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Postnatal Cocaine Exposure Affects Neonatal Passive Avoidance Performance and Cholinergic Development in Rats

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RICCERI, L., P. TIRASSA, L. ALOE AND E. ALLEVA. *Postnatal cocaine exposure affects neonatal passive avoidance performance and cholinergic development in rats.* PHARMACOL BIOCHEM BEHAV 45(2) 283–289, 1993.—Wistar rat pups received either cocaine HCl (25 mg/kg) or saline (0.9% NaCl) SC from postnatal days 1–11. On days 12 (acquisition) and 13 (retention), they underwent a passive avoidance task (step-off response; grid foot-shock at 0.35 mA). Slight deficits were found in cocaine-treated subjects for latency to step-off during acquisition and for generalized increase in the number of trials to criterion in retention. On postnatal day 13, the level of choline acetyltransferase (ChAT) enzymatic activity and the distribution of ChAT neuronal immunoreactivity in forebrain structures were examined. These morphometric and biochemical studies demonstrate a decrease of cholinergic enzymes in the septum, while the remaining basal forebrain cholinergic regions were unaffected.

Cocaine Forebrain cholinergic neurons Choline acetyltransferase Passive avoidance learning Development Rats

BECAUSE of its increasing abuse in Western countries (23), cocaine has received widespread attention in the last few years (16,21). The increased concern among pediatricians has stimulated a number of clinical studies aimed at characterizing the neurobehavioral deficits of infants born to addicted mothers [for historic perspective, see (25)] and the temporal pattern of cocaine abuse in pregnancy (7). Growth retardation, jitteriness, and irritability characterize children born to cocaine-abusing women (10). The neuropsychological deficits of the offspring appear to involve specific difficulties in early language development, while nonverbal tasks or general activity seem unaffected (37). Asymmetrical brain growth retardation (27) and Sudden Infant Death Syndrome (13) are reportedly caused by maternal cocaine addiction. Yet, some authors have found no reliable difference among cocaine-exposed and normal neonates or infants (30).

Several attempts have been made to investigate in animal models early behavioral deficits following either prenatal or postnatal exposure to cocaine. Dow-Edwards et al. (11) reported lasting changes of functional activity in several brain regions following prenatal cocaine exposure in rats, while Anderson-Brown and coworkers (5) found that cocaine acutely inhibits DNA synthesis in specific regions of the developing rat brain. Late-prenatal cocaine exposure resulted in accelerated behavioral maturation and in decreased locomotor response to both *d*-amphetamine and cocaine challenge on postnatal day 15 (34). Another study using prenatal cocaine found increased striatal D_2 binding, associated with an increase in ligand affinity (33). In adult rats, cocaine also induces reduction of neuropeptide Y synthesis dependent upon the medial prefrontal cortex (38).

The aim of the present experiment was to investigate whether or not early postnatal cocaine exposure can affect cholinergic development and passive avoidance learning in neonatal rats. Previous works indicated that high cocaine doses exert antimuscarinic effects (39), and passive avoidance learning is a behavioral response reportedly under cholinergic control during postnatal development (12,31). Passive avoidance is a reliable test in assessing early memory and learning capabilities of altricial rodents (2,36).

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METHOD

Animals

Rats of the Wistar strain purchased from Charles River Italia were used. At delivery (postnatal day 0), litters were culled to 8 pups (when possible, 4 males and 4 females), while litters delivering less than 10 pups were discarded. Animals were maintained under a reversed dark/light cycle (red lights on from 9:00 a.m. to 6:00 p.m.) and fed ad lib with Enriched Piccioni pellet food (20060-Gessate, Milano, Italy). Tapwater was always available, temperature was maintained at 21 ± 2°C, and relative humidity at 60 ± 10%. Dam and litter were housed in opaque Plexiglas boxes (56 × 34 × 20 cm) with metal tops.

Cocaine Treatment

A pilot study revealed that a prolonged SC treatment (from postnatal days 1–20) with cocaine (25 mg/kg) did not alter either the basal activity levels or the scopolamine-induced hyperactivity (scopolamine 2 mg/kg 20 min before the test) in an open-field arena at postnatal day 21. Therefore, the same dose of cocaine was used in the subsequent experiment.

