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Intrauterine Exposure to Cocaine Produces a Modality-Specific Acceleration of Classical Conditioning in Adult Rabbits

ANTHONY G. ROMANO,[1] WAYNE J. KACHELRIES, KENNY J. SIMANSKY AND JOHN A. HARVEY

Department of Pharmacology, Medical College of Pennsylvania, and Hahnemann University, Philadelphia, PA 19129

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ROMANO, A. G., W. J. KACHELRIES, K. J. SIMANSKY AND J. A. HARVEY. *Intrauterine exposure to cocaine produces a modality-specific acceleration of classical conditioning in adult rabbits.* PHARMACOL BIOCHEM BEHAV 52(2) 415–420, 1995. – Previous studies had demonstrated that in utero exposure to cocaine produces structural changes in the development of the rabbit's anterior cingulate cortex. Because the anterior cingulate cortex has been proposed to subserve a variety of cognitive processes including associative learning, we investigated the effects of intrauterine exposure to cocaine on the acquisition of the rabbit's classically conditioned nictitating membrane response. Adult, sexually mature rabbits born of dams that had received intravenous injections of either saline or cocaine (4 mg/kg, twice a day) from day 8 to day 29 of gestation were classically conditioned by pairing tone and light CSs with an airpuff US. Rabbits that had been exposed to cocaine in utero demonstrated a more rapid acquisition of CRs to a tone CS but not to a light CS as compared with saline controls. Control experiments indicated that the accelerated learning to the tone CS was not due to sensitization, pseudoconditioning, altered baseline rate of responding, an increased responsiveness to the airpuff US, or to a change in the intensity threshold of the tone CS for elicitation of CRs. We conclude that in utero exposure to cocaine alters the processing of auditory stimuli and this leads to an abnormally rapid acquisition of CRs. It is suggested that this functional consequence of prenatal exposure to cocaine is due to structural abnormalities in anterior cingulate cortex.

Cocaine In utero Associative learning Rabbit

A NUMBER of studies have noted significant behavioral abnormalities in neonates born to cocaine-using women, although there appears to be a considerable variation in the precise effects observed, their duration, and severity (1,2,4, 21,28). Some of the behavioral effects reported such as decreased animate and inanimate visual and auditory orientation, depressed interactive abilities and poor organizational response to environmental stimuli, suggest that intrauterine exposure to cocaine may alter cognitive processes that depend on normal cortical functioning (22,23). Recent experimental studies in the rat have tended to substantiate the existence of cognitive effects of prenatal exposure to cocaine at doses that are not associated with malformations that could be seen by gross observation (5,6,24). The effects of prenatal exposure to cocaine on learning in the rat can be of short (11) or long duration (12), and depend on the nature of the task. For example, cocaine exposure prevented the acquisition of conditioned place preference in the adult rat (12), but had no effect on the acquisition and retention of learning in a water maze (13).

Recently, the rabbit has been employed as a model for examining the neurobehavioral effects of fetal exposure to cocaine. Using the intravenous route of injection, to more closely mimic crack cocaine use by pregnant women, pregnant does were injected with cocaine (4 mg/kg, given twice daily) from gestational day 8 to 29 (16). This dosing regimen had no significant or consistent effects on body weight gain of the pregnant does, time to delivery, litter size, gender ratios, or on the body weight and other physical characteristics of the cocaine exposed kits (16). In spite of their otherwise normal appearance, rabbits exposed to cocaine in utero demonstrated

[1] Requests for reprints should be addressed to Anthony G. Romano, Department of Pharmacology, Medical College of Pennsylvania, 3200 Henry Ave., Philadelphia, PA 19129.

structural changes in the anterior cingulate cortex that persisted into adulthood. These changes were observed in all cocaine progeny examined and consisted of an abnormal dendritic development of pyramidal cells in anterior cingulate cortex (14) as well as a significant increase in the content of GABA immunoreactive neurons (27). Neither of these anatomical abnormalities were seen in primary visual cortex.

