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Intra-VTA Baclofen Attenuates Cocaine Self-Administration on a Progressive Ratio Schedule of Reinforcement

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BREBNER, K., R. PHELAN AND D. C. S. ROBERTS. *Intra-VTA baclofen attenuates cocaine self-administration on a progressive ratio schedule of reinforcement.* PHARMACOL BIOCHEM BEHAV **66**(4) 857–862, 2000.—The effect of microinjections of baclofen into the ventral tegmental area (VTA), nucleus accumbens, or striatum on cocaine self-administration reinforced on a progressive ratio schedule was investigated. Intra-VTA baclofen produced the most potent modulation of cocaine intake, causing a significant reduction in cocaine-reinforced break points at a dose (56 ng/side) that was substantially lower than doses necessary to produce comparable reductions in the nucleus accumbens or striatum. During the time that cocaine-reinforced responding was suppressed, rats demonstrated the capacity to complete several hundred responses on a concurrently available food-reinforced lever, indicating that the effect of baclofen on cocaine intake was not due to a generalized disruption in operant responding. The results indicate that $GABA_B$ receptors in the VTA may have the potential to modulate reward processes associated with cocaine use. © 2000 Elsevier Science Inc.

GABA Baclofen Cocaine Self-administration Ventral tegmental area Accumbens Striatum Progressive ratio schedule Intracerebral Dopamine

RECENT behavioral studies have indicated that drugs specific to gamma aminobutyric acid (GABA) synapses have powerful effects on cocaine reinforcement (2–4,9,18,27,28, 30). Several investigators have demonstrated that the selective $GABA_B$ receptor agonist baclofen attenuates cocaine self-administration across a wide range of conditions, including multiple (30), progressive ratio (PR) (3,28), fixed ratio (FR) (4), concurrent access (3), and discrete trials schedules of reinforcement (27). Taken together, these studies suggest that baclofen's effect on cocaine self-administration is dependent on the unit injection dose of cocaine and on the response requirements of the schedule (4).

The neural substrates that underlie GABAergic modulation of cocaine reinforcement are, as yet, unknown. Our working hypothesis is that baclofen's impact on cocaine self-administration is mediated through $GABA_B$ receptors on dopaminergic neurons within the ventral tegmental area (VTA). GABA has extensive interactions with the mesolimbic DA system, which has been shown to play a critical role in the reinforcing effects of cocaine (1,6,14,17,21). The majority of neurons in the nucleus accumbens (NAC) are GABAergic neurons that project to DA cells within the VTA and regulate their activity (15). The VTA contains two major cell types: the primary dopaminergic neurons, which release DA in the NAC and prefrontal cortex, and the secondary GABAergic neurons, which function as inhibitory interneurons to control the firing of primary DA neurons (13,31, 34,38). The DA cells of the VTA project principally to the NAC, thus forming a feedback loop that is presumably sensitive to cocaine-induced alterations in DA signals. Microinjection of baclofen into the VTA decreases extracellular DA in the NAC and the prefrontal cortex (14,16,35,37,41). Manipulation of GABAergic transmission in the VTA also attenuates the rewarding properties of intracranial self-stimulation (39), morphine-induced place preference (33), and heroin- (40) and cocaine-reinforced responding (30).

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At present, only one other report has examined the effect of intracerebal baclofen on cocaine self-administration. Shoaib et al. (30) demonstrated that under an FR5 schedule of reinforcement, microinjection of 200 ng of baclofen into the NAC, or 300 ng into the VTA produced a significant decrease in the rate of cocaine intake. They conclude that activation of $GABA_B$ receptors in both the NAC and in the VTA modulates the reinforcing properties of cocaine.

There is evidence that doses of baclofen that have little or no effect on cocaine intake under FR schedules markedly decrease break points on the PR schedule (3,28). The present investigation used a PR schedule of reinforcement to clarify whether $GABA_B$ receptors in the VTA or NAC are more important in mediating the effect of baclofen on cocaine self-administration. Separate groups of rats received bilateral microinjections of various doses baclofen into the VTA, NAC, or striatum (STR). Rats were given concurrent access to a food-reinforced lever during cocaine self-administration sessions to demonstrate that baclofen did not interfere with the capacity to respond during the period when cocaine-reinforced responding was suppressed.