Daily from postnatal days 1–11, pups received an SC injection (at the nape of the neck) of either cocaine HCl (25 mg/kg) or saline solution (0.9% NaCl) between 10:00 and 12:00 a.m. The same number of littermates were randomly assigned to each of the two treatment groups.

Assessment of General Development

Pups were assessed daily for appearance of righting and forelimb grasping reflexes and for cliff aversion response [see description in (1,3)]. Body weight was recorded on postnatal day 11.

Passive Avoidance Testing

The passive avoidance apparatus for immature rats was purchased from Ugo Basile (21025-Comerio, Varese, Italy). It consists of a Perspex arena (25 × 15 × 25 cm) with a metallic grid floor (bars of 2 mm diameter, spaced 5 mm) connected to a scrambling shocker (Colbourn Instruments, Model E13-08) set at 0.35 mA. A Plexiglas platform (diameter 70 mm) was placed at the center of the apparatus, 3 mm above the grid floor. Step-off responses from the platform were punished with a 3-s foot-shock. Latencies to step-off and number of trials to reach the learning criterion (two consecutive trials with at least 120-s step-off latency) were recorded for each conditioned pup. Nonreinforced, yoked, and retested only control groups were also used [in all cases, controls were littermates of conditioned animals; for the rationale of these control groups, see (31)].

Procedure

Acquisition phase (postnatal day 12). Conditioned pups underwent a multitrial passive avoidance training session. Single pups were placed on the central platform at the beginning of each trial. Immediately thereafter, the platform began vibrating and the timer was simultaneously activated. A trial ended either when the pup gave a step-off response or remained on the vibrating platform for 120 s, whichever event occurred first. Each step-off response was followed by a 3-s foot-shock. At the end of each single trial, pups were removed from the apparatus and left undisturbed for a 45-s intertrial interval. Pups were then repositioned on the platform for a new trial. The acquisition phase ended either when the conditioned subject had remained on the platform for 120 s in two consecutive trials (learning criterion) or after 15 trials ended by stepping off. Rats of the nonreinforced control group were subjected to a similar multitrial session in the same apparatus, but step-off responses were not punished by a foot-shock: nonreinforced pups were placed on the vibrating platform and their latency to step-off response was recorded; the number of step-off trials was cut off at 15 unless two consecutive trials of 120 s each occurred. Rats in the yoked control group received the same amount of shock and vibration and the same number of acquisition trials as were previously experienced by the conditioned littermate. Restrained in a Plexiglas cylinder, the rat received a period of vibration identical to the one administered to its conditioned littermate in that particular trial. If, in that trial, the conditioned littermate had been punished for stepping off the platform, the corresponding yoked subject was removed from the enclosed platform, placed on the grid, and given a 3-s foot-shock. If the conditioned littermate had attained criterion latency on that trial, the yoked subject received only 120 s vibration.

Retention phase (postnatal day 13). The retention procedure was identical for conditioned, nonreinforced, and yoked pups and replicated the one used for conditioned pups in the acquisition phase. A retested only control group was added in this phase, which followed the same retention procedure.

ChAT Immunocytochemistry

Six rats from each SC treatment were anesthetized with sodium pentobarbital and transcardially perfused with 50 ml cold phosphate-buffered saline (PBS), followed by 200 ml 4% paraformaldehyde dissolved in 0.1 phosphate buffer (pH = 7.4). Brains were then removed and postfixed in the latter solution overnight, followed by 20% sucrose solution in PBS for 24 h. Each brain was then mounted on the freezing microtome and 30-μm-thick sections containing the septum and nucleus basalis were cut and processed for ChAT immunohistochemistry. Briefly, free-floating sections were first rinsed in PBS and then left overnight in ChAT monoclonal antibodies (purchased by Boehringer, Mannheim, Germany) containing 0.2% Triton-X-100 and incubated at 4°C for 24 h. The primary antibody was then removed and the section exposed to the secondary antibodies, biotinylated antirat immunoglobulin (Ig)G, and then to avidin–biotin–horseradish peroxidase, followed by diaminobenzidine (4). Stained sections were examined using a Zeiss Axiphot microscope, and the presence of ChAT-positive neurons at the corresponding level of the

TABLE 1

GENERAL DEVELOPMENT OF COCAINE- AND SALINE-TREATED PUPS

	Day	Saline	Cocaine
Body weight	11	25.8 ± 0.1*	23.4 ± 0.1
Cliff aversion	6	31.2†	25.0
	8	56.2	62.5
Forelimb grasping	6	56.2	37.5
	8	62.5	43.7
Righting	6	81.2	62.5
	8	87.5	68.7

*Data refer to mean levels of eight animals ± SEs.
†Percentage of subjects, of 32, giving a mature response.