A number of cognitive and motivational functions have been demonstrated to depend on the integrity of the anterior cingulate cortex of rodents, rabbits, monkeys, and humans, including associative learning, attentional processes, and reactions to aversive stimuli (8,15,25). In the rabbit, acquisition of an avoidance response is associated with altered neural activity within the anterior cingulate cortex, whereas lesions of this cortex retard acquisition (7–9). Therefore, we hypothesized that the altered architecture of the anterior cingulate cortex in rabbits exposed to cocaine in utero might change cortical function sufficiently to affect the acquisition of CRs.

The present experiments addressed this question by examining classical conditioning of the rabbit's nictitating membrane (NM) response as a model for assessing the effects of prenatal exposure to cocaine on associative learning. Three experiments were conducted to examine effects on CR acquisition, on the intensive properties of the CS, and on nonassociative responding.

METHOD

Subjects

The Dutch belted rabbits employed in these studies were obtained from a NIDA supported, core breeding facility at the Medical College of Pennsylvania. The colony rooms were illuminated according to a 12 L : 12 D cycle at 23°C, and all animals had free access to food and water. The rabbits were male and female offspring of dams that had been injected with saline or cocaine during pregnancy as previously described (16). Briefly, proven female breeders obtained from Myrtle's Rabbitry (Thompson Station, TN), were housed individually until the day of mating. On gestational days 8 to 29, the dams received twice daily injections of saline or cocaine hydrochloride (4 mg/kg) via the marginal ear vein (in a volume of 2 ml/kg) for a total daily dose of 8 mg/kg. Kits were typically delivered on gestational day 30–31. Exposure to cocaine had no effect on time of delivery, litter size, gender ratios, or body weight or other physical features (16). Kits were allowed to stay with their natural mothers until weaning at 56 days of age. Postweanlings were housed one to two per cage for the duration of the experiment. The behavioral studies were initiated in offspring that were 90–120 days old, when they were sexually mature adults.

Apparatus and General Procedure

The conditioning apparatus, data acquisition system, and general procedures have been described in detail elsewhere (19). Briefly, each animal was placed in a Plexiglas restrainer and fitted with a headmount that supported a potentiometer that was directly coupled to a suture placed in the right NM. Movements of the NM were transduced to DC voltages and digitized every 5 ms, with a resolution of 0.03 mm of NM movement per analog-to-digital count. A response was defined as a 0.5 mm or greater extension of the NM and its onset latency was calculated from the time at which the response first deviated from baseline by at least 0.03 mm. The headmount also supported a tube for delivery of the airpuff US to the right cornea. The animals were trained in illuminated, sound-attenuated chambers with a stimulus and interconnection panel mounted above and in front of the animal. Several behavioral training and testing procedures were employed, as described below. One day prior to each of these procedures, animals were given one 60-min adaptation session, during which no stimuli were presented or drugs administered. However, to obtain a baseline measure of the frequency of NM responding, responses were recorded at the intervals to be used during the experimental sessions.

Experiment 1: Acquisition of CRs to Tone and Light CSs

Twelve rabbits that had been exposed to cocaine in utero and 12 rabbits of saline-treated dams received 10 days of acquisition training. Rabbits were given 5 days of acquisition training followed by a 2-day rest period and then 5 more days of acquisition. Two conditioned stimuli were employed: an 800 ms, 75 dB (20 $\mu N/m^2$ reference), 1 kHz tone, and an 800 ms flashing light produced by interruption of the houselights at a frequency of 10 Hz. The US was a 100 ms corneal airpuff exerting a pressure of 200 g/cm^2 measured at the end of the delivery tube. Each acquisition session consisted of 60 trials, composed of 30 pairings of the tone CS and airpuff US and 30 pairings of the light CS and airpuff US. The offset of the CS, either light or tone, coincided with the onset of the US. Trials were presented at an average intertrial interval of 60 s (range: 55–65 s), with the restriction that no more than three tone or light trials could be presented consecutively. A response was scored as a CR if it occurred within 800 msec of CS onset and as a UR if it occurred after US onset.

Experiment 2: Acquisition of CRs to a Tone CS and Tone CS Intensity Testing

Acquisition training to a tone CS. Eighteen saline controls and 21 cocaine-exposed animals received acquisition training to only the tone CS. Optimal training parameters were used to enhance the rate of acquisition in both groups. Thus, the CS was a 90 dB, 200 ms tone and its offset coincided with the onset of the 100 ms, 200 g/cm^2 airpuff US. Animals received 60 CS-US pairings per day at an average intertrial interval of 60 s (range: 55–65 s). Animals were trained daily until they reached a level of 80% CRs in a single session. Animals achieving this criterion were left undisturbed in their home cages until training was completed for the remaining animals.

