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Longevity of the Expression of Behavioral Sensitization to Cocaine in Preweanling Rats

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SNYDER, K. J., N. M. KATOVIC AND L. P. SPEAR. *Longevity of the expression of behavioral sensitization to cocaine in preweanling rats.* PHARMACOL BIOCHEM BEHAV **60**(4) 909–914, 1998.—The influence of the treatment-to-test interval on the expression of behavioral sensitization to cocaine was assessed following chronic cocaine exposure during the late preweanling period. From postnatal day 14 (P14) to P20, Sprague–Dawley rat pups received a daily intraperitoneal injection of either 30 mg/kg/2 cc cocaine or an equivalent volume of saline that was paired with placement in the treatment/test context for 30 min. Animals were challenged with 15 mg/kg cocaine in this context on the test day following drug-free intervals of 1, 3, 7, 14, or 21 days. Behavioral sensitization was evident following the preweanling cocaine regimen in terms of both matrix crossings and stereotypy. For matrix crossings, there was no evidence that this sensitization decreased across the time intervals examined, and sensitization was evident with stereotypy even at the 21-day injection–test interval. The expression of sensitization, however, was partially overshadowed by an overall reduced sensitivity to cocaine seen in testing during the periadolescent period (i.e., at P34 and P41). Thus, behavioral sensitization to cocaine can be expressed for weeks following chronic treatment during the late preweanling period, although the magnitude of behavioral expression may be influenced by age-related neurobehavioral alterations. © 1998 Elsevier Science Inc.

Cocaine Behavioral sensitization Ontogeny Preweanling Periadolescence Treatment-to-test interval

BEHAVIORAL sensitization, defined as a progressive increase in the behavioral response to repeated drug administration, is commonly observed following chronic administration of psychomotor stimulants to adult animals [e.g., (36)]. However, little evidence of behavioral sensitization has been found following chronic intermittent administration of psychomotor stimulants such as cocaine (5,6,33), methamphetamine (15,32), or amphetamine (15) to rat pups during the preweanling period. In these experiments long intervals of weeks to months were typically interpolated between treatment and test (15,32,33), with shorter treatment-to-test intervals occasionally being used for pups that were stimulant exposed during the first 7–10 postnatal days (5,6).

However, in a few instances, sensitization has been reported in preweanling animals following repeated administration of amphetamine (8,19) or cocaine (31,38). These studies differ from previous negative reports of sensitization in at least two potentially important ways. First the chronic drug administration was explicitly paired with a novel environment that would later serve as the test environment, whereas all other work examining the ontogeny of stimulant sensitization either stated that animals received their injections in the home cage or did not specify injection location. Second, in these studies, animals were tested for sensitization 1 or 2 days following the chronic exposure period rather than after longer treatment-to-test intervals as used in much of the other research in this area.

The pairing of the chronic stimulant exposure with a novel testing situation may have been critical in facilitating the early ontogenetic expression of sensitization (8,19). It has been well established that pairing drug injections with the novel context where testing will later occur facilitates sensitization, presumably at least in part via Pavlovian conditioning with the novel context serving as a conditioned stimulus (30). Indeed, Wood et al. (38) observed that expression of behavioral sensitization to cocaine was context dependent during the preweanling period. In that study, significant sensitization of cocaine-induced stereotypy was seen in rat pups that received their chronic co-

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caine injections in the test chamber, but not in pups receiving cocaine chronically in the home cage.

In the work by Wood et al. (38), animals were tested 1 day after the chronic treatment period; the short treatment-to-test interval may have facilitated the expression of sensitization in that study. Indeed, McDougall et al. (19) found sensitization to be evident in animals tested 2, but not 8 days, following chronic amphetamine treatment from 11–14 or 17–20 days of age, and concluded that the mechanisms for animals to express short- but not long-term sensitization are in place in preweanling animals. Treatment-to-test intervals have been shown to influence the amount of sensitized response in adulthood (1) and might have been long enough in much of the prior developmental work to obscure expression of sensitization following drug exposure during the preweanling period.