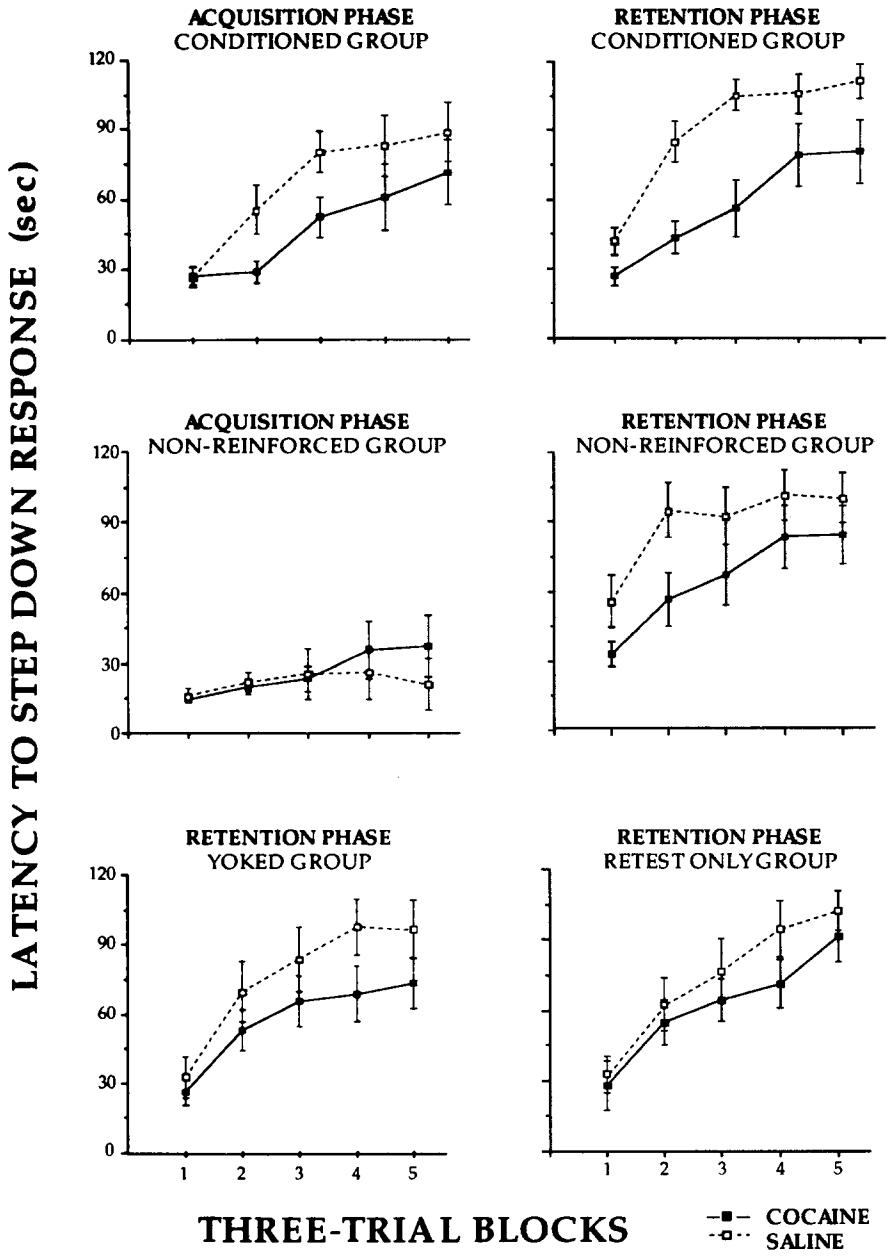

FIG. 1. Latency to step-down response throughout the 15 trials of each session. Data are mean of three subsequent trials (five blocks). A significant difference ($p < 0.05$) has been found only when comparing the saline-conditioned group with the saline-nonreinforced group (brokenlines of the two graphs of the acquisition phase).

