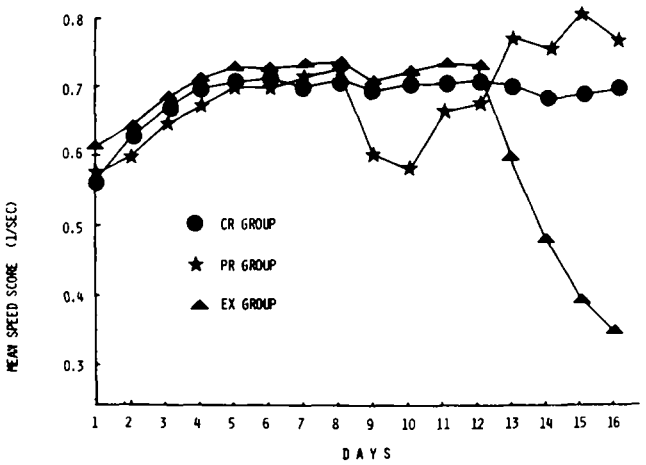


FIG. 1. Responses are expressed in reciprocal seconds. All groups were maintained on a continuous reinforcement schedule from Day 1–8. The PR group was then placed on a partial reinforcement schedule, Day 9–16. The EX group received 4 more days of continuous reinforcement (Day 9–12) and was then given 4 days of nonreward (Day 13–16). The CR group was maintained on the continuous reinforcement schedule (Day 1–16).

*Corticosterone and Ascorbic Acid*

The effects of behavioral treatment on these two physiological parameters of stress are given in Table 1. Corticosterone, which reflects the immediate stressfulness of the environment, was lower in the CR group relative to the concentrations found in the NC group. The concentration of corticosterone in the PR group was elevated, while that of the EX group was unchanged relative to the CR group.

Adrenal ascorbic acid, which has been taken as an indicator of long-term effects of stress, was also affected by treatment. The CR group showed higher concentrations relative to the NC group and the PR group had lower concentrations in comparison with the CR group. Ascorbic acid was found to be somewhat lower in the EX group, but this difference was not statistically distinguishable from the CR group.

*Neurochemistry*

The neurochemical consequences of behavioral treatment are given in Table 2. Statistical group comparisons were made between NC *vs* CR, CR *vs* PR and CR *vs* EX. In comparison with the NC group, the CR animals exhibited

TABLE 1

CONCENTRATION OF CORTICOSTERONE AND ASCORBIC ACID FOLLOWING BEHAVIORAL TREATMENT

| | NC | CR | PR | EX |
|---|---|---|---|---|
| Corticosterone* | 34.6 ± 3.1§ | 22.2 ± 2.3‡ | 31.1 ± 2.1§ | 24.7 ± 3.1 |
| Ascorbic Acid† | 775 ± 40§ | 902 ± 43 | 790 ± 35§ | 800 ± 55 |

*Concentration expressed as μg/100 ml serum.
†Concentration expressed as μg/g adrenal wt.
‡Values represent Mean ± SEM of 12 individual determinations.
§Statistically different from the CR concentrations ($p<0.05$, Student's $t$-test, two-tail).

TABLE 2

CONCENTRATIONS OF NEUROTRANSMITTERS IN DISCRETE BRAIN REGIONS FOLLOWING BEHAVIORAL TREATMENT*

| Treatment | Brain† Region | Neurotransmitter | Concentrations (μg/g) | Concentrations (μg/g) of CR Group |
|---|---|---|---|---|
| NC | OLF | NA | 0.41 ± 0.01‡ | 0.31 ± 0.01 |
| | HIP | NA | 0.31 ± 0.01 | 0.25 ± 0.01 |
| | SEP | GABA | 557 ± 13 | 521 ± 13 |
| PR | MID | DA | 0.18 ± 0.01 | 0.25 ± 0.01 |
| | HIP | 5HT | 0.55 ± 0.03 | 0.42 ± 0.03 |
| | EP | GABA | 563 ± 17 | 521 ± 13 |
| EX | OLF | NA | 0.38 ± 0.02 | 0.31 ± 0.01 |
| | OLF | DA | 0.49 ± 0.02 | 0.40 ± 0.02 |
| | HIP | 5HT | 0.53 ± 0.03 | 0.42 ± 0.03 |
| | SEP | GABA | 576 ± 12 | 521 ± 13 |

*The effects of NC, PR and EX treatment on neurotransmitter concentrations in discrete brain regions are presented alongside of the corresponding brain region-neurotransmitter concentrations of the CR group. Only those changes which were significantly altered ($p<0.05$) by treatment are represented in the Table. Statistical comparisons were made between NC-CR, CR-PR and CR-EX groups.
†Olfactory system (OLF), Hippocampus (HIP), Septal area (SEP), Midbrain Region (MID).
‡Mean ± SEM

decreased concentrations of noradrenaline (NA) in the hippocampus and olfactory system. GABA concentration in the septum was also lowered by CR. Both the EX and PR groups had elevated concentrations of 5-hydroxytryptamine (5HT) in the hippocampus and GABA in the septum. Furthermore PR appeared to lower dopamine (DA) in the mid-brain while EX raised DA and NA in the olfactory system.

## DISCUSSION

The behavioral paradigm which was used in this study was designed so that the underlying neurochemical changes could be evaluated. In this respect, the PR group was initially maintained on a CR schedule so that a basis for comparison with the CR or EX group could be made. The faster running speed normally found with a PR schedule [10] may have been impeded by prior CR, or limited by the capacity of the animal to attain speeds greater than the CR group ("ceiling effect"). The results show a pattern of behavior which is consistent with the expected effects of PR.