Tone CS intensity testing. One day prior to testing, 10 cocaine and 10 saline exposed animals, selected at random from the pool of 39 animals described in the previous paragraph, were returned to the experimental chambers for a refresher acquisition session. On the next day, all 20 animals were exposed to a single test session. The test session was similar to the acquisition sessions except that the intensity of the 200 ms tone CS was varied. Thus, there were 60 pairings of the tone CS and airpuff US consisting of 10 presentations of each of the following tone intensities (in dB): 0 (no tone), 50, 60, 70, 80, and 90. The different tone intensities were presented in random order within each block of six trials. On the 0 dB (no tone) trials, responses occurring during the 200 ms prior to US onset were recorded as baseline responses. Responses occurring during presentations of the 50–90 dB tones were recorded as CRs.

Experiment 3: Unpaired CS/US Procedure

Ten saline-exposed and 12 cocaine-exposed rabbits were given explicitly unpaired presentations of the CSs and US for

a total of ten sessions. In each session, 30 tone CSs, 30 light CSs, and 60 airpuff USs were presented in a randomized order with the restriction that no more than three trials of the same type could occur consecutively. The intertrial interval averaged 30 s (range, 25–35 s), all other parameters were the same as in Experiment 1. Responses were recorded if they occurred within 800 ms after tone or light onset. Responses occurring after US onset were recorded as URs, and their topography was calculated in terms of amplitude, onset latency, and latency to peak amplitude. Responses occurring in the 800 ms prior to US onset provided a measure of baseline responding.

Histological analysis. Some of the rabbits employed in these experiments were used by other laboratories for structural and neurochemical analysis of their brains. Results obtained in the laboratories of Pat Levitt and E. Hazel Murphy (personal communication) indicated that these rabbits demonstrated the same structural alterations in anterior cingulate cortex as had been previously reported by them in younger rabbits (14,27).

Data analysis. The data were analyzed with repeated-measures analyses of variance using the SYSTAT statistical package, version 5.0 (29). The alpha level for all tests was set at 0.05.

RESULTS

Experiment 1: Prenatal Exposure to Cocaine Produces a Modality-Specific Increase in CR Acquisition to a Tone CS

Rabbits prenatally exposed to cocaine demonstrated a higher level of CR acquisition to the tone CS (Fig. 1A) but not the light CS (Fig. 1B) as compared with saline-exposed controls.

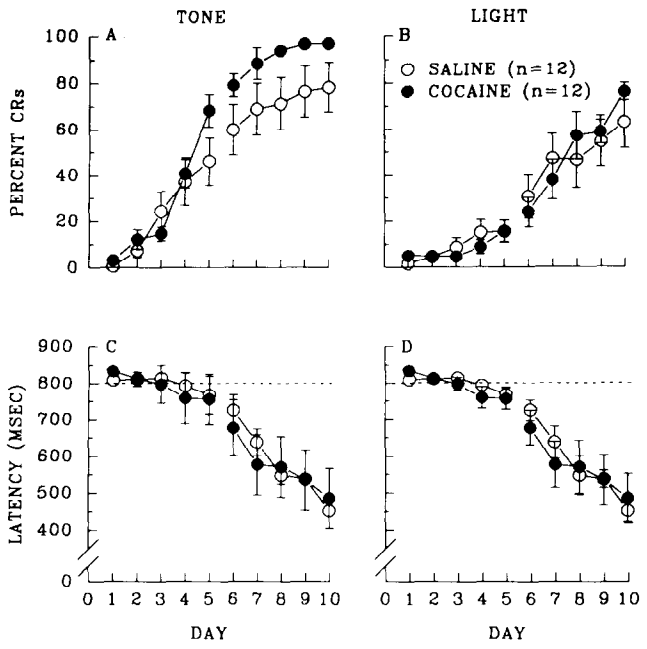

FIG. 1. CR acquisition to tone and light CSs in Experiment 1. Data are presented as mean percentage of CRs (A and B) or as mean response onset latencies (C and D). Vertical bars represent 1 SEM. In this and subsequent figures, the vertical bars are not visible when they fall within the symbol.