basal forebrain cholinergic region of control and cocaine-treated rats was evaluated. ChAT-positive neurons in the septum and nucleus basalis were measured using an automatic image analyzer (Vidas system, Kontron Electronics). All ChAT-positive neurons larger than 20 μm were included. In both control and cocaine rat brains, an average of 80 neurons per section were counted and compared.

Video Image Analysis

Quantitative analysis (distribution and cross-sectional size) of ChAT-positive neurons in the septum and nucleus basalis was carried out using a computerized image-analysis system (Axiophot Zeiss microscope equipped with a Vidas Kontron system). Representative sections (6–10) of immunoreactive cholinergic neurons, taken at regular intervals of 60 μm, were evaluated and divided into classes (mean cross-sectional area/neuron). The results of the different experimental groups were pooled and compared.

Biochemical Analysis

Eight rats were sacrificed at the time indicated and areas of the brain (cortex, hippocampus, striatum, septum, and cer-

ebellum) were rapidly dissected on ice and stored at −70°C. ChAT enzymatic activity (defined as a micromole of acetylcholine formed per minute at 37°C) was determined following the method of Fonnun (15) and values were expressed as units of enzymatic activity/mg protein.

Design and Statistical Analysis

A completely balanced split-litter design was adopted, as suggested by the Collaborative Teratology Study Group (22). Body weight data and some of passive avoidance data were analyzed by using nested-type analyses of variance (ANOVA) considering the litter random factor (8,9).

Five-trial blocks of latency to step-down response were analyzed by ANOVA for repeated measures (with Bonferroni's correction for type 1 errors).

Number of trials to reach criterion were analyzed by Friedman's nonparametric analysis and posthocs were performed by using partition of χ^2 by orthogonal contrasts. χ^2 tests were used for righting, forelimb grasping, and cliff aversion scores. The immunocytochemical and biochemical data were analyzed by the Wilcoxon–Mann test (*U*-test).

RESULTS

General Development

General development was similar in both cocaine and saline pups. As shown in Table 1, no significant differences in righting, grasping, or cliff aversion responses were evident on either postnatal day 6 or 8. However, on postnatal day 11 cocaine animals had a slight decrease in body weight gain that turned out to be significant, $F(1, 4) = 27.18, p < 0.01$.

Acquisition Phase (Passive Avoidance Learning)

Data concerning latencies to step-off response throughout the 15 trials of each session are reported in Fig. 1. A significant difference in latency time was evident only when comparing saline-conditioned animals to their corresponding saline-nonreinforced controls, $F(1, 9) = 14.14$, $p = 0.0045$, $p < 0.05$, after Bonferroni's correction, while cocaine animals of the same two groups had similar latencies throughout the session.

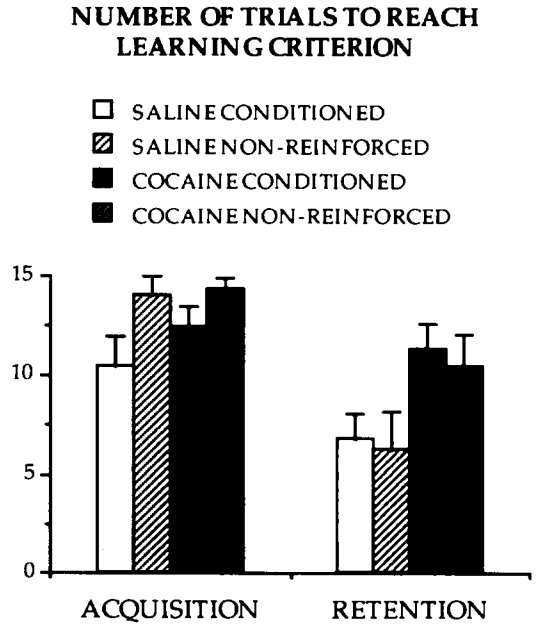

FIG. 2. Number of trials to reach criterion during both retention and acquisition phases in either saline- and cocaine- (25 mg/kg) conditioned and nonreinforced groups. The main effect of treatment (saline vs. cocaine) was significant ($\chi^2 = 10.8$, $p < 0.01$; partition of χ^2 by orthogonal contrasts after Friedman's nonparametric analysis).