METHOD

Subjects

Subjects were male Wistar rats (Charles River Farms, Quebec) weighing 275–300 g at the start of the experiment. All animals were placed under quarantine for 1 week following arrival at the facility and were maintained on a 12 L:12 D cycle (lights on at 1500 h). The care and treatment of all animals conformed with the standards of the Canadian Council on Animal Care and the guidelines promulgated by the Wake Forest University Animal Care and Use Committee and the National Institutes of Health.

Procedures and Apparatus

Following quarantine, animals were food deprived for 24 h, then trained to press a lever for food reinforcement on a FR1 schedule. Thereafter, Purina Rat chow was available ad lib, except as noted below. Each rat was implanted with a chronically indwelling Silastic® jugular cannula that exited through the skin on the dorsal surface in the region of the scapulae (29). Following cannulation, rats were individually housed in 25 × 25 × 25-cm operant testing apparatus. The cannula was connected through a stainless steel protective spring to a counterbalanced swivel apparatus that allowed free movement within the operant chamber. Water was available ad lib throughout all phases of the experiment.

Beginning the day after surgery, animals were given access to a single response lever that controlled the delivery of cocaine injections on an FR1 schedule. Concurrent with the start of each cocaine injection (1.5 mg/kg/injection in 0.12 ml saline) a stimulus light located above the lever was activated to signal a 20-s postinfusion time-out period, during which responses produced no programmed consequence. Rats received daily 6-h test sessions (0900–1500 h) that began with one priming injection. After the animals had established a stable daily pattern of intake of cocaine (3 consecutive days of >30 injections/6 h and regular postinfusion pauses) on an FR1 schedule, the reinforcement contingency was changed to a PR schedule. Cocaine infusions were contingent upon an increasing number of responses incremented through the following progression: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603. This procedure is described in detail in Richardson and Roberts (26).

Once stable responding on the PR schedule had been established (defined as 3 consecutive days of cocaine self-administration with break points within a range of 4), a food-reinforced lever was introduced. Rats were 16-h food deprived at the beginning of the session. Immediately following the session rats received access to Purina Rat chow for 2 h. The session began with the introduction of a food-reinforced lever that controlled the delivery of a 45-mg nutritionally balanced food pellet (Noyes Inc.) on an FR schedule of reinforcement. The lever controlling access to cocaine on the PR schedule was introduced 5 min later. Animals received a noncontingent food pellet and a drug injection immediately after each lever was introduced.

The food-reinforced schedule was incremented from FR1 to FR5 during the first four sessions, and daily baseline testing continued for at least 4 days before rats were stereotaxically implanted with a bilateral cannula for intracerebral (IC) injections. Rats were randomly assigned to one of three groups for surgery: VTA (n = 5), NAC (n = 6), and STR (n = 6). Cannulae were implanted into the VTA (A = −4.8, L = ±1.0, V = −7.2), the NAC (A = +1.0, L = 1.0, V −5.9), or the STR (A = +0.7, L = ±2.5. V = −4.0) with the incisor bar set 5 mm above the interaural line using coordinates from Paxinos and Watson (24). The tip of the injector was made to extend beyond the cannula by 1 mm. Delivery of baclofen was from a Hamilton syringe mounted in an infusion pump, connected to the injector by Silastic tubing.

Various doses of baclofen were administered IC 30 min before the session, according to a latinized design. The doses were 32, 56, or 100 ng/0.5 μl/side into the VTA, and 100, 180, or 320 ng/0.5 μl/side into the NAC and STR. (Note: a vehicle injection was included in the VTA group, to control for the injection procedure. The lowest dose of baclofen administered to animals in the NAC or STR groups failed to produce a significant decrease from baseline responding, and therefore served as a control). At least 3 days of baseline responding separated baclofen test days. Following completion of testing animals were deeply anesthetized with sodium pentobarbital and transcardially perfused with saline and formalin. Brains were removed, sliced, and stained with cresyl violet to confirm cannula placement.

Data Analysis

Break point was defined as the number of completed increments on the PR schedule before a 1 h period when no cocaine injections were obtained. The total number of responses on the food-reinforced lever was restricted to the first 2 h of the session when the effects of baclofen on cocaine self-administration were most evident. Data were analyzed by separate repeated-measures ANOVAs for each of the groups tested. Newman–Keuls tests (one tailed) were used to examine individual comparisons among animals that completed testing across all drug doses.

Drugs

Cocaine HCl was supplied by National Institute on Drug Abuse (Research Triangle, NC). (±)-Baclofen was purchased from Research Biochemicals International. All drugs were dissolved in pyrogen-free sterile saline. Dosages are expressed as the salt.

