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Pavlovian autoshaping procedures increase plasma corticosterone levels in rats

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Abstract

Pavlovian autoshaping conditioned responses (CRs) are complex sequences of conditioned stimulus (CS)-directed skeletal-motor responses that are elicited by CS objects predictive of food unconditioned stimulus (US). Autoshaping CRs are observed under conditions known to be conducive to elevations in plasma corticosterone levels, as, for example, in response to the eating of food as well as in response to signals predictive of food. Two experiments investigated the relationships between Pavlovian autoshaping procedures, the performance of Pavlovian autoshaping CRs, and plasma corticosterone levels in male Long–Evans rats. In Experiment 1, rats in the CS–US paired group ($n=30$) were given 20 daily sessions of Pavlovian autoshaping training wherein the insertion of a retractable lever CS was followed by the response-independent presentation of the food US. Tail blood samples obtained after the 20th autoshaping session revealed higher plasma corticosterone levels in the CS–US paired group than in the CS–US random control group ($n=10$). In Experiment 2, rats ($n=35$) were assessed for basal plasma corticosterone levels 2 weeks prior to autoshaping training. Plasma samples obtained immediately following the first autoshaping session, and prior to the acquisition of lever-press autoshaping CR performance, revealed higher plasma corticosterone levels in the CS–US paired group ($n=24$) relative to basal levels. This effect was not observed in the CS–US random control group ($n=11$). Data suggest that corticosterone release is a physiological endocrine Pavlovian CR induced by lever CS–food US pairings during Pavlovian autoshaping procedures, rather than a by-product of autoshaping CR performance. Implications of the link between autoshaping procedures and corticosterone release are discussed.

Keywords: Pavlovian; Autoshaping; Corticosterone; Rats

1. Introduction

In Pavlovian autoshaping procedures, the presentation of a localized visual stimulus (conditioned stimulus, CS) is followed by the response-independent presentation of a rewarding substance (unconditioned stimulus, US). Repeated CS–US pairings lead to the acquisition of the Pavlovian autoshaping conditioned response (CR), which is a complex sequences of skeletal-motor responses that are directed at the CS. For example, studies reporting lever-press autoshaping in rats have employed procedures wherein the brief insertion of a retractable lever CS precedes each response-independent delivery of the food US. In rats that develop the autoshaping CR, the topography includes lever CS-directed approach responses, following by grasping, gnawing, and chewing of the lever CS, typically recorded as Pavlovian lever-press autoshaping CRs (Brown and Jenkins, 1968; Tomie et al., 1989).

Tomie et al. (2000) have reported that lever-press autoshaping CR performance in rats may be related to plasma corticosterone levels. Specifically, rats were subjected to the painful procedures involved in cutting the tail and collecting blood samples, both of which were done immediately prior to their 20th autoshaping session. A second tail blood sample was obtained immediately following the 20th autoshaping session, approximately 40 min after the initial tail-cutting procedures, to assess stress corticosterone levels. Individual rats that exhibited higher frequencies of lever-press autoshaping CRs during the first 10 autoshaping sessions yielded higher stress corticosterone levels following the 20th autoshaping session. While the overall increase in plasma corticosterone levels was attributed to the pain and stress of the presession tail cut, the role of the inter-

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vening 20th autoshaping session remains unclear. It is possible that the intervening autoshaping procedure itself, experienced during the 20th autoshaping session, or alternatively, the intervening expression of autoshaping CRs during Session 20, may also have contributed to the overall increase in plasma corticosterone levels.

It is not surprising that corticosterone release may be related to autoshaping. While corticosterone release has been extensively reported to accompany experience with aversive Pavlovian conditioning procedures, typically as indicated by elevations in corticosterone levels following training with aversive Pavlovian fear-conditioning procedures utilizing shock as US (Coover et al., 1978; Cordero et al., 1998), there is a growing body of evidence suggesting that corticosterone release may also be engendered by appetitive Pavlovian procedures. For example, Anisman and his associates point out that alterations of HPA activity, which traditionally has been associated with stressors, may actually be indicative of arousal per se and, therefore, HPA activity may be influenced by appetitive stimuli such as food (Merali et al., 1998). They report that in response to food intake, as in response to stressors, CRF (corticotrophin-releasing factor), ACTH (adrenocorticotrophic hormone), and corticosterone levels are elevated (Merali et al., 1998), and this is consistent with other investigators who have reported that food consumption itself, as well as other rewarding or appetitive stimuli, may promote glucocorticoid secretion (Piazza and Le Moal, 1996; Piazza et al., 1993).