Retention Phase (Passive Avoidance Learning)

Cocaine treatment appeared to affect pup performance in a way that does not seem to relate with what has previously been experienced in the acquisition phase. Step-off latencies (Fig. 1) were similar in all groups; no significant differences between conditioned, on the one hand, and the three control groups, on the other, were evident in the number of trials to reach criterion within each drug treatment. However, the main effect of treatment (saline vs. cocaine) was significant for the number of trials to reach criterion ($\chi^2 = 10.8, p < 0.01$, partition of χ^2 by orthogonal contrasts after Friedman's nonparametric analysis; Fig. 2). No significant change in the performances of conditioned pups, when compared to the corresponding acquisition level, was evident.

Immunocytochemical localization carried out on the septum, nucleus basalis, and striatum of control and cocaine-treated rats showed a decrease in the number of ChAT-immunoreactive neurons in the mediolateral and ventrolateral septum in cocaine-treated animals. Neurite length and branching were also affected by drug treatment (Fig. 3).

A slight reduction in the number of ChAT-positive neurons was also observed in the nucleus basalis. No change in ChAT immunoreactivity was evident in other forebrain regions following cocaine injection as compared to brain areas of control rats. The distribution of ChAT-positive neurons was evaluated by means of video image analysis. Cell death was not detected. ChAT-positive neuron distribution in the septum was divided into classes (area/neuron), ranging from 100–500 μm, and the percentage of each class of neurons calculated and reported in Fig. 4.

Figure 5 shows the level of ChAT enzymatic activity in the cortex, hippocampus, striatum, septum, and cerebellum. The results of these biochemical determinations indicate that ChAT activity decreases more than 20% in the septum of cocaine-injected rats compared to saline-treated groups ($U = 36$; $n1 = n2 = 36$; $p < 0.01$). Slight differences were observed in the cortex and striatum but not in the hippocampus.

DISCUSSION

A recent study reports that prenatal cocaine exposure (from midgestation to delivery) does not alter either physical or behavioral maturation of rats (17). More extended prenatal exposure only evidenced subtle and limited effects in Pavlovian conditioning and in sensory preconditioning among infant rat pups (19), possibly due to alteration of the dopaminergic system (35).

Definite conclusions about early cocaine treatment and learning/retention capabilities in rats cannot be drawn from the present results mainly because of the short postnatal exposure, limited to the first 11 days of postnatal life.

Two slight behavioral changes have been evidenced: The first concerns the mean latencies during the acquisition phase and the second the number of trials to reach criterion during the retention phase. Saline-conditioned pups showed longer latencies than nonreinforced controls in the acquisition phase as a result of the aversive foot-shock to which conditioned pups are exposed following step-down response. The cocaine treatment prevented conditioned pups from showing such a