RESULTS

The histological localizations of the bilateral injection cannulae in the different brain regions are shown in Fig. 1. A total of five animals were included in the VTA group, and the NAC and STR groups contained six animals each. In all re-

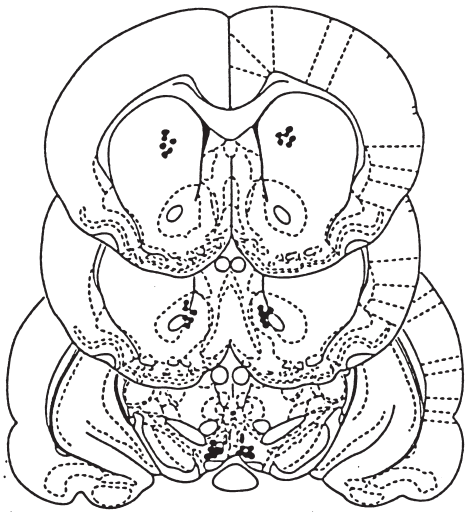

FIG. 1. Histological diagrams showing placement of microinjections into the striatum (top), NAC (middle), or VTA (bottom). Each point reflects the location of the baclofen infusion. Sections are modified from Paxinos and Watson (25).

gions studied, intracerebral injections of baclofen produced dose-dependent decreases in cocaine-reinforced break points.

Figure 2 (left) shows the effect of several doses of baclofen on responding under a PR schedule of reinforcement. Although baclofen significantly decreased cocaine-reinforced break points in all three groups of animals [VTA, $F(4, 16) = 10.49$, $p < 0.01$; NAC, $F(3, 15) = 36.16$, $p < 0.01$; and STR, $F(3, 15) = 4.05$, $p < 0.05$] the doses of baclofen required to produce a significant effect were substantially lower when injections were made into the VTA. Multiple comparisons demonstrated that the 56 and 100 ng doses of intra-VTA baclofen produced a significant decrease in cocaine self-administration ($p < 0.05$). In the NAC group, larger doses of baclofen (180 and 320 ng) were required to produce a similar impact on break points. In the STR group, a significant decrease in cocaine self-administration was only evident after the highest dose of baclofen (see Fig. 2, left).

The effect of IC baclofen pretreatment on responding for food reinforcement on an FR5 schedule is shown in Fig. 2 (right). Separate repeated-measures ANOVAs indicated that during the first 2 h of the test session when baclofen reduced cocaine self-administration, there was no significant effect on responding for food. Animals in all three groups completed several hundred responses on the food-reinforced lever, after even the largest doses of baclofen, indicating that they retained their capacity to complete the operant response.

Figure 3 (top left) shows the pattern of responding for concurrently available food- or cocaine-reinforcement in a representative animal. At the beginning of the daily sessions, the food-reinforced lever was introduced into the cage 5 min before the cocaine lever. Baseline responding (top left) was characterized by vigorous responding on the food-reinforced lever until the cocaine lever was introduced, at which point rats switched to responding almost exclusively on the cocaine-reinforced lever. Responding on the food lever was reinstated as the animal approached the break point for cocaine. Each session continued for 6 h. The figures have been truncated to 3 h, since almost all responding occurred within this time frame. The effect of baclofen on responding on the concurrent access schedule is shown for representative animals in Fig. 3. The doses of baclofen shown represent the lowest dose at which a significant decrease in cocaine-reinforced responding was observed in the group of rats. Following baclofen pretreatment, responding for food was initiated much earlier, and was sustained throughout

