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Decreased Accumbens Dopamine Release After Cocaine Challenge in Behaviorally Sensitized Female Rats

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JOHNSON, D. W., P. EODICE, H. WINTERBOTTOM AND D. J. MOKLER. *Decreased accumbens dopamine release after cocaine challenge in behaviorally sensitized female rats*. PHARMACOL BIOCHEM BEHAV **65**(4) 659–664, 2000.—The effects of the competitive NMDA receptor antagonist CPP on the initiation of behavioral sensitization to acute cocaine and basal and acute cocaine-induced dopamine (DA) release in the nucleus accumbens (NAC) were assessed in female Sprague–Dawley rats. Cocaine pretreated rats (30 mg/kg IP, once daily for 7 days) challenged with cocaine (10 mg/kg) on day 8 displayed increased motor activity relative to controls challenged with cocaine on day 8. This effect was blocked in rats receiving CPP (2 mg/kg) 15 min prior to all cocaine pretreatments. Basal DA levels in the NAC of both cocaine-pretreated and CPP plus cocaine-pretreated rats were higher on day 8 compared to controls. Acute cocaine challenge on day 8 resulted in increased extracellular DA concentrations in the NAC in control rats, no increase in rats pretreated with CPP plus cocaine, and a decrease in rats pretreated with cocaine only. These data demonstrate that development of behavioral sensitization to cocaine in female Sprague–Dawley rats can be completely blocked by a peripherally administered competitive NMDA receptor antagonist and that an increase in DA release in the NAC after a cocaine challenge is not an absolute requirement for expression of motor sensitization to cocaine in female rats.

Sensitization Cocaine Microdialysis NMDA Rats Dopamine Nucleus accumbens

IT has been known for some time that repeated exposure to psychostimulants such as cocaine produces behavioral sensitization, characterized in part by an increase in stereotypical behavior, and an exaggerated motor response to subsequent challenge administration of these drugs (8,17). Understanding how behavioral sensitization occurs is of interest, as chronic use of ilicit drugs that produce this phenomena can result in psychosis (20), or an increased craving for the illicit drug (17). Efforts to elucidate the neurochemical mechanisms involved in the development of behavioral sensitization to cocaine have found that this phenomena is at least partly due to increasing basal extracellular levels of DA in the mesolimbic terminal areas of the rat brain, particularly the NAC, over the time period the animal is receiving daily cocaine injections (3,6,25). These increased extracellular DA levels in the NAC decline towards normal within 7 days after stopping daily cocaine injections. Furthermore, the DA response in mesolimbic terminal fields to a challenge dose of cocaine after cocaine pretreatments tends to be greater the more days that have passed since the pretreatments were terminated (6).

It has also been demonstrated in recent years that activation of the *N*-methyl-D-aspartic acid (NMDA) receptor, one of the three major subtypes of excitatory amino acid (EAAs) receptors in the CNS, is involved in the process of development of behavioral sensitization to cocaine, while non-NMDA types of EAA receptors are more involved in the actual expression of cocaine behavioral sensitization to a challenge dose of cocaine (10,19). In fact, several studies have shown that coadministration of an NMDA receptor antagonist along with cocaine blocks the development of behavioral sensitization to a subsequent challenge dose of cocaine (9,26). In the present study, we determined the basal levels of extracellular DA in the NAC 1 day after termination of a series of daily cocaine injections (with and without coadministration of

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an NMDA receptor antagonist), which produces behavioral sensitization, as well as changes in basal extracellular DA and the DA metabolite DOPAC to a challenge dose of cocaine. Furthermore, because the vast majority of cocaine sensitization studies have utilized male rats, we chose to use females, to find whether our results might differ from those commonly found in male rats.

METHOD

Materials

Female Sprague–Dawley rats purchased from Charles River Laboratories (Wilmington, MA) and weighing 275–326 g, were housed in the University animal quarters, on a 12 L:12 D cycle, with free access to food and water. CPP (3-(2-carboxypiperazin-4yl)propyl-1-phosphonic acid) and cocaine HCl were purchased from Sigma Chemical Company (St. Louis, MO). All other reagents were obtained from standard commercial sources.

