Effects on monoamine levels in rat CNS after Chronic administration of Cocaine.

Mario E. Alburges[1,3] and James K. Wamsley[2].

[1]Center for Human Toxicology, Department of Pharmacology-Toxicology, University of Utah, Salt Lake City, Utah 84108, USA, [2]Departments of Psychiatry, New York Medical College, Valhalla, New York 10595, USA, [3]Cátedra de Toxicología, Escuela de Bioanálisis, Facultad de Medicina, Universidad del Zulia, Maracaibo, Zulia, Venezuela.

Abstract. We have previously reported time-dependent and dose-dependent changes in the rat dopaminergic receptor system following chronic administration of cocaine (upregulation of cocaine, D_1, and DA-uptake sites). We have now evaluated the effects of chronic cocaine exposure on the central catecholamine/indolamine neurotransmitter systems. Groups of rats were injected with cocaine (15 mg/kg, i.p., b.i.d.) or saline for 1, 3, 7, 14 or 21 days. Cortical and striatal tissues were analyzed for norepinephrine, dopamine, serotonin and their primary metabolites using a HPLC-ECD method. Chronic administration of cocaine did not change the cortical and striatal concentrations of the neurotransmitters under study; except, for a transient increase in the cortical MHPG concentration on day 3. These results suggest that changes in the dopaminergic receptor system following chronic cocaine exposure are not due to changes in the neurotransmitter concentrations.

Abreviations used: 3,4-dihydroxyphenylethylamine, dopamine (DA); 3,4-dihydroxyphenylacetic acid (DOPAC); 3-methoxy-4-hydroxyphenylacetic acid (HVA); norepinephrine (NE); epinephrine (E); 3-methoxy-4-hydroxyphenethyleneglycol (MHPG); 5-hydroxytryptamine, serotonin (5-HT); 5-hydroxyindoleacetic acid (5-HIAA); high-performance liquid chromatography with electrochemical detection (HPLC-ECD).

INTRODUCTION

One of the actions of cocaine is the potentiation of neurotransmission in neurons that utilize biogenic amines as neurotransmitters. Biochemical evidence supports the hypothesis that the molecular mechanism of action of cocaine in the central nervous system (CNS) involves the inhibition of neuronal uptake of biogenic amines (10, 12, 26, 28, 32).

Investigators have shown that the dopaminergic neuronal network that innervates the nucleus accumbens is capable for modulating the reinforcing and discriminative effects of cocaine (9). These properties of cocaine are related more to the dopaminergic system than to the other monoaminergic systems (8, 9, 22, 27) in addition. Hurd and Ungerstedt (13) reported that the presence of cocaine in the rat corpus striatum produced an increase of extracellular dopamine in this brain area. In support of these results, other researchers using *in vivo* microdialysis have found increased concentrations of dopamine in different brain areas after cocaine administration (5, 16, 23, 24, 25). On the other hand, several groups of investigators have reported decreases in the synthesis and levels of dopamine and other catecholamines in brain after animals have been exposed to cocaine (6, 17, 29, 33, 35). Still others report no changes occur in the brain neurotransmitter systems after exposure to cocaine (11, 18, 36, 37)

In the last decade, much information about the mechanism of action of cocaine has been obtained. However, there is still no well defined mechanism to explain the psychotropic effects of cocaine. This is in spite of the fact that one of the major actions of cocaine is its ability to block the reuptake of monoamines in the CNS. This effect cannot explain the abuse liability of cocaine because other drugs, such as some tricyclic antidepressants that also block monoamine reuptake, are not abused to the same degree (7). In an attempt to more clearly define the effects of chronic cocaine on the monoaminergic system, we previously monitored binding to dopamine receptor and transporters. This was accomplished over time and with various doses in order to define a protocol which would maximize these receptor effects of cocaine. We now include the measurement of biogenic amine neurotransmitters and their metabolites over time in the same two brain areas (striatum and cortex) previously shown to manifest receptors alterations following chronic administration of cocaine.

MATERIALS AND METHODS

Male, Long-Evans rats were acquired from Simonson Laboratories (Gilroy, CA, USA). These animals were kept on a 12 h light/dark cycle and acclimatized to the housing facilities with food and water available *ad libitum*. Individual groups (5 to 6 animals per group) were injected with saline or cocaine (15 mg/kg, free base, intraperitoneal b.i.d.) for a period of 1, 3, 7, 14 or 21 days. Twelve hours after the last injection, animals were deeply anesthetized with carbon dioxide and an intracardial perfusion with ice-cold isotonic saline solution was performed. Cortices and striata were dissected and

immediately stored at -70 °C until the biogenic amines and metabolites were measured by HPLC-ECD.