The purpose of the present study was to examine the influence of the treatment-to-test interval on the expression of behavioral sensitization after chronic exposure to cocaine during the late preweanling period. Following a 7-day chronic exposure period that ended on postnatal 20, animals were tested following drug-free intervals of 1, 3, 7, 14, or 21 days [i.e., at postnatal days (P) 21, 23, 27, 34, and 41] to determine the longevity of cocaine sensitization induced in preweanlings. The expression of sensitization on test day was promoted by pairing the daily chronic injections with the novel context in which testing would later be conducted [see (38)]. Both stereotyped behavior and locomotor activity were used to index cocaine sensitization given that both of these drug-induced behaviors have been reported to sensitize to psychomotor stimulants in adulthood [e.g., (36)] as well as during development (19).

METHOD

Subjects

A total of 183 pups aged P14 at the onset of the experiment were used as subjects. Four animals succumbed during the chronic treatment period (two males chronically treated with cocaine, one cocaine-treated female, and one saline-treated female), leaving a final sample size of 179 animals. The rats were derived from established Charles River (Wilmington, MA) VAF Sprague–Dawley breeding pairs in our colony room. The colony room was maintained under a 12 L:12 D cycle with the lights on at 0700 h. Litters were considered to be 0 days old on the day of birth, and were culled to 8–10 pups (equating gender as much as possible) on the day after birth; litters containing less than eight pups were not used. Animals were weaned on P20, housed in groups of two to three same-sexed littermates, and given ad lib access to food and water throughout the experiment.

Apparatus

Ten individual experimental chambers were used as the treatment and test chambers. The floors of the tanks ($13 \times 16 \times 19$ cm) were marked with thin black adhesive tape into six 7.5×5 cm squares. A removable transparent acrylic plate, provided with several holes for air circulation, served as the lid. The tanks were placed on individual heating pads on a large table in a sound-attenuated room used for treatment and testing. The room was illuminated by fluorescent light and kept at the same ambient temperature as the colony room (approximately 21°C). Due to the slow development of homeothermia, the ambient temperature of the treatment/test chamber of pups at younger ages (P14–P23) was maintained at approximately 28 ± 2°C through the use of heating pads. Between successive sessions, the chambers were cleaned with 70% ethanol solution and allowed to dry thoroughly.

Experimental Design

The design of the experiment was a 2 (chronic treatment: saline vs. cocaine) $\times$ 5 (test interval since last chronic injection: 1, 3, 7, 14, or 21 days) factorial. To minimize contamination of results by litter variance, all 10 experimental groups were represented whenever possible within a litter, with no more than one subject in a given litter being assigned to any treatment/test group. Both genders were examined, with all pups of one sex from a given litter receiving cocaine injections and the opposite sex receiving saline, and gender assignments to the chronic treatments being alternated between litters. In cases where the gender distribution of a litter was such that there were not five pups of each gender to distribute to the five test interval conditions, fewer than 10 pups were tested for that litter. Eight to nine pups per gender were examined within each of the 10 experimental groups.

Procedures

Chronic treatment. Beginning on P14, the pups were weighed, marked for identification, and carried in a breeder tub into the testing room. The animals were then placed individually into the treatment/test chambers and left for a preinjection period of 5 min. After the preinjection period, the animals were injected intraperitoneally (IP) with a 30 mg/kg/2 cc dose of a freshly prepared solution of cocaine HCl or an equivalent volume of the vehicle, 0.9% saline. After injection, the pups were placed back into their respective treatment/test chambers for 30 min and then reunited with their littermates and returned to the home nest. This chronic treatment procedure was repeated once daily through P20. All chronic treatments and testing were conducted between 1100 and 1300 h.

Testing. Each animal was tested only once at either 1, 3, 7, 14, or 21 days following the last chronic injection of cocaine or saline (i.e., on P21, P23, P27, P34, or P41, respectively). For testing, pups were placed individually into the same treatment/test chambers as used during the chronic exposure phase. Groups of up to four pups were examined at a time, with the individual test chambers arranged across the table so that the pups could all be viewed easily by the observers. Pups were placed in the test chambers for a 5-min preinjection period, during which their behavior was scored using the procedures outlined below. All pups were then injected IP with a challenge dose of 15 mg/kg/2 cc of cocaine HCl and immediately returned to their test chambers where their behavior was scored for 30 min. Data collected during the postinjection period were divided for analysis into six blocks of 5 min each.