Drug Administration

Cocaine HCl and CPP were dissolved in saline. Both drugs were dissolved in a concentration that allowed administration at 1 μl/g of b.wt. to achieve the desired dosage. Control rats were injected with an equivalent volume of saline.

Motor Activity

All rats used in motor activity studies were assigned to one of four treatment groups: 1) rats receiving a daily saline injection, followed 15 min later by another saline injection, followed by a challenge dose of saline (SAL/SAL/SAL group); 2) rats receiving a daily saline injection, followed 15 min later by another saline injection, followed by a challenge dose of cocaine HCl (SAL/SAL/COC group); 3) rats receiving a daily saline injection, followed 15 min later by a cocaine HCl injection, followed by a challenge dose of cocaine HCl (SAL/COC/COC group); and 4) rats receiving a daily CPP injection, followed 15 min later by a cocaine HCl injection, followed by a challenge dose of cocaine HCl (CPP/COC/COC group). CPP was injected at a dose of 2 mg/kg. Daily cocaine HCl injections were 30 mg/kg once a day for 7 days, and challenge cocaine HCl injections were administered at 10 mg/kg on day 8. Challenge doses of saline were also administered on day 8. All injections were given IP.

Rats from each treatment group were brought daily from the animal facility to the room housing the activity monitors and injected as described above. After the daily injections, rats were placed immediately in the activity boxes and allowed to acclimate for 60 min, and subsequently returned to their home cages in the animal facility. When the cocaine HCl or saline challenge injections were given on day 8, rats were immediately placed in activity boxes and total motor activity was recorded to 60 min thereafter. All rats were subsequently brought back to the activity boxes and rechallenged with cocaine HCl or saline 14 days later, to check for persistency of behavioral sensitization

Dialysis Experiments

For microdialysis experiments, rats were anesthetized with pentobarbital sodium (50 mg/kg), and atropine, 1 mg/kg. Rats were stereotaxically implanted with guide cannulae (CMA Microdialysis, Acton, MA) into the NAC (coordinates were rostral +1.6 and lateral +1.5 from bregma, and ventral −4.6 from the skull surface). Rats were allowed a minimum of 2 days of recovery before beginning daily injections. The same treatment groups were used as in the motor activity experiments. Rats from each treatment group were brought daily from the animal facility and injected as described above. After injections, rats were placed in the microdialysis chamber for 60 min to acclimate, and then returned to their home cages. Approximately 5 h after the last injection on day 7, the dummy guide was removed from the surgically implanted guide cannula, and a microdialysis probe (CMA 10, 2-mm tip, CMA Microdialysis, Acton, MA) was inserted. Following this, rats were placed in the microdialysis chamber and perfusion of the probe with artificial cerebrospinal fluid (NaCl, 145 mM; KCl, 2.7 mM; CaCl, 1.2 mM; MgCl, 1.0 mM; ascorbate, 0.05 mM, pH 7.4) was begun at a flow rate of 0.1 μl/min. The following morning the perfusion flow rate was increased to 1.0 μl/min for 60 min, and then sample collection was begun over 20-min periods. Four baseline samples were obtained and the challenge injection of cocaine or saline was given immediately after obtaining the fourth sample. Six postinjection samples were then obtained, whereupon rats were euthanized with an overdose of sodium pentobarbital, decapitated, and probe placement confirmed histologically. All dialysate samples were frozen at −80°C, and analyzed within 2 weeks for DA and DOPAC by HPLC, with electrochemical detection.

Data Analysis

Data were analyzed using a two-factor ANOVA with repeated measures over time. Post hoc analysis was performed, when appropriate, with the Student–Newman–Keuls range test for multiple comparisons of means.