The tissue preparation and the chromatographic analysis was performed as reported earlier (4). Cortices and striata from each animal were homogenized in a 0.05 N perchloric acid solution containing the following: octanesulfonic acid (0.064% w/v); heptanesulfonic acid (0.060% w/v); sodium ethylenediamine tetracetic (0.004% w/v); sodium metabisulfite (0.010% w/v), and 25 ng/ml dihydroxybenzylamine (as an internal standard). After homogenization, samples were centrifuged (30,000 x g for 20 min at 4 °C) and the resulting supernatant was filtered using 0.45 m HV Millipore filters and injected in the HPLC-ECD system. For the chromatographic analysis, a Nova-Pak C_{18} column (3.9 mm x 300 mm, 4 µm) was used and the mobile phase consisted of 90% (v/v) of a citrate solution (0.020 M citric acid trisodium salt, 0.010 M monobasic sodium phosphate, 0.003 M octanesulfonic acid, 0.003 M heptanesulfonic acid, 0.0001 M sodium ethylenediamine tetraacetate, 6.0 ml of o-phosphoric acid, 85% and 2.0 ml of diethylamine per liter of solution) , 7% (v/v) acetonitrile, and 3% (v/v) methanol. The final mixture was adjusted to pH 3.1. The analysis was carried out isocratically and performed at room temperature using a flow rate of 1.0 ml/min. The retention times (min) and the capacity factors (absolute value) for the monoamines and their metabolites were: MHPG, 3.54 and 0.59; DOPAC, 450 and 1.02; NE, 5.74 and 1.58; E, 6.93 and 2.12; DHB, 8.85 and 2.98; 5-HIAA, 10.63 and 3.78; DA, 12.81 and 4.77; HVA,

14.82 and 5.67; and 5-HT, 31.15 and 13.03, respectively.

The data were expressed as the mean value, plus or minus the standard error of the mean (S.E.M.) from 5 to 6 animals per group and were analyzed for variance using two way ANOVA test. Specific comparisons were made using a t-test. The degree of significance was set at p< 0.05.