The higher concentration of corticosterone and the lower ascorbic acid concentration produced by PR are consistent with the hypothesis that PR involves conditioned frustration [2,10]. Extinction, like PR, should also produce a frustration effect and therefore changes in corticosterone and ascorbic acid would be expected to occur. The lack of any change in corticosterone concentration would suggest that the conflict induced by EX may have been resolved or substantially reduced by the time of killing. The reduction in ascorbic acid in the EX group, although not statistically significant from the CR group, may be indicative of a partial recovery from the long-term effects of stress. The differences in the concentration of corticosterone and ascorbic acid between the NC and CR groups may have arisen from the behavioral condition imposed on the NC group (non-contingent reward) or that imposed on the CR group (contingent reward). The most basic interpretation of NC-CR comparisons is that the difference in ascorbate, corticosterone or neurotransmitter concentration is partly an expression of the difference in contingent and noncontingent reward schedules.

The decrease in NA and GABA associated with CR may represent the underlying process which maintains the behavior, as opposed to those processes which facilitate the acquisition of behavior. This argument would follow from the fact that the time of killing coincided with the maintenance or elaboration, rather than the acquisition of the behavioral response. From this perspective, any deviation in CR behavior might be expected to alter or possibly reverse these effects. The decrease in NA and GABA following CR were reversed by EX. The increase in hippocampal 5HT under EX or PR conditions may have developed in opposition to the decrease in hippocampal NA found with CR.

The hippocampal 5HT concentration appears to be related to the behavioral consequences of both PR and EX. Tye *et al.* [28] have suggested that a "5HT punishment" system is critically involved in the suppression of behavior in conflict situations. Several studies, using a one-trial passive avoidance condition, have found that increased concentration of 5HT in the hippocampus was necessary for appropriate response conditioning [18, 24, 30]. The present study would further suggest that hippocampal 5HT is of importance in nonreward as well as punishment. This would support Gray's [13] assertion that signals of punishment and nonreward are functionally identical and act through the same neurohumoral system. However, the present results do not support the view that an increase in hippocampal 5HT concentration leads to the suppression of behavior. The increased 5HT concentration appears to be a necessary but not sufficient factor in this regard, since the PR group exhibited similar changes in 5HT but did not exhibit response suppression.

One of the factors which distinguishes EX from PR is the rise in NA and DA in the olfactory system. Olfactory bulbectomy has been reported to retard behavior associated with suppression of a prior rewarded behavior [26,27], thereby implicating the involvement of this system in response suppression. The animals' response to punishment or negative reinforcement may be contingent, therefore, on hippocampal 5HT as well as olfactory NA and/or DA. An animal's inability to extinguish an appetitive response following 6-OHDA depletion of forebrain NA has been ascribed to hippocampus NA depletion [20]. But, from the present result, such treatment effects could be reflective of a depletion of NA in the olfactory system.

Changes in midbrain DA concentrations appear to be of significance to the PR effect. Herberg *et al.* [16] have suggested that dopamine plays a motivational role in self-stimulation. Also Ungerstedt [29] have postulated that the ascending dopaminergic pathway mediates nonspecific motivational states. The resistance to extinction found in animals treated with apomorphine [4] and amphetamine [22] illustrates that large changes in reward may have relatively little effect on response strength as long as dopamine and/or noradrenaline drive states are maintained. In the present study, the increase in hippocampal 5HT may reflect changes in reward (as previously discussed) whereas midbrain dopamine may correspond to an increase in drive or motivation. This increase in motivation or drive in the face of variable reward is illustrated by the partial reinforcement effect, i.e., increased runway speed as an effect of variable reward. The study of Alberts *et al.* [1] supports the involvement of dopamine in variable reward schedules by finding that under a variable time schedule in which rats received unequal numbers and quantities of reinforcement, dopamine metabolism was increased. Rats which were under a fixed ratio schedule did not show this effect.

Unlike the catecholamines and 5-hydroxytryptamine, the involvement of GABA in learning, motivation or general behavior is virtually unexplored. The present investigation directly implicates a role for GABA in appetitive behavior, in particular under nonreward conditions. Rats exposed to a nonreward situation in the runway show a characteristic hippocampal theta rhythm at 7.7 Hz [11]. Also drugs which block hippocampal theta activity appear to block the behavioral consequences of nonreward [15]. The septum appears to mediate hippocampal theta under these conditions and septal stimulation will generate theta rhythm in the hippocampus [11,12]. Chlordiazepoxide, which has been suggested to exert its influence on behavior by acting on the GABAergic mechanisms [5], blocks septal generation of theta rhythm as well as the behavioral consequences of nonreward [15,22]. Thus, GABA may exert some influence on hippocampal theta activity and therefore on nonreward behavior by a direct influence on the septum.

In conclusion, changes in the concentration of GABA in the septum and 5-HT in the hippocampus following PR and EX may be attributed to the effects of nonreward conditions. Furthermore, the catecholaminergic-olfactory system may be necessary for appropriate extinction of food-motivated behavior while the midbrain dopaminergic system may func-

tion to maintain drive or motivation under conditions of variable reward. The results of NC and CR treatment may be attributed to noncontingent reinforcements which differ with respect to limbic NA and GABA, and levels of stress or arousal.

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