The data are plotted collapsed over gender as this variable had no effect on the percentage of conditioned responding, $F(1, 20) < 1$, nor did it interact with prenatal treatment condition, $F(1, 20) < 1$. However, acquisition to the tone CS was more rapid than to the light CS, regardless of prenatal treatment condition (compare Fig. 1A and B). Because this difference in CS modality yielded a significant main effect, $F(1, 20) = 64.79$, $p < 0.001$, a significant interaction with prenatal treatment, $F(1, 20) = 6.62$, $p < 0.05$, but no significant two-way interaction with gender, $F(1, 20) = 1.40$, or three-way interaction with gender and prenatal treatment, $F(1, 20) < 1$, separate analyses were subsequently conducted for each CS modality regardless of gender.

The differential performance in rate of acquisition to the tone CS produced a significant prenatal treatment × days interaction, $F(9, 198) = 2.36$, $p < 0.025$, but no significant main effect of prenatal treatment, $F(1, 22) = 2.43$. In contrast, acquisition of CRs to the light CS failed to reveal any significant effect of prenatal treatment, $F(1, 22) < 1$, or significant prenatal treatment × days interaction, $F(9, 198) < 1$.

Figure 1C and D illustrate the significant decrease in response latencies over the course of training to both the tone CS, $F(9, 198) = 90.22$, $p < 0.001$, and light CS, $F(9, 198) = 39.13$, $p < 0.001$. However, prenatal exposure to cocaine did not alter the response latencies to either the tone or the light CS, $F(1, 22) = < 1.5$, for both modalities.

Experiment 2: Prenatal Exposure to Cocaine Increases CR Acquisition to a Tone CS Without Affecting the Tone CS Intensity Function

The purpose of this experiment was to train cocaine- and saline-exposed animals to a common criterion of acquisition to measure CS intensity effects from equivalent levels of CR performance. In agreement with the results of Experiment 1, adult rabbits that had been exposed to cocaine prenatally demonstrated a significantly more rapid rate of CR acquisition to a tone CS. The rate of acquisition was assessed by determining the number of trials required to achieve criteria of 5 and 10 consecutive CRs (Fig. 2). Cocaine-exposed animals required 89 trials to achieve a criterion of 5 consecutive CRs compared to 129 trials for saline offspring. This difference was significant, $F(1, 37) = 7.92$, $p < 0.01$. Cocaine-exposed animals also required significantly fewer trials to reach a criterion of 10 consecutive CRs, 116 trials vs. 151, $F(1, 37) = 4.21$, $p < 0.05$. Gender information was available for a random sample of 22 of the 39 animals trained. In agreement with Experiment 1, gender failed to produce a significant main effect or a significant interaction with prenatal treatment using either 5 or 10 consecutive CRs as the criterion measure (all Fs < 1).

Because the 18 saline and 21 cocaine progeny were trained to a common criterion of acquisition (achievement of 80% CRs in a single session), the mean percentage of CRs during the subsequent refresher training session, carried out on a subset of the trained animals, was equivalent for the sample of 10 cocaine-exposed (88.9 ± 6.1%) and 10 saline-exposed rabbits (89.4 ± 4.6%). The results of the subsequent tone CS intensity testing session are shown in Fig. 3. Decreases in CS intensity from the original training value of 90 dB produced an orderly and significant decrease in the percentage of CRs, $F(4, 72) = 155.25$, $p < 0.001$. However, there was no significant difference between cocaine- and saline-exposed offspring in this CS intensity function, $F(1, 18) = 0.7$. The CS intensity for elicitation of 50% CRs was approximately 68 dB for both groups.