RESULTS

The effects of chronic cocaine administration on the central neurotransmitter system was studied by analyzing catecholamines, indolamines and their major metabolites in two areas of the brain (cortex and striatum) at different time intervals. The results of repeated cocaine administration on dopamine and its metabolites in cortical and striatal tissues are shown in the Fig. 1. The concentration of DA, DOPAC and HVA in cortices and striata from animals injected with cocaine (15 mg/kg, i.p., b.i.d.), during the scheduled period of time (1, 3, 7, 14 and 21 days), were not significantly different from control animals. The cortical concentration of DA and HVA (Fig. 1A and 1C) in animals injected with cocaine or saline remained unchanged during the 21 days of drug administration; values ranged from 0.62 ± 0.12 to 2.00 ± 0.23 pmol/mg of tissue and from 0.73 ± 0.08 to 3.05 ± 0.69 pmol/mg of tissue, respectively. Cortical values of DOPAC (Fig. 1B) in cocaine and saline animals were parallel from the beginning (day 1) through the end of the experiment (day 21); the DOPAC values increased from 1.21 ± 0.51 to 5.23 ± 1.45 pmol/mg of tissue.
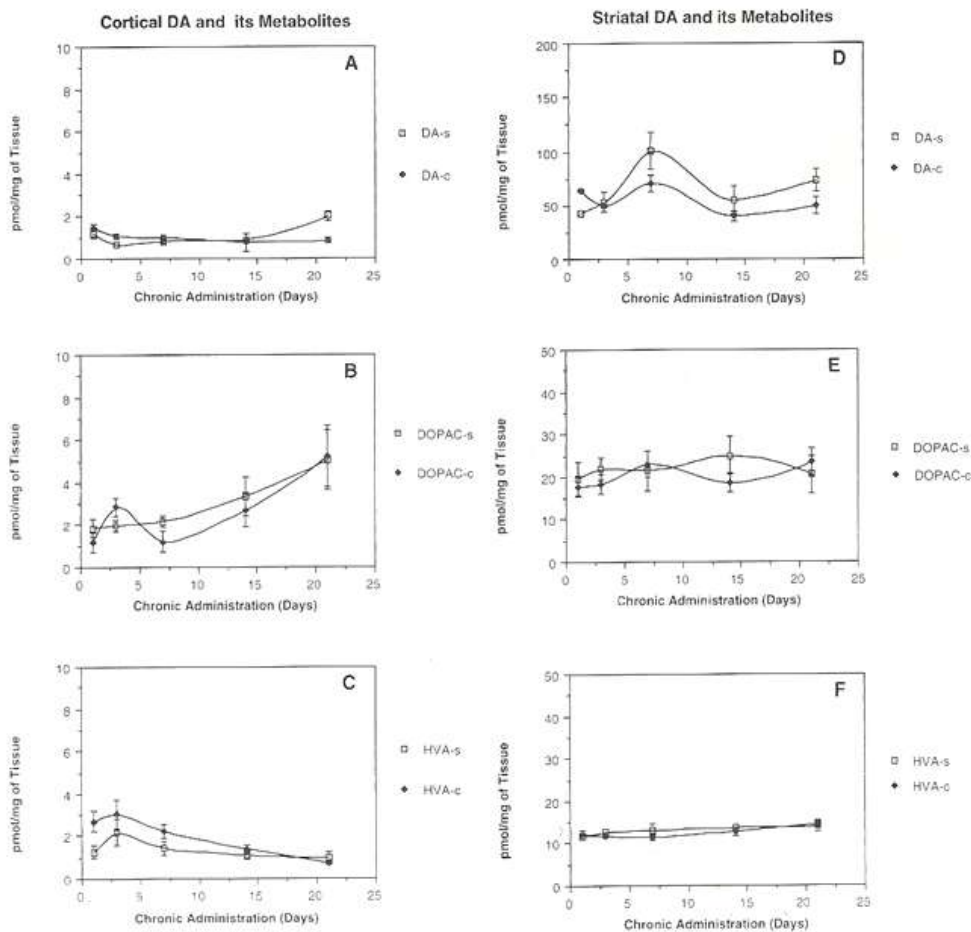
Fig. 1.   Effects of chronic administration (15 mg/kg, i.p., b.i.d. for 1, 3, 7, 14 or 21 days) on
rat cortical (A, B and C) and striatal (D, E and F) concentrations of DA, DOPAC and
HVA. Results are expressed as pmol/mg of tissue and represent the means $\pm$ S.E.M.
of 5 to 6 animals per group. Concentrations of DA, DOPAC and HVA in cortices and
striata from animals injected with cocaine (c) were not significantly different from
saline control animals (s).

Striatal concentrations of DOPAC (Fig. 1E) and HVA (Fig. 1F) in animals exposed to cocaine or saline were consistent during the 21 days schedule period; the DOPAC values ranged from 17.62 ± 2.28 to $23.47 3.28$ pmol/mg of tissue, the HVA from 11.44 ± 0.64 to 14.54 ± 0.74 pmol/mg of tissue. In both the control and cocaine treated animals, the striatal DA concentration was higher at seven days compared to the initial concentration. At day 14, the DA concentration returned to the initial levels in both groups. The striatal DA concentration in these groups of animals (cocaine and saline) were in the range of 40.29 ± 4.59 to 100.61 ± 16.74 pmol/mg of tissue.

Repeated cocaine injection was without effect on the concentrations of NE and E in the cortices and striata (Fig. 2), although a transient two-fold increase on the cortical levels of MHPG was found after three days of exposure (Fig. 2C). There was no significant differences in striatal concentrations of MHPG between the control and cocaine treated animals. The cortical concentrations of NE, E, and MHPG in cocaine or saline injected animals varied from 2.00 ± 0.06 to 5.03 ± 0.22, from 0.60 ± 0.18 to 2.32 ± 0.55, and from 1.31 ± 0.38 to 5.25 ± 0.54 pmol/mg of tissue (Figs. 2A, B and C), respectively, while in striatal tissue these concentrations ranged from 0.31 ± 0.02 to 0.52 ± 0.07, from 0.69 ± 0.40 to 1.82 ± 0.16, and from 0.21 ± 0.03 to 0.48 ± 0.05 pmol/mg of tissue (Figs. 2D, E and F) respectively.

Figures 3 (A, B, C and D) show that the chronic cocaine administration did not significantly affect the concentrations of either 5-HT or 5-HIAA in cortical and striatal brain tissue. The levels of these two compounds in animals exposed to chronic cocaine, were slightly higher than the control group during the study. This increase was not statistically significant. The cortical levels of 5-HT and 5-HIAA were from 1.09 ± 0.50 to 4.00 ± 0.44 and from 1.56 ± 0.08 to 4.22 ± 0.93 pmol/mg of tissue. The striatal concentration values ranged from 0.95 ± 0.09 to 3.60 ± 0.33 pmol/mg of tissue for 5-HT, and from 3.04 ± 1.05 to 5.15 ± 0.40 pmol/mg of tissue, for 5-HIAA.