Behavioral scoring was conducted by two trained observers who were blind to the treatment that the pups had received; within- and between-observer reliabilities using this scoring protocol ranged between 0.82 and 0.89. The animals were scored for two types of behavior, matrix crossings and stereotypy (head bobbing and scanning), with each observer scoring one behavior for squads of four test pups at a time. Stereotypy was defined as repetitive movements of the head, either up or down, directed toward one wall or corner of the chamber, or side-to-side motions in which the nose usually contacted the floor (20). Stereotypy was scored using a fixed-interval instantaneous sampling technique (18), employing a timing schedule that uses a large stopwatch [see Wood et al. (38), for a recent example of the use of this procedure in our laboratory]. Briefly, each of the four pups was observed over

a series of 15-s samples interspersed by periods of 45 s, during which the remaining test animals were examined. Each 15-s sampling period was divided into five intervals of 3 s each; the first second of each interval, the observer noted whether or not stereotypy was occurring. The total number of intervals during which stereotypy was observed was tallied over each 5-min test block, with a maximum possible score of 25 during each 5-min block (five intervals per 15-s time sample/min × 5 min).

Matrix crossings were recorded continuously within the 15-s samples for each animal. Matrix crossings was defined as displacement of the rear end of the body over the marked lines of the floor of the test chamber, with the number of lines crossed by an animal being tallied during each 15-s sampling period.

Statistical Analysis

To assess potential age and conditioning effects on baseline locomotor activity, matrix crossing data during the 5-min preinjection period were analyzed via a 2 (sex) × 2 (chronic treatment) × 5 (test interval) analysis of variance (ANOVA). Given that there was a significant effect of chronic treatment in this analysis (see below), these baseline data were included as a covariate in the analysis of the postinjection matrix crossing data using a 2 (sex) × 2 (chronic treatment) × 5 (test interval) × 6 (5-min time blocks) repeated measures analysis of covariance (ANCOVA). The stereotypy data were analyzed similarly, except that no stereotypy was exhibited during the preinjection time period and, hence, was not included as a covariate when analyzing the postinjection data. Body weight data during the chronic treatment period were analyzed by a 2 (sex) × 2 (chronic treatment) × 7 (day) repeated measures ANOVA, with body weights on the test day being analyzed by a 2 (sex), × 2 (chronic treatment) × 5 (test interval) ANOVA. All significant main effects and interactions in the ANOVAs are presented, and were further investigated by Tukey's HSD post hoc tests, with probabilities of $p \leq 0.05$ being considered significant in all instances.

RESULTS

Matrix Crossings

Analysis of the baseline matrix crossing data revealed a significant main effect of chronic treatment, $F(1, 159) = 4.50$, $p < 0.05$, with no significant main effects or interactions involving test interval. Although baseline levels of activity were low during the preinjection period in all the groups, animals that had been previously exposed to cocaine crossed slightly but significantly fewer matrices (3.14 ± 0.35) than animals chronically treated with saline (4.44 ± 0.47).

When the postinjection matrix crossing data were analyzed using the baseline data as a covariate, significant main effects of chronic treatment, $F(1, 158) = 18.76$, $p < 0.001$, test interval, $F(4, 158) = 7.21$, $p < 0.001$, and time block, $F(5, 795) =$