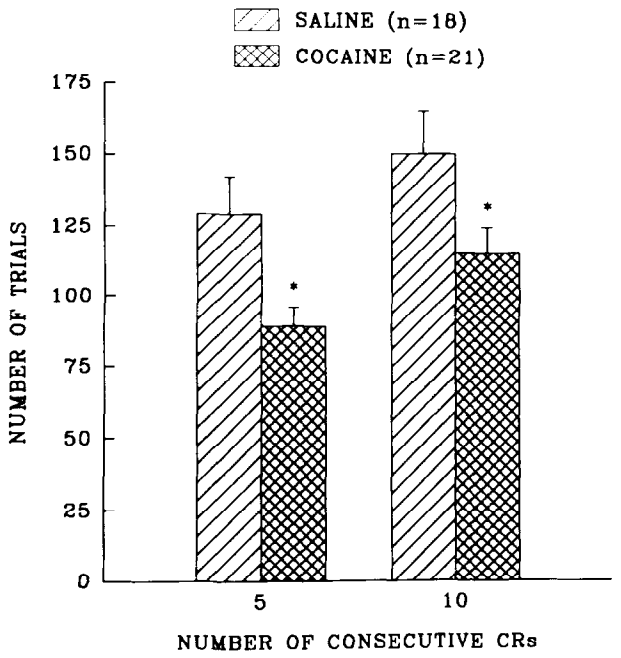

FIG. 2. Rate of criterion CR acquisition to a tone CS in Experiment 2. Data are expressed as the mean number of trials required to reach a criterion of 5 or 10 consecutive CRs. Vertical bars represent 1 SEM. Asterisk indicates a significant difference from control ($p < 0.05$).

Experiment 3: Unpaired CS/US Training

As shown in Fig. 4, nonassociative responding was infrequent and there was never any significant difference between rabbits that had been exposed prenatally to cocaine or saline. Both groups exhibited a small but significant increase in baseline responding over the 10 days of testing, $F(9, 180) = 2.76$, $p < 0.005$, from the lowest level of 1% on day 4 to the highest level of 4% on day 9 (Fig. 4A). Responding in the presence of the light showed a less than 5% difference between the lowest level of responding on day 3 and the highest level of responding on day 9 (Fig. 4B). For both groups, the increase in response frequency in the presence of the light failed to achieve significance, $F(9, 180) = 1.77$. Both groups demonstrated equivalently small but significant increases in responding during tone presentations (Fig. 4C) from less than 1% on day 1 to nearly 11% on day 9, $F(9, 180) = 6.47$, $p < 0.001$.

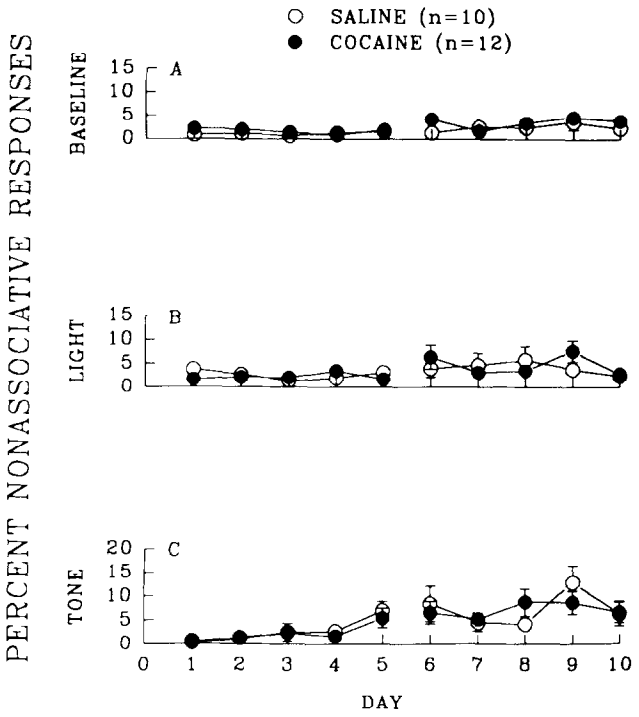

FIG. 4. Responding during unpaired presentations of CS and US in Experiment 3. Data are presented for baseline responding, responding during the 800 ms prior to US onset (A), and responding during the 800 ms presentations of light (B) and tone (C) stimuli. Vertical bars represent 1 SEM.