Corticosterone release may also be triggered by signals predictive of food or the opportunity to engage in feeding behavior. For example, Wallace et al. (1983) reported a significant increase in plasma corticosterone levels under conditions where there was a scheduled delivery of food, but this effect was not observed when the food delivery was nonscheduled, and this is consistent with reports of elevations in corticosterone levels that coincide with the time of the initiation of feeding (Choi et al., 1998; Jhanwar-Uniyal et al., 1986; cf. Hiroshige et al., 1986). Finally, there is evidence that corticosterone release may be conditioned to cues related to diurnal cycles (de Boer and Van der Gugten, 1987; Ottenweller et al., 1987) or to daily lab regimens, such as the placing of the subjects into feeding chambers (Mitchell and Flaherty, 1998). The time of the daily feeding is a reliable signal for food when rats are placed on a strict daily feeding protocol, and increases in corticosterone levels at the time of day of these daily feedings are well documented (Davidson and Stephan, 1999; de Boer and Van der Gugten, 1987; Honma et al., 1986, 1987; Ottenweller et al., 1987; cf. Coover et al., 1977).

In view of the evidence that corticosterone release may be conditioned to stimuli predictive of food, the present studies ask if Pavlovian autoshaping procedures condition corticosterone release in rats. A pseudoconditioning control group, receiving presentations of lever CS and food US randomly with respect to one another, allows for assessment of the degree to which corticosterone release is induced merely by experience with repeated, intermittent presentations of the food US or to repeated intermittent presentations of the lever CS. This is an important consideration, as periodic presentations of the food US may induce motor activity and psychomotor activation (Wise and Rompre, 1989), and intermittent insertions of the lever CS may incite target biting (Tomie et al., 1993). While neither of these effects are derived from the experience of CS–US pairings, psychomotor activation (Kant et al., 1982; Kirby et al., 1997) and aggressive behavior (Haller, 1995; Haller et al., 1995; Peterson et al., 1989) are both associated with increases in corticosterone levels. The pseudoconditioning control estimates effects of nonspecific or nonassociative arousal due to factors other than Pavlovian CS–US pairings, and will serve to clarify the degree to which Pavlovian autoshaping procedures induce corticosterone release beyond that due to pseudoconditioning.

Differences in corticosterone levels between groups receiving autoshaping (CS–US paired) vs. pseudoconditioning (CS–US random) procedures (Experiment 1) may be attributed to the differences in their experiences with the lever CS and food US, or, alternatively to the differences in lever-directed autoshaping CR performance induced by those different procedures. To clarify whether the relationship between autoshaping and corticosterone levels is due to experience with autoshaping procedures per se or to the performance of autoshaping CRs induced by that experience, corticosterone levels are assessed from plasma samples obtained following experience with autoshaping procedures, but prior to the initiation of autoshaping CR performance (Experiment 2).

2. Method

2.1. Animals

Seventy-five adult male Long–Evans (Blue Spruce strain) rats obtained from Harlan Sprague–Dawley (Almont, NY) weighing approximately 300 g at the beginning of the study were used. The rats in Experiment 1 were divided into two groups, paired ($n=30$) and random ($n=10$). The rats in Experiment 2 were divided into two groups, paired ($n=24$) and random ($n=11$). All rats were housed individually in suspended steel cages in a colony room with a 12 L:12 D (on 0200 h) cycle. Rats had continuous access to water in their home cages and were maintained at 80% of their free-feeding body weights by providing supplemental rat chow after each daily session, as needed. Principles of laboratory animal care (ILAR Guide for the Care and Use of Laboratory Animals) were followed.

2.2. Apparatus

For both experiments, autoshaping chambers were four Plexiglas cubicles ($23\times23\times21$ cm) for rats, with stainless-