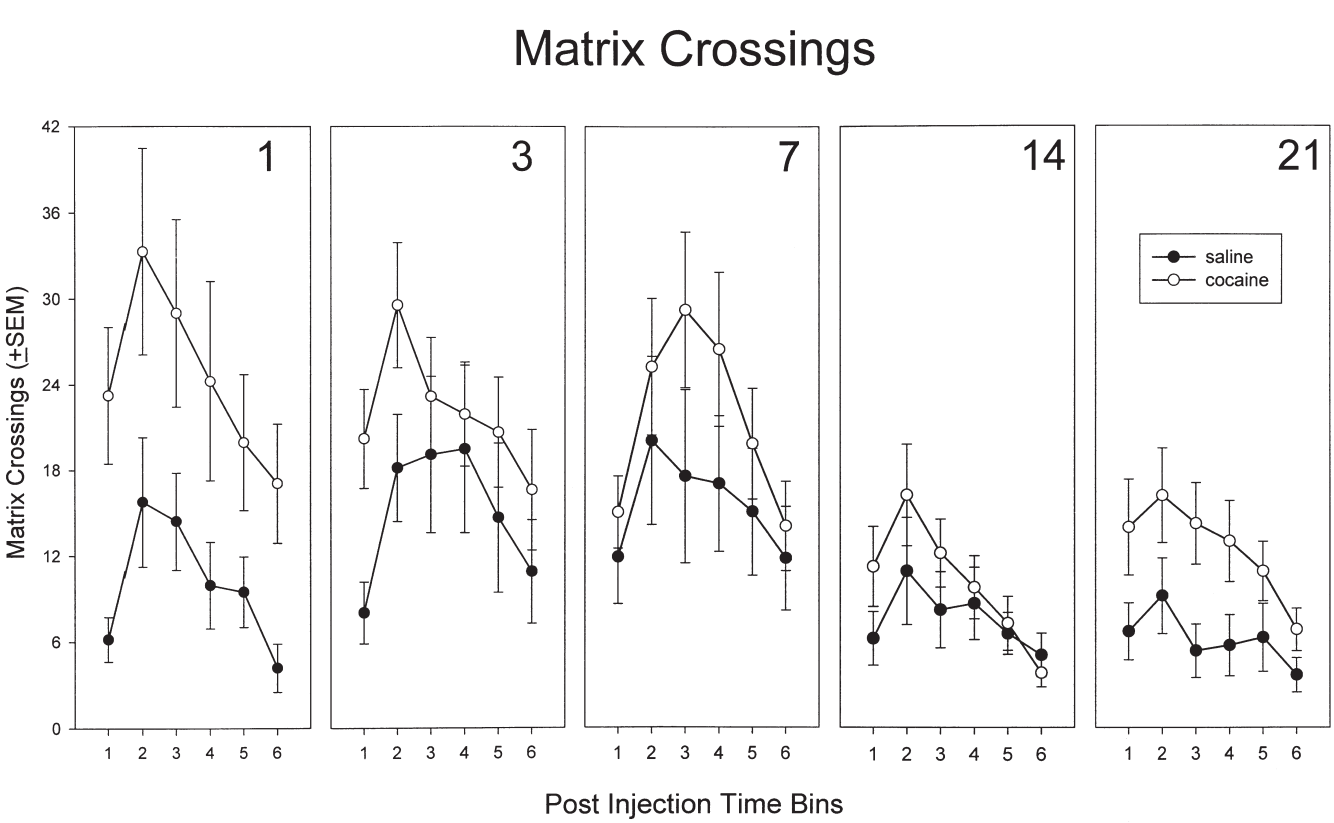

FIG. 1. Mean number of matrix crossings following challenge with 15 mg/kg cocaine on the test day by animals treated chronically with 30 mg/kg cocaine or saline from postnatal days 14–20 and tested after treatment-to-test intervals of 1, 3, 7, 14, or 21 days. Data represented are unweighted means. Error bars reflect SEMs.

25.94, $p < 0.001$, were obtained. There were no significant interactions involving any of these variables in the ANCOVA; of particular interest, the chronic treatment × test interval interaction did not reach significance, $F(4, 158) = 1.69, p < 0.16$. Thus, while animals receiving cocaine chronically exhibited more matrix crossings following cocaine challenge than animals chronically treated with saline, there was no evidence that this sensitization varied significantly with the treatment-to-test interval. Post hoc analyses on data collapsed over chronic treatment and time block to determine the locus of the test interval main effect revealed that more cocaine-induced matrix crossings were seen at test intervals of 1, 3, and 7 days (i.e., P21, P23, and P27) than at the 14 day test interval (P34), with more matrix crossing also being evident at 3 and 7 days (P23 and P27) than at the 21 day test interval (P41) (see Fig. 1). Post hoc analyses on data collapsed over test interval and chronic treatment to examine the main effect of time block revealed that matrix crossings peaked during the second postinjection time block and decreased gradually thereafter.