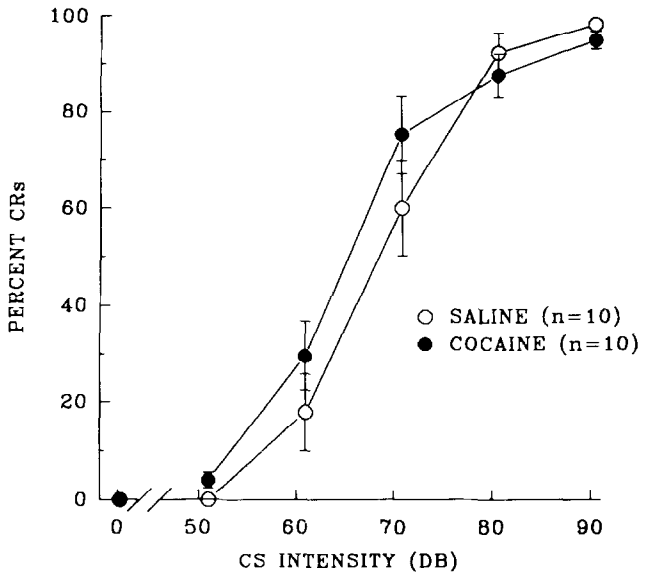

FIG. 3. Tone CS intensity function of Experiment 2. Each CS intensity was presented 10 times. The points above 0 dB represent trials on which no tone was presented and, thus, serve as a measure of baseline rate of responding. Vertical bars represent 1 SEM.

The percentage of URs and UR topographies obtained on US alone trials are shown in Fig. 5. Neither percent URs (Fig. 5A), UR onset latency (Fig. 5C), nor latency to peak UR amplitude (Fig. 5D) yielded significant main or interaction effects. By contrast, UR amplitudes (Fig. 5B) increased significantly over days, from an initial low of 2 mm to slightly over 3 mm at the end of training, $F(9, 180) = 3.95$, $p < 0.001$. There was also a consistent tendency for cocaine-exposed animals to show slightly lower UR amplitudes than saline offspring throughout the 10 days. However, the 0.7 mm difference between the two groups failed to achieve significance, $F(1, 20) = 2.98$, $p = 0.10$.

DISCUSSION

The results of these studies confirmed our hypothesis that prenatal exposure to cocaine would have functional conse-

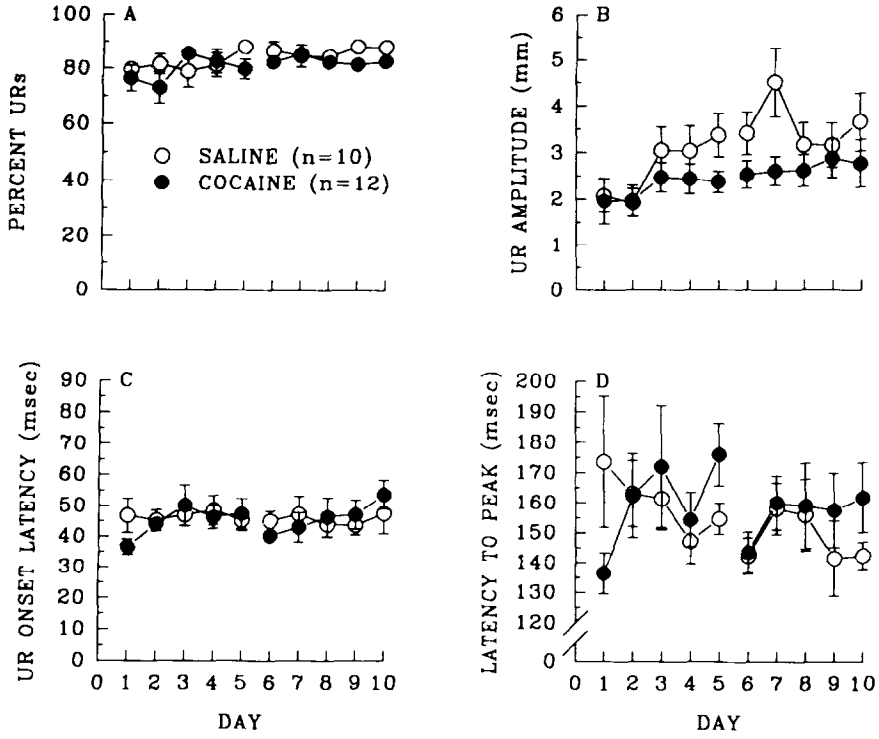

FIG. 5. UR topography during unpaired presentations of CS and US in Experiment 3. Data are presented as percentage of URs (A), peak UR amplitude (B), UR onset latency (C), and latency to peak UR amplitude (D). Vertical bars represent 1 SEM.