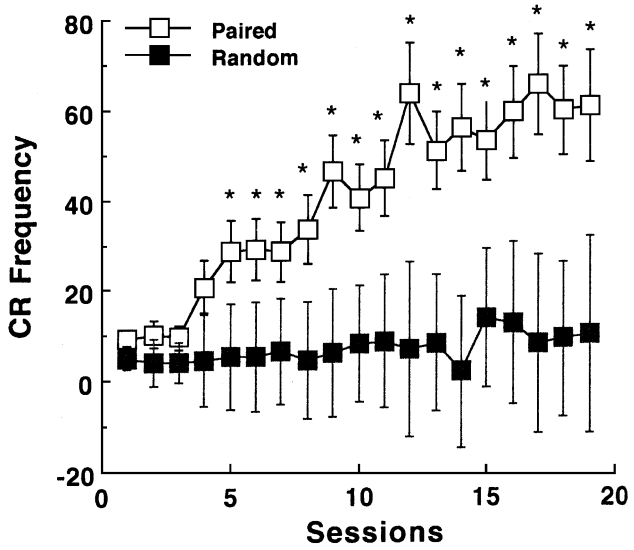

Fig. 1. Mean number of lever-press autoshaping CRs as a function of 19 daily autoshaping sessions for rats in the paired ($n=30$) and random ($n=10$) groups. Vertical bars indicate the standard errors of the means (S.E.M.) for each daily session. Asterisks (*) indicate significant group differences on the given session (Fisher's LSD, $P<.05$).

steel grid-floors, enclosed in sound-attenuating, ventilated outer casings. One house light (GE 1821, 28 v DC, 0.17 A, 3.5 MSCP, 44 luminance) was mounted directly above the operant chamber, on the ceiling of the outer hull. The front panel of each chamber was equipped with a retractable lever (BRS/LVE #RRL/005), mounted 8.5 cm above the floor and 7 cm off to the left side of the centerline. A food receptacle was mounted on the centerline of the front panel, 3 cm above the floor. Operation of a PDC/PPD pellet dispenser delivered 45 mg food pellets (BioServ, Frenchtown, NJ) into the food receptacle. Masking noise (88 dB, linear scale) was provided by the operation of ventilating exhaust fans mounted on the outer hull. Session events and data collection were controlled by an IBM PC.

2.3. Autoshaping procedures

In Experiment 1, rats were run 5–6 days per week between 0900 and 1200 h (during the light cycle) and received a total of 20 daily sessions of autoshaping. Prior to each autoshaping session, rats were weighed, and then immediately placed in the autoshaping chamber. In the paired procedure, each autoshaping trial consisted of the insertion of the stainless-steel lever, the CS, into the chamber for 5 s. Withdrawal of the lever was followed immediately by the response-independent operation of the pellet dispenser for 0.70 s, resulting in the delivery of one 45-mg food pellet, the US. Each autoshaping session consisted of 25 autoshaping trials wherein the lever CS and the food pellet US were presented in a paired fashion. The random procedure was similar except the lever CS and the food US were presented independent of each other. The rat's response to the lever (gnawing, chewing, pressing) had no effect on the food reward delivery. The mean interval separating trials was 60 s, with a minimum intertrial interval of 45 s and a maximum intertrial interval of 75 s. The session duration was approximately 30 min. The total number of lever-press responses for each subject was recorded on each trial. Immediately following the 20th autoshaping session, rats were sacrificed by rapid decapitation. A trunk blood sample was obtained during sacrifice to determine postsession levels of corticosterone.

For Experiment 2, rats received only 10 sessions of training with the paired or random autoshaping procedures, which were identical to those described in Experiment 1. Approximately 2 weeks prior to the first autoshaping session, and after the animals had been habituated to the colony room for approximately 3 weeks, tail blood was collected to determine basal levels of corticosterone. To obtain the tail blood sample, the rat was manually restrained and a scalpel was used to remove the last 5–10 mm of the tail tip, then 100 μl of tail blood were collected. For all rats, latency to collect the tail blood samples was 1–2 min. In addition, for all rats in Experiment 2, immediately following the first autoshaping session, a 100-μl sample of tail blood was collected to assess the levels of corticosterone.

2.4. Corticosterone assay

Blood samples for corticosterone assay were collected in heparinized tubes. Plasma, obtained after centrifugation, was stored at −20 °C until assay. Plasma corticosterone was measured by radioimmunoassay (RIA kit, ICN Biomedicals, Los Angeles, CA) using a tritium label for corticosterone and a highly specific corticosterone antiserum with a detection threshold of 0.1 μg/100 ml.