DISCUSSION

One of the actions of cocaine in the CNS is to interfere with the uptake of dopamine into the catecholamine-containing neurons. Thus, some of the behavioral effects of cocaine exposure may be due to the action of DA present in the synaptic cleft. Chronic blockade of dopamine uptake with an antagonist like cocaine might be expected to cause an upregulation in cocaine binding/dopamine uptake sites. Likewise, the chronic presence of dopamine in the synaptic cleft, again resulting as a consequence of cocaine's ability to block dopamine uptake, might be expected to downregulate binding to dopamine receptors.

In previous studies, using the same treatment protocol, we were able to demonstrate time-dependent (1, 3) and dose-dependent (2, 34) increases in dopamine transporter binding in response to chronic administration of cocaine. This was accomplished with two uptake inhibitors [3H] cocaine and the DA-specific compound [3H]BTCP.
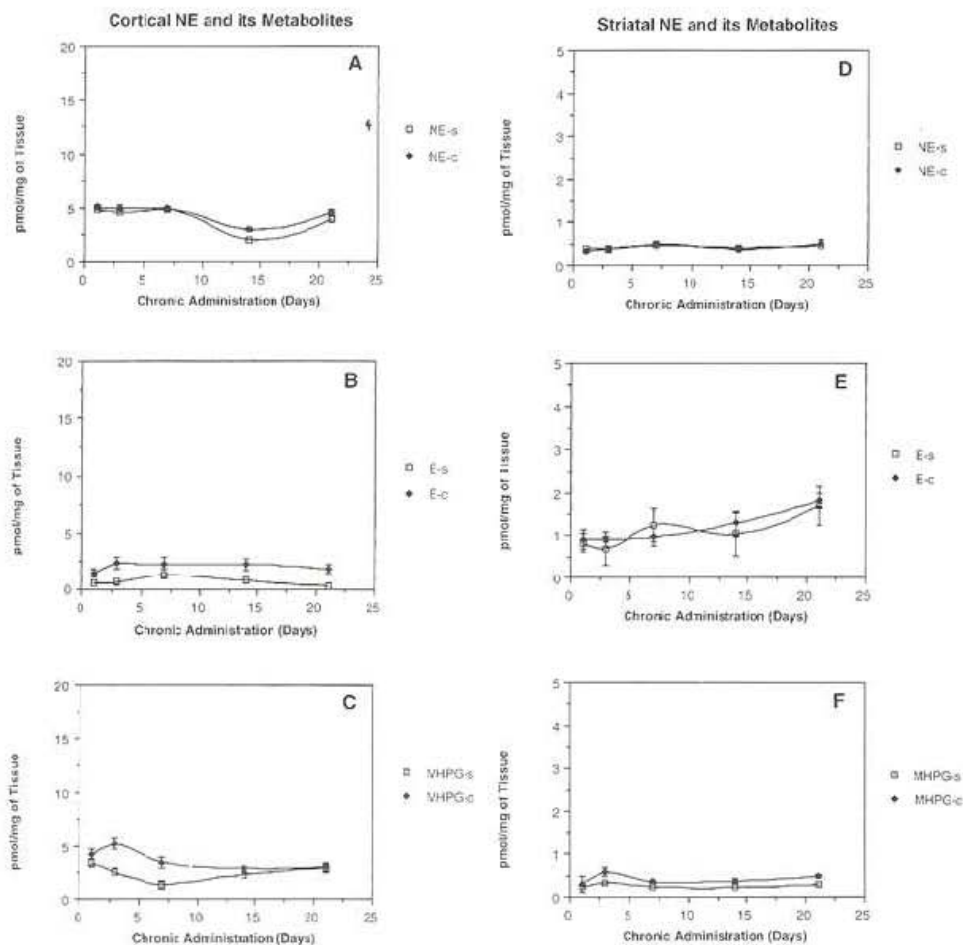
Fig. 2.   Effects of chronic cocaine administration (as scheduled in Fig. 1) on rat cortical (A, B and C) and striatal (D, E and F) concentrations of NE, E and MHPG. Results are expressed as pmol/mg of tissue and represent the means ± S.E.M. of 5 to 6 animals per group. Concentrations of NE, E and MHPG in cortices and striata from animals injected with cocaine (c) were not significantly different from saline control animals (s).
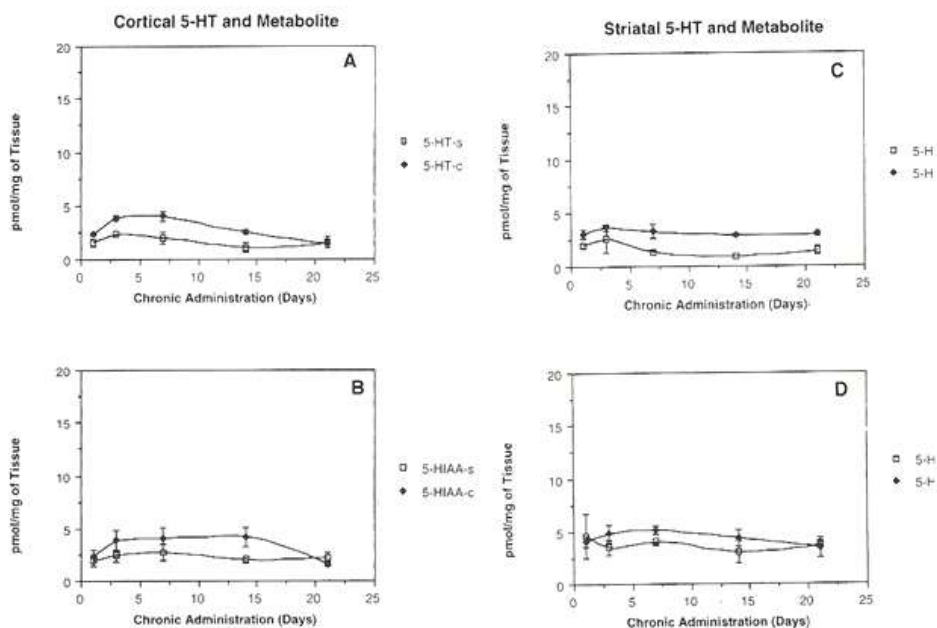
Fig. 3. Effects of chronic cocaine administration (as scheduled in Fig. 1) on rat cortical (A and B) and striatal (C and D) concentrations of 5-HT and 5-HIAA. Results are expressed as pmol/mg of tissue and represent the means ± S.E.M. of 5 to 6 animals per group. Concentrations of 5-HT and 5-HIAA in cortices and striata from animals injected with cocaine (c) were not significantly different from saline control animals (s).