quences on the acquisition of CRs. Adult rabbits that had been exposed to cocaine prenatally acquired CRs to a tone CS at an accelerated rate and achieved higher asymptotic levels of responding than saline-exposed animals. Although litter effects might have influenced the present results, it may be argued that litter effects cannot account for the accelerated rate of acquisition seen in cocaine offspring because the phenomenon was observed in two separate experiments involving different training procedures as well as different litters. The replication of the phenomenon in an independent experiment argues most strongly for an effect of prenatal exposure to cocaine per se and against an effect due to litter differences. The effect of prenatal exposure to cocaine was also not due to some general effect on learning, because acquisition of CRs to a light CS was not affected. The accelerated rate of CR acquisition to the tone CS exhibited by cocaine-exposed rabbits represented an increase in associative learning, because the results of Experiment 3 indicated that there was no increase in nonassociative responding to the tone. Finally, the accelerated rate of CR acquisition to the tone CS by cocaine-exposed rabbits did not appear to be due to some alterations in the sensory properties of the tone CS, because both cocaine- and saline-exposed rabbits demonstrated similar psychophysical functions relating tone CS intensity to CR elicitation in Experiment 2. The fact that prenatal exposure to cocaine had no effect on the intensive properties of the tone CS, and the absence of any general effect on learning, suggests that the accelerated rate of CR acquisition in cocaine-exposed offspring was due to an alteration in attentional factors. An alteration in attentional factors, leading to an increased salience of the auditory stimulus, could account for the more rapid entry of the tone CS into associative learning.

Exposure to cocaine in utero alters the development of anterior cingulate cortex (14,27), and this may be the basis of the accelerated acquisition of CRs to a tone CS noted in the present study. Although total removal of anterior cingulate cortex retards acquisition of CRs to a tone CS (7), other types of lesions that alter the circuitry and/or the afferent projections to the cingulate have been reported to accelerate CR acquisition to a tone CS (7–9). For example, enhanced training-induced neuronal activity in limbic thalamus has been reported after fiber-sparing lesions of anterior cingulate cortex produced by ibotenic acid (9) as well as after interruption of afferent inputs from posterior cingulate cortex or hippocampus (7,10). It has been pointed out that such an acceleration of CR acquisition can represent a failure to modulate processing of stimuli and this would, in turn, predict a loss of attentional factors required to both selectively attend to and selectively ignore stimuli (8,25). The altered structure of the anterior cingulate cortex in cocaine-exposed animals may very well affect its ability to process inputs from other cortical regions including hippocampus and, thus, affect attentional processes. For example, the abnormal dendritic structure of pyramidal cells (14) and the increased number of GABA immunoreactive neurons (27) produced in rabbits that had been exposed to cocaine in utero strongly suggests an alteration in the balance of excitation and inhibition within the anterior cingulate cortex. The modality specificity of the effects on CR

acquisition obtained in the present study may be related to anatomical differences in how visual and auditory stimuli engage the cingulate cortex (26).

An attentional deficit resulting from alterations in functioning of the cingulate cortex is consistent with a wide variety of studies in humans and experimental animals (8,15,25). Studies employing positron emission tomography in normal human subjects have demonstrated that the anterior cingulate cortex selectively increases its activity during performance of attentional tasks (3,17,18). In the rabbit, electrophysiological studies have demonstrated the occurrence of learning-dependent changes in the activity of cingulate cortex that precede learning to attend to significant stimuli during discrimination training (7,8). The role of the rabbit's cingulate cortex in attentional tasks has been confirmed by the finding that the interruption of inputs or direct damage to the cingulate cortex impairs the acquisition of a discrimination (7,8). We have also found that prenatal exposure to cocaine produces a deficit in attentional processes as measured by a severe impairment in acquisition of a discrimination (20).

In summary, this study has demonstrated that prenatal exposure to cocaine can have long-term effects on associative learning in the rabbit, an effect that appears to be related to alterations in attentional processes. These behavioral effects appear to be related to the long-term alteration in the cytoarchitecture of anterior cingulate cortex produced by prenatal exposure to cocaine.

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