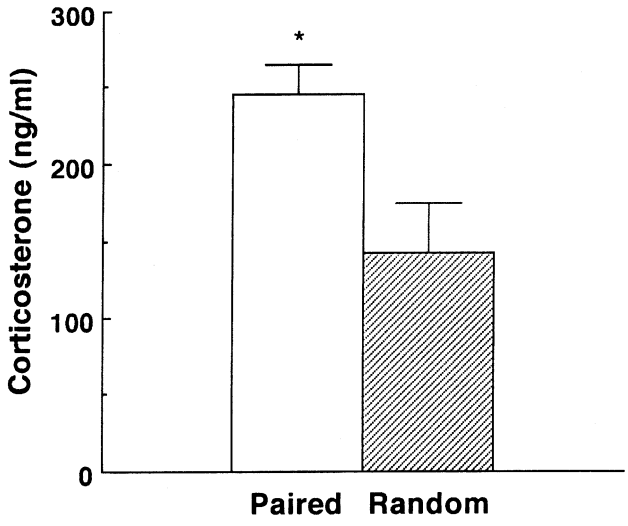

Fig. 2. Mean corticosterone levels (ng/ml) from trunk blood samples taken immediately following the 20th autoshaping session for rats in the paired ($n=30$) and random ($n=10$) groups. Vertical bars indicate the S.E.M.s. The asterisk (*) indicates a significant group difference ($P<.05$).

2.5. Statistical analyses

For each subject, for each session, the total number of lever-press CRs was derived (CR Frequency). Effect of groups (paired vs. random) on mean lever-press frequency during autoshaping sessions were assessed by two-way repeated-measures multivariate analysis of variance using MANOVA (SYSTAT). Fisher's LSD provided pairwise comparisons on individual sessions ($\alpha = .05$). Effects of groups on mean levels of corticosterone were assessed by one-way analysis of variance (ANOVA) (SYSTAT). Effects of corticosterone sample (basal vs. Day 1) on mean levels of corticosterone were assessed for each group by one-way ANOVA (SYSTAT). Correlations between an individual subject's autoshaping CR performance and corticosterone levels were assessed by step-wise multiple regression techniques (SYSTAT).

3. Results

3.1. Experiment 1

3.1.1. Lever-press autoshaping

Two-way MANOVA of CR frequency during Autoshaping Sessions 1–19 revealed a significant main effect of groups (paired vs. random) [$F(1,38) = 8.64$, $P < .01$], a significant main effect of sessions [$F(18,684) = 2.92$, $P < .01$], and a significant Sessions×Groups interaction effect [$F(18,684) = 2.02$, $P < .01$]. Fisher's LSD revealed that groups differed significantly on Sessions 5–19 (Fig. 1).

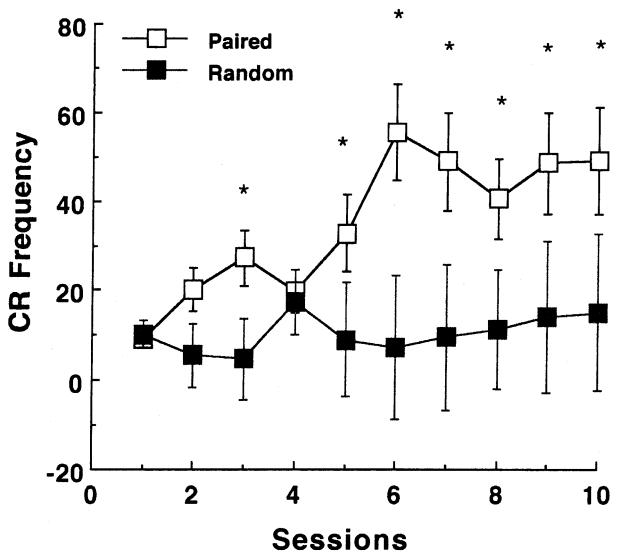

Fig. 3. Mean number of lever-press autoshaping CRs as a function of 10 daily autoshaping sessions for rats in the paired ($n = 24$) and random ($n = 11$) groups. Vertical bars indicate the S.E.M.s. Asterisks (*) indicate significant group differences on the given session (Fisher's LSD, $P < .05$).

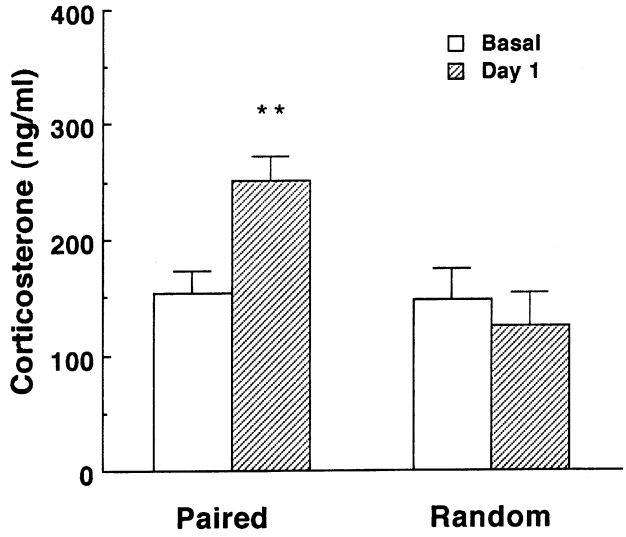

Fig. 4. Mean basal and Day 1 postsession corticosterone levels (ng/ml) for rats in the paired ($n = 24$) and random ($n = 11$) groups. Vertical bars indicate the S.E.M.s. The double asterisks (**) indicate a significant difference between basal and Day 1 postsession corticosterone levels for the paired group ($P < .01$).