Stereotypy

The ANOVA of the stereotypy data revealed main effects of chronic treatment, $F(1, 159) = 97.37, p < 0.001$, and time block, $F(5, 795) = 28.81, p < 0.001$, along with a significant interaction of these two variables, $F(5, 795) = 9.19, p < 0.001$. Tukey's tests revealed that animals chronically treated with cocaine exhibited significantly more stereotypy than animals chronically treated with saline at all postinjection time blocks, with a significant peak in stereotypy appearing at time block 2 and gradually decreasing thereafter. There was also a significant main effect of test interval, $F(4, 159) = 4.25, p < 0.005$, and a test interval × time block interaction, $F(20, 795) = 1.64$, $p < 0.05$, with animals tested at 1, 3, and 7 days posttreatment generally exhibiting significantly more stereotypy than those tested at 14 days and exhibiting more stereotypy than animals tested at the 21 day test interval during the time of peak stereotypy (see Fig. 2). The chronic treatment × test interval interaction approached significance, $F(4, 159) = 2.25, p < 0.066$; because of the potential importance of this interaction for tempering conclusions drawn in the present investigation, this trend was further explored by Tukey's tests. These tests revealed that animals chronically treated with cocaine exhibited significantly more stereotypy following the cocaine challenge than chronic saline-treated animals at all the test intervals except 14 days.

Body Weights

The analysis of body weights during the chronic treatment period revealed a significant main effect of day, $F(6, 1050) = 1215.53, p < 0.001$, along with significant interactions of chronic treatment × day, $F(6, 1050) = 6.68, p < 0.001$, and chronic treatment × sex × day, $F(6, 1050) = 18.60, p < 0.001$. Tukey's tests indicated that males chronically treated with cocaine weighed less than their saline-treated counterparts on