In the same animals, we examined binding to two subtypes of dopamine receptors (D_1 and D_2). Not only we were able to demonstrate that the D_2 receptor population remains unchanged in response to cocaine, but to show a significant increase in D_1 receptor binding.

The increase in D_1 receptor binding could indicate that the dopamine receptor system (the D_1 subtype) is becoming desensitized in response to the chronic presence of cocaine. This observation could have important ramification on the addictive nature and reinforcing properties of cocaine. Another equally plausible explanation is that the chronic blockade of dopamine reuptake by cocaine has resulted in a depletion of dopamine from the neuronal terminals. This seem unlikely since the increased D_1 receptor binding can be measured as soon as day 3 of the treatment schedule. Still, the possibility exists that the D_1 receptor population is undergoing simple upregulation in response to the reduction in synaptic dopamine brought on by the chronic cocaine treatment.

In order to address this issue, and gain further insight into possible mechanisms of action of cocaine, the effects of cocaine on the concentrations of dopamine and its metabolites were studied. The exact cocaine exposure protocol used to cause the increase in D_1 receptor binding was used in the present study. In addition, the concentrations were monitored in cortex and striatum; brain regions where the increase in D_1 binding in response to cocaine was manifest. The measurements of dopamine were contrasted with similar analysis of norepinephrine, serotonin and their metabolites.

Results from this study suggest that animals exposed to previous published drug regimen (cocaine, 15 mg/kg, i.p., b.i.d.) failed to produce significant changes in levels of these neurotransmitters and their metabolites in either brain area examined (cortex and striatum). The results support those of previous studies (11, 18, 36, 37), where use of equivalent drug schedules or even continuous infusion of high doses of cocaine did not produce significant changes in DA, 5-HT, NE and their metabolites.