3.1.2. Corticosterone

One-way ANOVA of mean corticosterone levels (CORT) in plasma samples obtained after Autoshaping Session 20 for groups (paired vs. random) revealed a significant effect of groups [$F(1,38) = 7.44$, $P < .05$] (Fig. 2). There were no correlations between an individual subject's autoshaping performance and corticosterone levels in either the paired or the random groups, all P's $> .10$.

3.2. Experiment 2

3.2.1. Lever-press autoshaping

Two-way MANOVA of CR Frequency during Autoshaping Sessions 1–10 revealed a significant main effect of groups (paired vs. random) [$F(1,33) = 4.98$, $P < .05$], a significant main effect of sessions [$F(9,297) = 2.12$, $P < .05$], and a significant Sessions×Group interaction effect [$F(9,297) = 1.91$, $P < .05$]. Fisher's LSD revealed that the paired group was significantly higher than the random group on Session 3 and sessions 5–10 (Fig. 3).

3.2.2. Corticosterone

One-way ANOVA of mean basal and mean Day 1 corticosterone levels (CORT) for the paired group revealed a significant main effect of CORT (basal vs. Day 1) [$F(1,23) = 14.16$, $P < .01$]. This same analysis revealed no significant main effect of CORT for the random group [$F(1,11) < 1$] (Fig. 4).

4. Discussion

In both experiments, repeated paired presentations of lever CS and food US yielded reliable acquisition and asymptotic

maintenance of Pavlovian lever-press autoshaping CR performance in the paired groups. Acquisition of autoshaping CRs in the paired groups was revealed by systematic increases in mean lever-press CR frequency as a function of sessions of experience with lever CS–food US pairings. The random control groups, on the other hand, showed no evidence of systematic changes in mean lever-press frequency as a function of experience with random presentations of lever CS and food US, suggesting that the increasing and higher frequencies of lever-pressing observed in the paired groups cannot be attributed to pseudoconditioning.

In Experiment 1, plasma samples obtained after the 20th autoshaping session revealed that corticosterone levels were significantly higher in the paired group relative to therandom group. This effect cannot be attributed to experience with either food US presentations per se or to experience with lever CS insertions per se, as both groups received the same number of food US and lever CS presentations during Session 20 and during Sessions 1–20. In addition, group differences in corticosterone levels cannot be attributed to the entrainment of diurnal cycles based on the daily routine of the running of training sessions or to the possible signaling properties of the autoshaping context (Tomie, 1976a,b), as these aspects of training were not varied between groups. These group differences in plasma corticosterone levels can only be attributed to the intrasession signaling relationship between the lever CS and the food US, and these data, therefore, imply that corticosterone release may be a physiological endocrine Pavlovian CR engendered by experience with Pavlovian autoshaping procedures.

In the paired group, there was no evidence of a relationship between an individual rat's lever-press autoshaping CR performance and that rat's postsession levels of corticosterone, even though between-subjects variability in both measures was considerable. While this seemingly contrasts with results obtained in a previous study (Tomie et al., 2000), there are important differences in procedures between studies. The positive correlation between autoshaping CR performance and corticosterone levels, reported in the earlier study, was observed in rats that provided plasma corticosterone samples before and after the 20th autoshaping session, while in the present study, there were no tail cuts given prior to the 20th autoshaping session. The tail cuts preceding the 20th autoshaping session that were given in the earlier study were presumably painful and stressful, and likely contributed to the release of corticosterone (Tomie et al., 2000). The data from Experiment 1 are consistent with this interpretation, as they show that in the absence of corticosterone release induced by the tail-cut procedures, individual differences in autoshaping CR performance and postsession corticosterone levels were unrelated to one another.