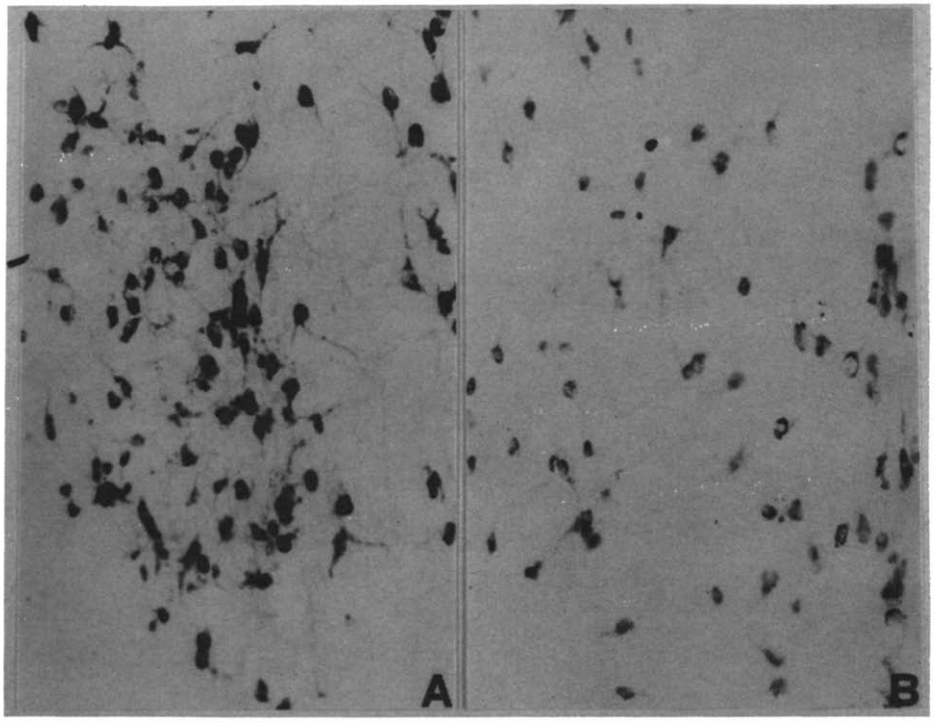

FIG. 3. Choline acetyltransferase (ChAT)-immunoreactive neurons in the septum of 12-day-old rats treated from birth to day 11 with saline (A) or cocaine (B). Note reduction of immunostained neurons in the mediolateral and ventrolateral septum of cocaine-treated rat. A decrease in immunoreactivity is also evident in B.

difference when compared to nonreinforced controls. The higher number of trials to reach criterion in cocaine-treated rats (when compared to saline controls) is the only significant effect found during the retention phase. Such increase is both specific because it is confined to the retention phase and generalized because it is present in all cocaine groups, irrespectively of previous experience in the passive avoidance apparatus.

The present data cannot exclude the possibility of nonassociative effects induced by cocaine treatment, namely, an alteration in foot-shock sensitivity (14); however, they indicate a subtle behavioral change interfering with the ability to per-

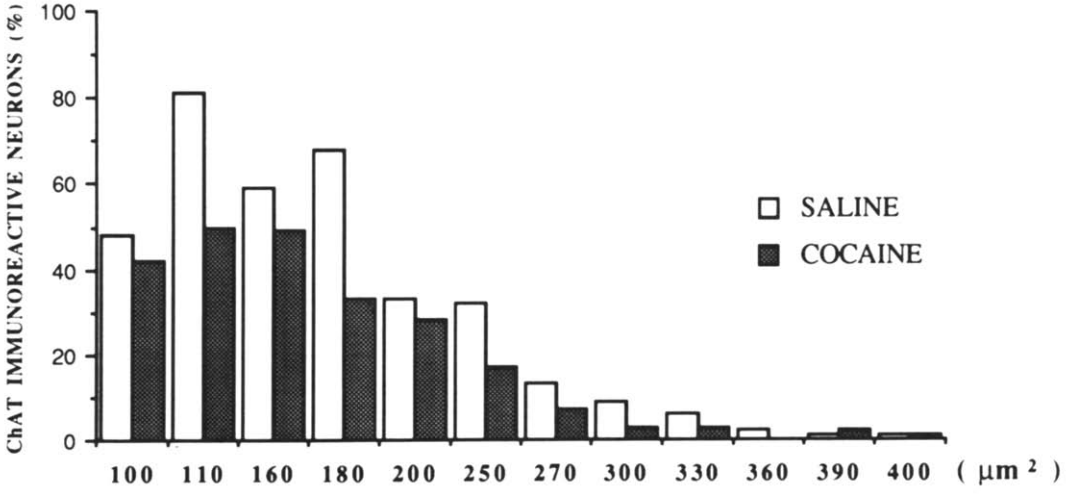

FIG. 4. Influence of 11 days of cocaine or saline treatment on the distribution of choline acetyltransferase (ChAT)-positive neurons in the septum, evaluated with a computerized image analyzer. The mean areas of ChAT-positive neurons were pooled and divided in different categories (abscissa). The ordinate indicates the percentages of the total number of immunoreactive neurons present in each category.