RESULTS

As seen in Fig. 1A, rats receiving cocaine for the first time on day 8 (SAL/SAL/COC group) had greater total motor activity counts at all times than control rats receiving a saline injection on day 8 (SAL/SAL/SAL group; $p < 0.01$ to 0.001.). Furthermore, those rats receiving cocaine on day 8, and pretreated with cocaine (SAL/COC/COC group) had higher total motor activity counts at all times than the SAL/SAL/COC rats ($p < 0.04$ to 0.01). This regimen of daily cocaine injections over 7 days was, therefore, adequate to produce behavioral sensitization to a challenge dose of cocaine on day 8. In addition, rats pretreated with CPP and cocaine produced similar activity counts at all times as those rats receiving cocaine for the first time. Therefore, daily CPP injections 15 min prior to daily cocaine injections were able to block the production of behavioral sensitization to a challenge dose of cocaine (Fig. 1A, the CPP/COC/COC group vs. the SAL/COC/COC group, $p < 0.05$ to 0.01). This sensitization persisted for at least an additional 14 days, although activity counts were only greater in the SAL/COC/COC group for the first 30 min compared to the SAL/SAL/COC group (Fig. 1B; $p < 0.01$ to 0.05), and for the first 20 min compared to the CPP/COC/COC group (Fig. 1B; $p < 0.05$).

The basal extracellular DA concentrations in the NAC on day 8 were no different among rats pretreated with saline (SAL/SAL/SAL and SAL/SAL/COC; 10.3 ± 1.8 vs. 13.4 ± 2.3 nM, respectively, Fig. 2). However, extracellular DA concentrations were approximately fourfold higher in rats pretreated with cocaine (SAL/COC/COC; 49.6 ± 8.8) compared to rats pretreated with saline ($p < 0.01$, Fig. 2). Furthermore, rats coadministered CPP along with cocaine also had extra-