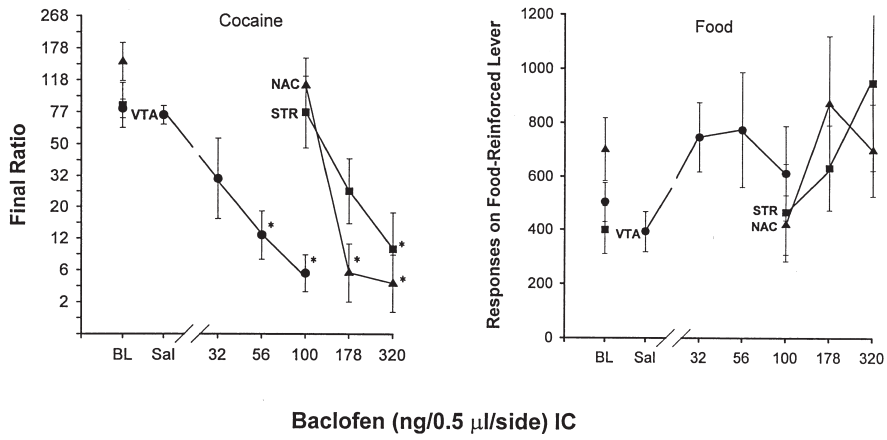

FIG. 2. (Left) Effect of intracerebral baclofen on cocaine self-administration reinforced under a PR schedule. Points represent the mean (±SEM) break points on a PR schedule of cocaine reinforcement following microinjection of various doses of baclofen (−30 min) into the VTA ($n = 5$), NAC ($n = 6$), or STR ($n = 6$). Animals in the VTA group also received microinjections of saline. In all three groups, baclofen pretreatment caused a dose-dependent decrease in cocaine-reinforced breakpoints compared to baseline (*$p < 0.05$). Although significant reductions in cocaine intake were observed after intra-NAC or intra-STR baclofen, the doses required to produce this effect were threefold higher than those that produced similar reductions in the VTA. (Right) Effect of intra-VTA, NAC, or STR baclofen on operant responding under an FR5 schedule of food reinforcement. Points represent the mean (±SEM) number of responses on a concurrently available food-reinforced lever during the cocaine self-administration session. Baclofen pretreatment did not affect responding on the food-reinforced lever in any of the groups of animals.

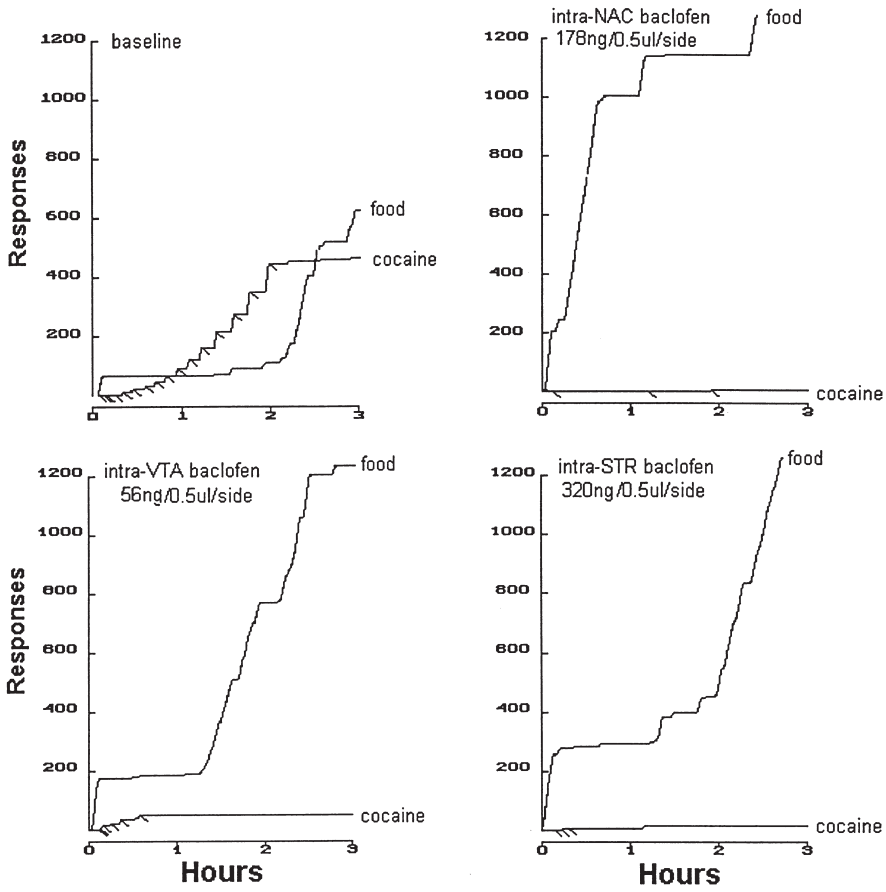

FIG. 3. Representative records from each of the four groups illustrate the effect of baclofen on responding for concurrently available cocaine under a PR schedule, and food under an FR5 schedule of reinforcement. Short downward lines represent cocaine infusions while upper increments in the record represent lever responses. Under baseline conditions (upper left), all animals demonstrated high rates of responding on the food-reinforced lever before the cocaine lever was introduced into the chamber. Typically, animals responded almost exclusively on the cocaine-reinforced lever following the initial infusion of cocaine and returned to vigorous responding on the food-reinforced lever as the break point for cocaine self-administration was approached. Following baclofen pretreatment, animals responded on the cocaine-reinforced lever only at low ratios and switched to exclusive responding on the food-reinforced lever very early in the session. Note that different doses are represented: this pattern of responding was conserved in all three groups of animals; however, the doses of baclofen required to attenuate cocaine self-administration were lowest in the VTA (lower left).