In Experiment 2, basal corticosterone levels, determined from plasma samples obtained 2 weeks prior to the first autoshaping session, provided a baseline from which changes in corticosterone levels could be evaluated. Comparing basal corticosterone levels to those obtained following the first autoshaping session revealed that there was a significant increase in corticosterone levels in the paired group, while corticosterone levels for the random group did not change from basal levels. As noted previously, this effect cannot be attributed to experience with food US presentations or to experience with lever CS insertions, as these aspects of training were not varied between groups. The observed changes within the paired group in plasma corticosterone levels can only be attributed to the signaling of the food US by the lever CS, implying, as noted previously, that corticosterone release is conditioned by experience with Pavlovian autoshaping procedures.

It is important to note that in Experiment 2, the change in corticosterone levels in the paired group is not due to group differences in lever-pressing performance. During the first session, the paired and random groups provided comparably low levels of lever-pressing, suggesting that autoshaping CRs had not yet been acquired; yet, only for the paired group did postsession corticosterone levels differ from basal corticosterone levels. The corticosterone elevation observed in the paired group, therefore, cannot be due to the performance of autoshaping CRs, and can only be attributed to the experience of Pavlovian autoshaping procedures per se. It is important to note that only a single autoshaping session, consisting of 25 pairings of lever CS and food US, was sufficient to reliably induce release of corticosterone, and this is fewer autoshaping trials than that required to engender levels of lever-pressing beyond that due to pseudoconditioning.

The data from these two studies support the conclusion that corticosterone release may be a by-product of arousal that is not necessarily indicative of fear (Merali et al., 1998). These data add to the existing literature that report the induction of corticosterone release by food rewards (Piazza and Le Moal, 1996; Piazza et al., 1993) or by entrainment with regularly and predictably scheduled deliveries of food (Davidson and Stephan, 1999; Honma et al., 1986, 1987; Mitchell and Flaherty, 1998; Ottenweller et al., 1987; Wallace et al., 1983). These data broaden the range of situations in which the food-induced release of corticosterone is reported, extending this effect, for the first time, to the Pavlovian autoshaping procedure. In this regard, the release of corticosterone appears to be a physiological endocrine Pavlovian CR, the acquisition of which requires fewer lever CS–food US pairings than is required to engender the expression of the skeletal-motor autoshaping CR performance in rats.

The neurobiological basis of the relationship between autoshaping and corticosterone has yet to be explored. Data on the effects of adrenalectomy or metyraprone-induced suppression of corticosterone synthesis on autoshaping are not available. Furthermore, there are no studies in the literature reporting the effects of blocking corticosterone's access to glucocorticoid receptors by the administration of GR antagonists, such as RU 38486 or RU 40555. The effects of applying these variables, either before or after experience

with autoshaping procedures and before or after the emergence of the performance of autoshaping CRs, would serve to clarify the interrelationships between autoshaping and corticosterone release.

One possible mechanism of the interrelationship between corticosterone and autoshaping may be based on corticosterone's effects on memory consolidation. Corticosterone is well known to facilitate postsession memory consolidation in animals exposed to learning tasks (Cahill and McGaugh, 1998). McGaugh and his associates have noted that following experience with a learning task, postsession corticosterone levels are associated with improved retention and this effect may be mediated by glucocorticoid receptors in the amygdala, which serve to enhance memory consolidation (Roozendaal et al., 1997). While the memory-enhancing effects of postsession corticosterone elevations have not been reported in studies of autoshaping, it is notable that the role of corticosterone in memory consolidation has been particularly well documented in studies of spatial orientation learning and these tasks share in common with autoshaping several salient features, namely the directedness of skeletal-motor performance in a spatial navigation task. These commonalities, in conjunction with the present data, suggest that autoshaping procedures may be well suited for studying the effects of corticosterone on memory consolidation processes.

These data reveal that autoshaping procedures induce the release of corticosterone prior to the initiation of autoshaping CRs; therefore, it is conceivable that corticosterone release may serve to mediate the subsequent expression of autoshaping CRs. This is of particular interest because corticosterone release appears to activate mesolimbic dopamine neurons (Piazza and Le Moal, 1996), and autoshaping is positively correlated with elevations of tissue levels of dopamine and DOPAC in the nucleus accumbens (Tomie et al., 2000). This pattern of results suggests that corticosterone release may activate mesolimbic dopamine neurotransmission producing psychomotor activation (Robinson and Berridge, 1993; Wise and Bozarth, 1987) as well as the facilitation of the expression of autoshaping CRs. The possibility that corticosterone release may contribute to autoshaping CR expression as well as to vulnerability to drug abuse adds to the growing list of common features shared by both (Tomie, 1995, 1996, 2001).

Acknowledgments

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