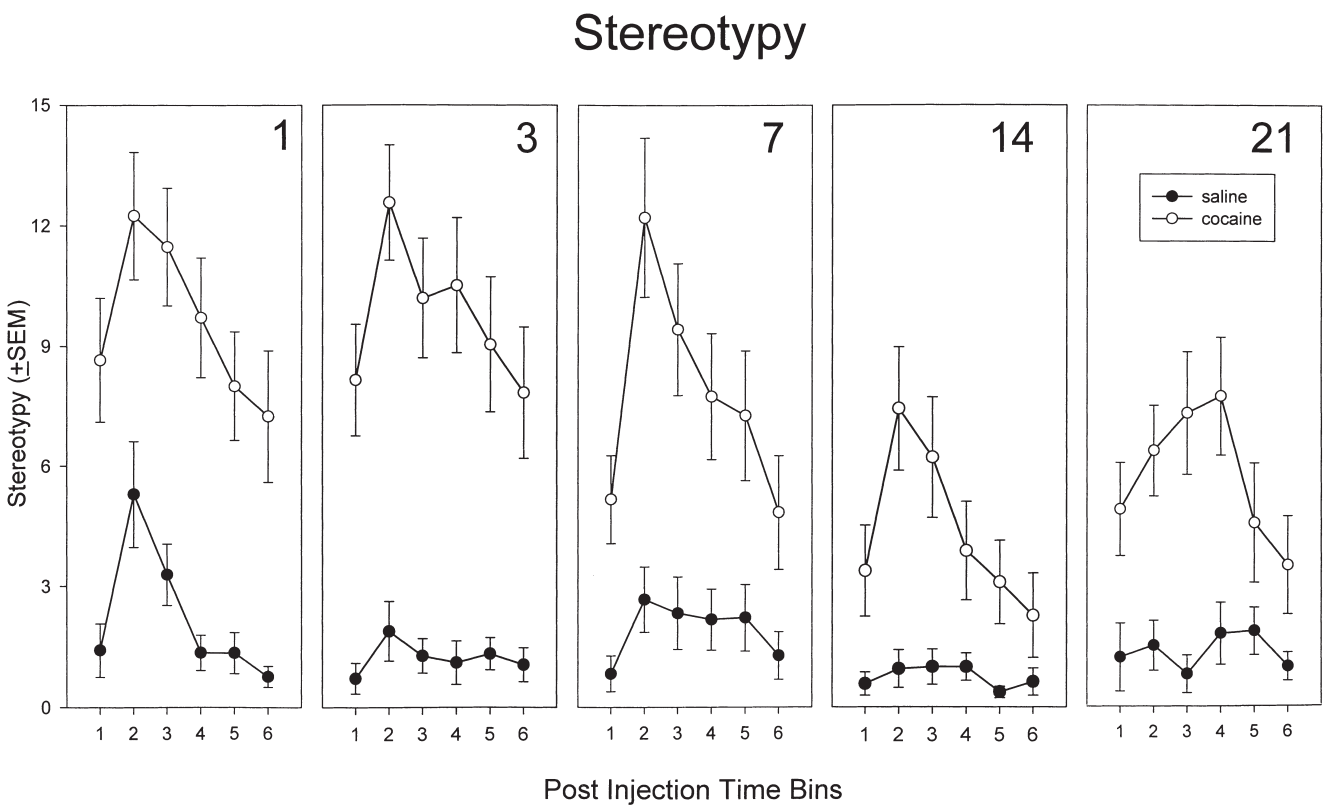

FIG. 2. Mean amount of stereotypy following challenge with 15 mg/kg cocaine on the test day by animals treated chronically with 30 mg/kg cocaine or saline from postnatal days 14–20 and tested after treatment-to-test intervals of 1,3,7,14 or 21 days. Error bars reflect SEMs.

postnatal days 17–20 during the chronic treatment period. This difference was not evident in females, and may be spurious in that no chronic treatment effects were revealed in the ANOVA of body weights on the test day. This test day ANOVA revealed only significant main effects of sex, $F(1, 159) = 22.48$, $p < 0.001$, and test interval, $F(4, 159) = 480.73$, $p < 0.001$, along with a significant interaction of these two variables, $F(4, 159) = 7.80$, $p < 0.001$. Body weights increased as the animals were tested at progressively older ages, with males weighing significantly more than females by the last test interval (i.e., at P41).

DISCUSSION

Long-lasting behavioral sensitization was observed following chronic cocaine exposure during the late preweanling period, with this sensitization expressed in terms of increases in both stereotypy and locomotion. No statistical evidence was obtained for a decrease in the expression of locomotor sensitization across the time intervals examined, and sensitization of cocaine-induced stereotypy was evident even at the 21 day injection–test interval. These data were partially overshadowed, however, by a general age-related attenuation in responsiveness to cocaine at the later test ages.

Analysis of the matrix crossing data revealed that chronic cocaine-treated animals crossed more matrices when challenged with cocaine on the test day than animals chronically treated with saline. There was no statistical evidence that this sensitization varied with the treatment-to-test interval, although regardless of chronic treatment condition animals exhibited significantly more matrix crossing when challenged with cocaine after drug-free intervals of 1–7 days (i.e., at P21, P23, and P27) than after 14 or 21 days (i.e., at P34 and P41) (see Fig. 1). Similar findings were obtained when examining cocaine-induced stereotypy, with significant sensitization of stereotypy being seen regardless of test interval (although this sensitization was not convincing at the 14 day treatment-to-test interval). Regardless of pretreatment condition, cocaine-induced stereotypy was more pronounced after shorter treatment-to-test intervals (P21, P23, and P27) than after 14 or 21 drug-free days (i.e., P34 and P41).