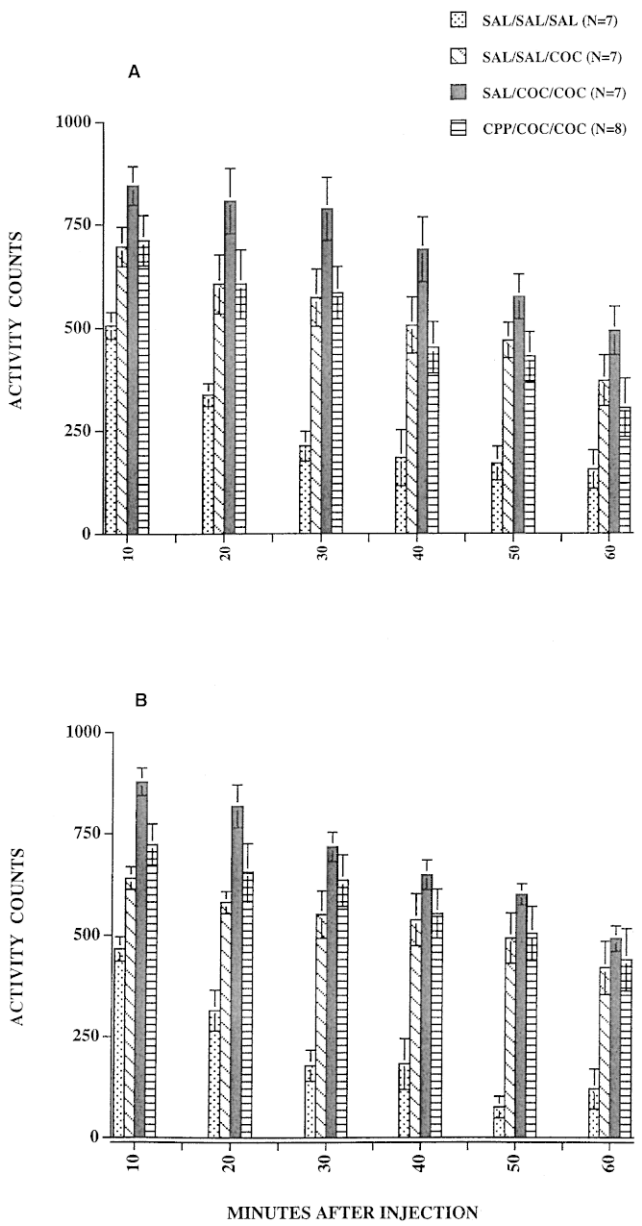

FIG. 1. The effect of cocaine, cocaine plus CPP, or saline pretreatments on the locomotor-activating effects of an acute dose of cocaine or saline on day 8. (A) Rats receiving cocaine for the first time on day 8 (SAL/SAL/COC group) had greater total motor activity counts at all times than control rats receiving a saline injection on day 8 (SAL/SAL/SAL group; $p < 0.01$ to 0.001). Rats receiving cocaine on day 8 that were pretreated with cocaine (SAL/COC/COC group) had higher total motor activity counts at all times than rats receiving cocaine for the first time (SAL/SAL/COC group; $p < 0.05$ to 0.01). Rats pretreated with both CPP and cocaine (CPP/COC/COC group) produced similar activity counts at all times that were not different from those rats receiving cocaine for the first time. (B) The behavioral sensitization to acute cocaine seen in the SAL/COC/COC group on day 8 was still present 14 days later for the first 30 min after acute cocaine, when compared to the SAL/SAL/COC group ($p < 0.05$ to 0.01) and for the first 20 min after acute cocaine when compared to the CPP/COC/COC group ($p < 0.05$). See text for explanation of groups.

cellular DA concentrations in the NAC that were greater than rats pretreated with the saline (CPP/COC/COC group; 39.4 ± 8.3, $p < 0.01$). Basal DA concentrations were not different between rats pretreated with cocaine (CPP/COC/COC vs. SAL/COC/COC, respectively; Fig. 2), and basal DOPAC concentrations in the NAC were not different among any groups (data not shown).

The increase in concentration of DA in the NAC after a challenge dose of cocaine on day 8 was greatest in rats pretreated with saline (SAL/SAL/COC), with increased concentrations seen at 20, 40, 60, and 80 min postinjection (vs. SAL/SAL/SAL controls; $p < 0.05$ to 0.01), and peak concentrations occurring at 40 min postinjection (Fig. 3). Rats pretreated with both cocaine and CPP (CPP/COC/COC) had elevations in basal DA concentrations in the NAC at 20 and 40 min after cocaine injection, but this was not different from the changes in SAL/SAL/SAL controls (Fig. 3). In rats pretreated with cocaine but not CPP (SAL/COC/COC), basal DA levels declined from 40 to 120 min in the NAC following an acute injection of cocaine ($p < 0.05$ at 40 and 120 min, compared to SAL/SAL/SAL; Fig. 3). The concentration of DOPAC in the NAC declined within 40 min after acute cocaine injection in all groups, when compared to SAL/SAL/SAL controls (Fig. 4). However, the decline in DOPAC concentration after acute cocaine was greater between 40 and 120 min in those rats pretreated with cocaine (SAL/COC/COC) and 40 and 100 min in rats pretreated with cocaine plus CPP (CPP/COC/COC), when compared to declines in DOPAC in rats receiving co-