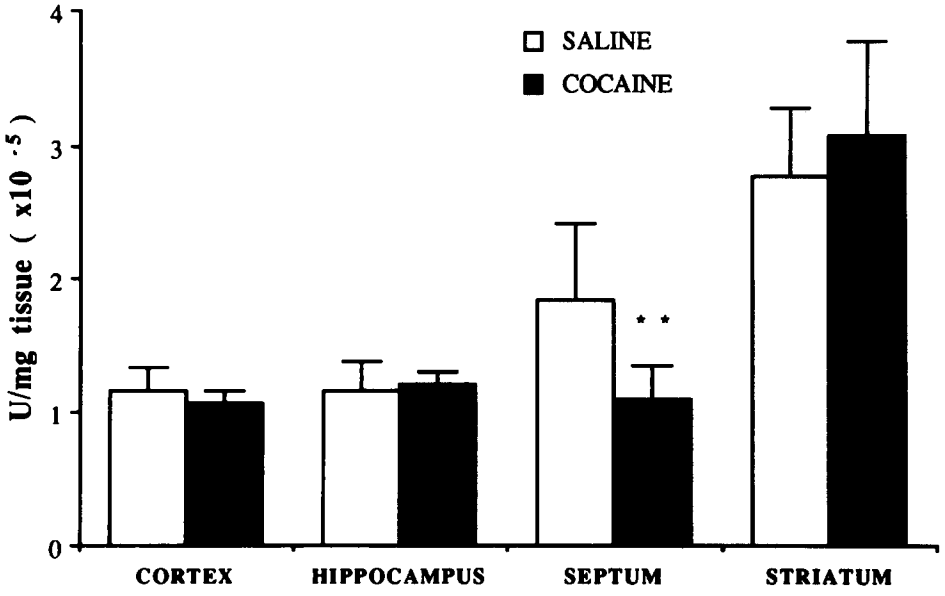

FIG. 5. ChAT enzymatic activity in different brain regions of rats treated for 11 consecutive days with cocaine as compared to saline. A statistically significant difference is present only in the septum ($p < 0.01$). *Values represent mean ± SE ($n = 8$).

form a passive avoidance task. Latencies of nonreinforced groups were similar in both treatments, making aspecific effects on general activity of cocaine treatment unlikely while supporting the hypothesis of a direct associative deficit. More systematic data are necessary to provide a better picture of this latter point, but the present data nevertheless confirm that passive avoidance task acquisition is already present in 11-day-old rats, a time when the cholinergic system is still immature (18,29,36). Our findings also suggest that alterations of cholinergic function in the septum affect passive avoidance acquisition at an early stage of rat development. We do not have a straightforward explanation for the absence of cocaine-induced effects on the hippocampus, the major target of septal cholinergic neurons; one possible interpretation is that growth factors that are known to be synthesized in the hippocampus (24,26,28) reduce or compensate for the cocaine-induced alterations in local cholinergic enzymes activity levels. Therefore, the effect of cocaine could be limited to cell bodies of cholinergic neurons in the septum, without affecting terminals. In rats, anticholinergic drugs impair passive avoidance learning starting as of postnatal day 11 and integrity of function in the amygdaloid region and hippocampus are necessary for passive avoidance conditioning (6,12).

The long-lasting changes caused by cocaine on the functional activity of the dopaminergic system are known (21,32), but no data are available on lasting cocaine-induced effects in the functioning of the central cholinergic systems (see the introductory section). Our results suggest that cocaine significantly decreases ChAT activity in the septum, and to a lesser extent in the nucleus basalis, leaving its level in other forebrain structures unchanged.

The effect in these two forebrain structures is localized and occurs during development: this raises the question as to whether this is a direct or mediated effect. However, because cocaine may cause an impairment of the CNS cholinergic system (20,39) our results favor the hypothesis that early developmental cocaine exposure exerts a direct effect on septal cholinergic neurons.

Thus, although additional studies are required to assess the mechanism accounting for reduction of cholinergic expression in the septal area, our preliminary studies indicate significant neurobiological alterations of systems other than the dopaminergic one as a result of early exposure to cocaine.

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