This expression of behavioral sensitization for up to 3 weeks following chronic preweanling drug exposure contrasts with the findings of McDougall and colleagues (19). They reported behavioral sensitization 2, but not 8 days following four daily injections of amphetamine or the DA D_1/D_2 agonist R-propylnorapomorphine during the late preweanling period. They did, however, observe a trend for animals chronically treated beginning at P17, but not P11, to exhibit sensitization after the 8-day treatment-to-test interval, which they suggested might indicate "that the mechanisms responsible for long-term behavioral sensitization were beginning to mature by 17 days of age" [(19), p. 488]. Development and maintenance of sensitization involve a series of time-dependent adaptations occurring successively in different brain regions [e.g., (13,37)]. The development and expression of this sensitization depends on drug potency, dose, timing, and duration of treatment (21,23); differences along these dimensions may have contributed to the disparity in findings between McDougall et al. (19) and the present study. However, together these two sets of findings do support the suggestion that mechanisms responsible for initiating and expressing long-term behavioral sensitization begin to emerge during the late preweanling period, at least when (as in these two studies) the drug is chronically paired with the test context. Indeed, the similarity of the cues presented during the chronic treatment and test phases may well have been critical for the expression of long-term sensitization in the present study, with others reporting little evidence of sensitization in studies where preweanlings did not receive the chronic injections paired with the test environment (15,32,33,38).

The analysis of matrix crossing during the preinjection period revealed that, regardless of the treatment-to-test interval, animals chronically treated with cocaine locomoted slightly but significantly less than animals chronically treated with saline. There are two possible explanations of these data. First, the chronic cocaine exposure regimen may have altered the developmental expression of locomotion, reminiscent of other reports of either hypoactivity (35,38) or hyperactivity (3,4) following chronic stimulant exposure during the preweanling period; to the extent that this is the case, such hypoactivity should also be evident in other test situations. Alternatively, the attenuated activity could reflect conditioned hypoactivity to the test chamber. Although conditioned hyperactivity has been more typically reported following chronic treatment with psychomotor stimulants [e.g., (7)], conditioned drug effects sometimes oppose and other times mimic unconditioned drug responses, with factors determining the directionality of these processes a subject of theoretical speculation [e.g., (9,22)]. Although conditioned activity to the drug exposure context often is assessed following placebo injection on the test day, to conserve animal usage the present study assessed activity in the drug context during a 5-min preinjection period. This preexposure occurred daily during chronic treatment, and thus served as an accurate predictor of the upcoming injection, perhaps promoting development of compensatory hypoactivity to the expected drug event [e.g., see (22)].

One notable finding of the present study was that, regardless of chronic treatment condition, animals exhibited a reduced sensitivity to cocaine at the later injection-to-test intervals, corresponding to testing at P34 and P41. These ages are within the so-called "periadolescent period," which has been defined in rats as encompassing the 7–10 days prior to the onset of puberty and the first few days thereafter (i.e., approximately P30–P42). Periadolescents differ behaviorally on a number of dimensions from younger or older animals [see (26) for review], and are less responsive to catecholamine (CA) agonists [e.g., (12,16,17)] but more sensitive to CA antagonists (28). Given evidence that behavioral suppressant and neurochemical responses to low-dose DA receptor agonists only emerge during adolescence (2,11,24,25,34), this ontogenetic discontinuity in CA sensitivity has been hypothesized to be related to a transient reduction in mesolimbic DA activity resulting from maturation of inhibitory DA autoreceptors (26). Not all data are consistent with this suggestion (10), however, and other developmental events, such as maturation of postsynaptic D_3 receptors in forebrain (29), may be involved.

Taken together, the results of the present study suggest that sensitization to cocaine is evident for weeks following chronic cocaine treatment during the late preweanling period, although the expression of this sensitization may be influenced by age-related neurobiological events and their behavioral ramifications. Interestingly, while periadolescents often exhibit a diminished locomotor response to cocaine upon first exposure (27) or when expressing a previously sensitized response (present study), they conversely exhibit an exacerbated locomotor response to cocaine following a series of cocaine injections during adolescence (17). Yet, periadolescents appear less likely to initiate cocaine sensitization in terms of

stereotypy (17). Thus, age should seemingly be included on the list of factors that may differentially influence the initiation vs. expression of sensitization (14,36). Neural mechanisms underlying the induction and expression of sensitization may not only be anatomically and functionally distinct [e.g., (14)], but may also undergo differential regulation during ontogeny.

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