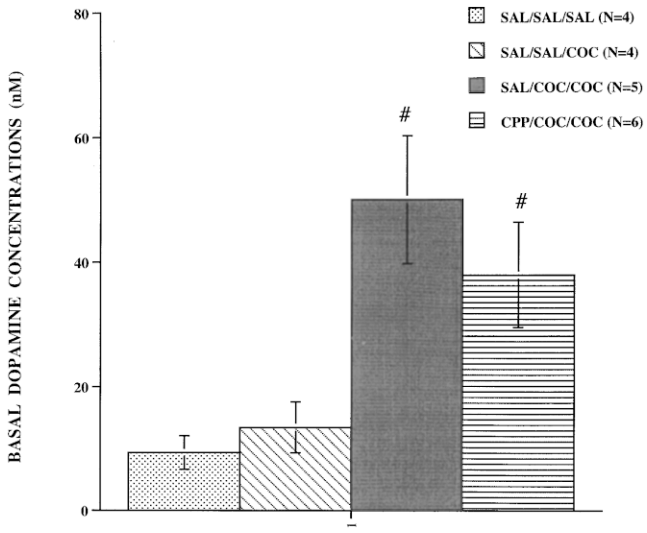

FIG. 2. The basal concentrations of dopamine (DA) in the microdialysate obtained from the nucleus accumbens (NAC) of female rats on day 8, following 7 days of daily saline, cocaine, or cocaine + CPP injections. The basal dialysate DA concentrations in the NAC on day 8 were not different among rats pretreated with saline (SAL/SAL/SAL group vs. SAL/SAL/COC group). Dialysate DA concentrations were approximately fourfold higher in rats pretreated with cocaine (SAL/COC/COC group) compared to rats pretreated with saline. Rats administered CPP 15 min prior to cocaine (CPP/COC/COC group) also had dialysate DA concentrations in the NAC that were greater than rats pretreated with saline. Basal dialysate DA concentrations were not different between rats pretreated with cocaine. #$p < 0.01$, compared to both SAL/SAL/SAL and SAL/SAL/COC groups. See text for explanation of groups.

caine for the first time (SAL/SAL/COC, $p < 0.01$ to 0.001, vs. $p < 0.05$ to 0.01, respectively).

DISCUSSION

This study clearly shows that, under our conditions, expression of behavioral sensitization to acute cocaine can be demonstrated within 24 h after completion of 7 days of daily cocaine injections. Furthermore, these data also show that the competitive NMDA receptor antagonist CPP is capable of disrupting the production of behavioral sensitization to cocaine, when given IP, 15 min prior to daily cocaine injections (Fig. 1A). Furthermore, this CPP-induced blockade of behavioral sensitization to repeated cocaine injections persists for at least 14 days (Fig. 1B).

The increased basal concentrations of DA seen in the NAC of cocaine-pretreated rats in our study have been found elsewhere (6,25). It is known that basal DA concentrations in the NAC are highest within 1 day or 2 days after terminating repeated cocaine injections, and then decline from that point onward (6). This is likely due to a somatodendritic impulse-regulating DA autoreceptor subsensitivity in the A10 region of the ventral tegmental area that is produced by repeated cocaine treatments (1). Rats pretreated with cocaine or cocaine plus CPP in this study received their last daily cocaine injection in the afternoon of day 7, and were dialyzed on the morning of day 8. Therefore, the actual elapsed time between final cocaine pretreatment and measurement of basal DA concentrations in the NAC on day 8 was approximately 17 h.