Other investigations of the effects of repeated administration of cocaine on central neurotransmitter systems in rat brain have provided contradictory results. Brain concentrations of neurotransmitters have been reported to increase (5, 16, 23, 24, 25), decrease (6, 17, 29, 33, 35) or remain unchanged (11, 18, 31, 36, 37) following chronic cocaine exposure. In studies where elevated concentrations of brain catecholamines have been reported, the high values of DA have been observed from 15 to 30 min after the last injection. These effects are brief and return to base line levels between 80 and 180 min after cocaine administration. It is difficult to make comparisons between these investigations due to different dosing schedules. Our results were obtained twelve hours after the last dose (measurements were made 12 hr after 1, 3, 7, 14 or 21 days of chronic exposure to cocaine), in order to determine more lasting changes in neurotransmitter levels. Shorter time periods might well show transient changes, but these would been unrelated to the receptor alterations noted previously. Studies which describe a

decrease in the concentrations of DA, DOPAC and HVA in frontal cortex and striatum, also involve a minimal and transient reduction in the levels of the neurochemicals (in the order of 19 to 33% of basal levels). Again, these differences are presumably due to differences in experimental methodology such as dosing schedule, protocols, or time after drug treatment. However, our findings are in agreement with results from studies where similar drug protocols were used. For example, Taylor and Ho, (31) and Kleven et al., (18), reported no changes in brain catecholamine concentrations after chronic administration of cocaine (10 mg/kg, i.p., for 5 or 10 days), and the measurements were made at least 24 to 36 hr after the last injection. In addition, Hanson et al., (11); Yu et al (37); and Yeh and DeSouza, (36); used repeated injections of cocaine (20 mg/kg, s.c or i.p., for 1, 7 or 8 days), and brain tissues were obtained at least 18 to 24 hr after the last dose. These investigations were unable to observe changes in the concentration of DA, 5-HT, NE and their metabolites in rat brain samples.

The present study demonstrates that chronic cocaine administration does not produce a significant persistent change in the concentration of DA, NE, 5-HT or their major metabolites in rat cortical or striatal tissues after chronic exposure to cocaine. Cocaine is a psychostimulant that acts as an indirect catecholaminergic agonist (14, 21, 30) and the psychotogenic potency of this drug has been correlated with its effects on DA mediated activity (15, 20). This would suggest that chronic exposure to cocaine might cause long-term changes in the brain DA neurotransmitter system. However, in the present study, we observed that a persistent change did not occur. Probably, the behavioral sensitization phenomena observed during chronic cocaine administration is not due to changes in the neurotransmitter levels. It is possible that the behavioral effects resulting from long-term cocaine exposure may more likely be associated with changes in the dopaminergic receptor system, as we have suggested in previous communications (1, 2, 3, 34).

In summary, the results of the present study, in addition to others, provide evidence that chronic exposure to cocaine does not produce long-term effects on the levels of dopamine, serotonin or noradrenaline, or their metabolites. Therefore, depletion of dopamine from the synaptic cleft does not appear to represent a plausible explanation for the D_1 receptor upregulation induced by chronic exposure to cocaine. This strengthens the hypothesis that the D_1 receptor upregulation may represent a sensitization process (reverse tolerance) that may have important biobehavioral consequences in the addict.

ACKNOWLEDGEMENTS

RESUMEN

Efecto de la administración crónica de cocaína sobre los niveles de monoaminas en el Sistema Nervioso Central de la rata. Alburges, M. (Center for Human Toxicology, Department of Pharmacology, University of Utah, Salt Lake City, Utah 84108, USA), Wamsley, J.K. *Invest Clin 34(4): 181-192, 1993.*

En estudios previos hemos reportado cambios en el sistema de receptores dopaminérgicos de las ratas (incremento de los sitios de fijación de cocaína, D_1, y de DA-reincorporación), los cuales dependen del tiempo y de las dosis de cocaína administradas crónicamente. En éste trabajo hemos evaluado los efectos de la administración crónica de cocaína en el sistema de neurotransmisores catecolamínicos e indolamínicos. Grupos de ratas fueron inyectadas por 1, 3, 7, 14 o 21 días, con cocaína (15 mg/kg, i.p., b.i.d.) o solución salina. Norepinefrina, dopamina, serotonina y sus metabolitos primarios fueron analizados en tejidos corticales y estriatales usando un método de HPLC-ECD. La administración crónica de cocaína no cambió las concentraciones de estos neurotransmisores en los tejidos estudiados, excepto, por un incremento transitorio de MHPG en la corteza, que ocurrió al tercer día de la administración de cocaína. Estos resultados sugieren que los cambios observados en el sistema de receptores de dopamina después de una administración crónica de cocaína no son debidos a cambios en las concentraciones de neurotransmisores.

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