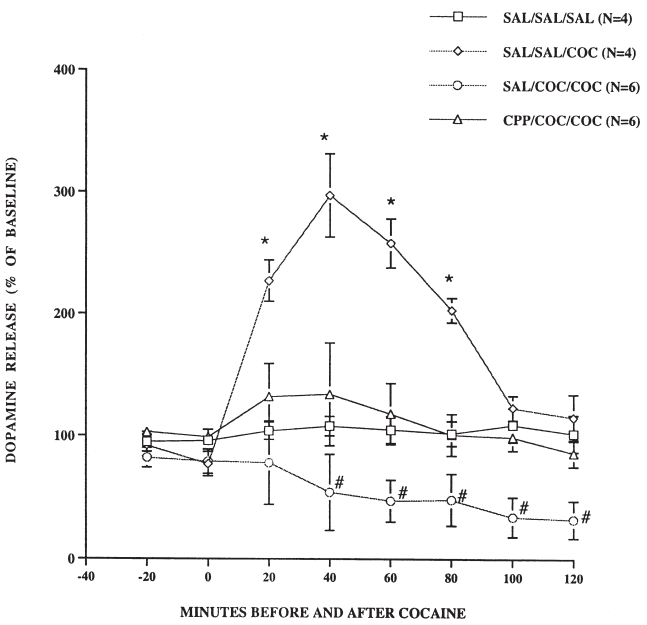

FIG. 3. The effects of acute cocaine or saline on day 8 on dialysate dopamine (DA) concentration obtained from the nucleus accumbens (NAC), following 7 days of daily saline, cocaine, or cocaine + CPP injections. Saline injection did not alter dialysate DA concentration from baseline. Dialysate DA concentration after a challenge dose of cocaine on day 8 was greatest in rats pretreated with saline (SAL/SAL/COC group), with increases seen at 20, 40, 60, and 80 min postinjection. Dialysate DA concentrations after acute cocaine did not differ in the CPP/COC/COC group at any time compared to saline-injected controls. In rats pretreated with cocaine (SAL/COC/COC group), basal dialysate DA concentrations declined from 40 to 120 min, following acute cocaine. Cocaine was injected at time 0. *$p < 0.05$ to 0.01 compared to SAL/SAL/SAL group; #$p < 0.05$ at 40 to 120 min, compared to SAL/SAL/SAL group. See text for explanation of groups.

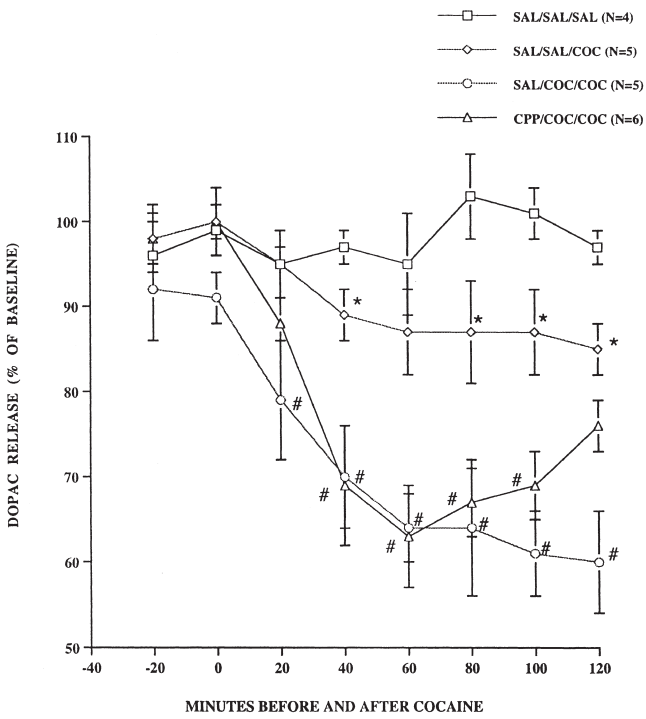

FIG. 4. The effects of acute cocaine on day 8 on dialysate DOPAC concentration in the nucleus accumbens (NAC), following 7 days of daily saline, cocaine, or cocaine + CPP injections. The dialysate DOPAC concentration declined within 40 min in the SAL/SAL/COC group when compared to SAL/SAL/SAL controls. The dialysate DOPAC concentration declined within 20 min in the SAL/COC/COC group, and within 40 min in the CPP/COC/COC group, when compared to the SAL/SAL/COC group. Cocaine was injected at time 0. *$p < 0.05$ to 0.01; #$p < 0.01$ to 0.005. See text for explanation of groups.

Differences in basal DA concentrations in the NAC may be responsible for the varied DA response in the NAC seen between groups after a cocaine challenge on day 8 (Fig. 3). Higher basal concentrations of DA in the NAC tend to blunt the relative (percentage of basal) DA overflow to a challenge injection of cocaine (25). This agrees with our current findings in rats pretreated with both cocaine and CPP, which had high basal DA concentrations. The expected increase in DA concentration after acute cocaine challenge was blunted in these animals compared to rats challenged with cocaine for the first time on day 8 (Fig. 3). This phenomena may be due to a relative depletion in vesicular DA, which is present in the mesolimbic DA terminals in the NAC for the first days following chronic cocaine injections. Additionally, high concentrations of cocaine or cocaine metabolites that might still be present in the NAC during the first days following cessation of chronic cocaine treatments could also decrease the efficacy of an acute dose of cocaine to increase basal DA concentrations (14–16).

The most difficult finding to explain in the present study is the actual decline in the percentage of basal extracellular DA present in the NAC following acute cocaine on day 8 in those rats chronically pretreated with cocaine only (SAL/COC/

COC; Fig. 3). Most studies using models similar to ours demonstrate a response to acute cocaine in cocaine-pretreated rats like that seen in our CPP/COC/COC group, which is an increase in the DA concentration in the NAC that is not as great as that seen in naive rats receiving the same dose of cocaine. This is generally true as long as the acute dose is being administered within 2 or 3 days of terminating the cocaine pretreatments (21,25). However, this findings in our SAL/COC/COC group was robust and seen consistently in this group. At least one other study has shown a subtle decline in basal DA concentrations in the NAC in rats receiving a challenge injection (saline) soon after receiving repeated cocaine injections (7).

One possible explanation for this unusual finding is our use of female rats, because all similar studies of which we are aware that measured the DA response to acute cocaine in the NAC shortly after cessation of chronic daily cocaine treatments used male rats. Female rats are known to be more sensitive to both acute and chronic behavioral effects of cocaine, compared to males (22,24). The rat estrous cycle, possibly because of changing quantities of gonadal steroids over the 5-day cycle, has been shown to alter stimulant-induced DA release in at least the striatum. Peris et al. (13) ovarioectomized female rats and subsequently implanted them with exogenous steroids, then injected cocaine for 8 consecutive days. They found that within 24 h after terminating cocaine injections, amphetamine-stimulated release of [^{3}H]DA from striatal slices was significantly lower among ovarioectomized female rats that had been implanted with progesterone only, and significantly higher among those implanted with estradiol only, compared to control rats. This suggests that C21 progestins like progesterone diminish stimulant-mediated DA release in the striatum, while C18 estrogens such as estradiol enhance it.

It has also been shown using microdialysis that progesterone and estrogen modulate DA efflux in the NAC similar to the striatum, when the NAC DA release is mediated through DA receptor stimulation of the entorhinal cortex (18). Thus, female rats in the late proestrous phase of the estrous cycle (when progesterone levels are high) might be expected to have a blunted DA response in the NAC to a stimulant, compared to a male rat.

An effect of gonadal steroids on DA release has been found elsewhere as well. Castner et al. (4), using in vivo microdialysis, demonstrated that a single SC injection of estradiol enhanced amphetamine-stimulated striatal DA release in ovarioectomized female rats, but had no effect on castrated male rats. A similar effect of estrogen has been seen on potassium-stimulated release of striatal DA in castrated male and female mice (12). The fact that gonadal steroids seem to play a role in modulating DA release in the brain may partly explain why beta estradiol and progesterone have been shown to be directly involved in modifying cocaine self-administration (5) and cocaine facilitation of behavioral lordosis (2).

We cannot ascertain with certainty in the present study why dialysate DA concentrations declined steadily in female rats after acute cocaine administration less than 24 h after being chronically pretreated with cocaine (the SAL/COC/COC group). Both the SAL/COC/COC group and the CPP/COC/COC group experienced similar large declines in DOPAC compared to rats receiving cocaine for the first time (SAL/SAL/COC group; see Fig. 4). This suggests that the decline in DA in the SAL/COC/COC group was not directly due to a significant change in reuptake or metabolism of DA. Therefore, a reasonable conclusion might be that the decline in DA in the SAL/COC/COC group was due to a change in DA release by mesolimbic dopaminergic neurons terminating in the NAC. The fact that a DA decline after cocaine challenge was not seen in the rats that were administered CPP 15 min prior to cocaine during pretreatments suggests that chronic activation of NMDA receptors was a prerequisite for this putative change in release of accumbens DA after acute cocaine. This is interesting, as NMDA receptors in both the NAC and ventral tegmental area are known to play important roles in modulating mesolimbic dopaminergic neuron activity (11), and it is well established that NMDA receptors present in the NAC modify DA release in this structure (27). However, further studies are obviously required to prove this hypothesis.

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