the first 2 h of the test period. Cocaine responding, however, was markedly reduced and abruptly stopped early in the session. In very rare instances sporadic sampling of the cocaine-reinforced lever was observed toward the end of the 6-h session. Baclofen pretreatment produced the same patterns of responding regardless of the site of the microinjection. Significant reductions in cocaine self-administration were observed at the 56 ng dose in the VTA (lower left), after 180 ng in the NAC (upper right), and after 320 ng in the STR (lower right).

DISCUSSION

The present results demonstrate that intracerebral injections of the $GABA_B$ agonist baclofen into the VTA, NAC, or STR reduce cocaine self-administration under a PR schedule of reinforcement. Microinjections of baclofen into the VTA produced the most potent modulation of cocaine self-administration, decreasing cocaine-reinforced break points at doses that were three times lower than those required to produce comparable reductions from injections into the NAC or STR. Several other studies have demonstrated an apparently specific effect of systemic pretreatments of $GABA_B$ agonists on cocaine self-administration (2–4,27,28,30). The results of the present investigation are consistent with previous reports showing that baclofen selectively attenuates the reinforcing effects of cocaine in rats, and suggests that the site of action for this effect includes $GABA_B$ receptors within the region of the VTA.

Shoaib et al. (30) were the first to investigate the effects of intracerebral injections of baclofen on cocaine self-administration. They reported that microinjections of 200 and 300 ng baclofen into the NAC or VTA (respectively) were required

to produce decreases in cocaine self-administration on an FR5 schedule. In the present study, we showed that doses as low as 56 ng into the VTA were statistically effective in reducing break points on a PR schedule. The different schedules used probably contributed to the differential sensitivity within regions. Several reports have demonstrated that the magnitude of the suppressant effects of baclofen on self-administration behavior depends on the dose of cocaine and the schedule of reinforcement (2–4,27,28,30). For example, a dose of baclofen that had little or no effect on intake of high unit injection doses of cocaine on an FR1 schedule markedly decreased break points on a PR schedule (3,28). Campbell et al. (4) have argued that cocaine dose and the response requirements of the schedule are constituents of unit price (responses/mg/kg), and that baclofen appears to have greater efficacy as the unit price increases. If cocaine self-administration is indeed more susceptible to the effects of baclofen at a high unit price, then the large number of responses required by the PR schedule (or high unit price) may account for the increased sensitivity to the low doses of baclofen.

The observation that the effect of baclofen on cocaine self-administration is proportional to the demand characteristics of the schedule raises the issue whether sedative or other nonspecific effects might account for the reductions in cocaine-reinforced responding. Baclofen has muscle relaxant properties, and high doses have been associated with sedative effects that may interfere with the ability of an animal to complete an operant response (21,23). It therefore becomes an important issue whether the animals retain the capacity to perform. Data from the concurrent schedule show that animals pretreated with baclofen were capable of responding several hundred times on the food-reinforced lever at a time when cocaine-reinforced responding was suppressed. These data would seem to rule out a generalized effect on responding and demonstrate that baclofen produced a redirection of responding from the cocaine- to the food-reinforced lever.

The concurrent schedule offers a unique method for evaluating the nonspecific effects of baclofen, with minimal impact on the major focus of the experiment, which is cocaine-reinforced responding. During different phases of the session, animals tended to respond almost entirely on either the food- or the cocaine-reinforced lever. That is, when the cocaine-reinforced lever is introduced into the cage, rats generally respond exclusively on it until the break point on the PR schedule is approached; only then does response rate on the food-reinforced lever increase. Thus, the food component does not appear to interfere with cocaine self-administration. Alghough it has been reported that a concurrently available nondrug reinforcer can affect cocaine-reinforced behavior (5,7,8,11,12), the cocaine-reinforced break-points in the present investigation were comparable to those in previous investigations in which animals were responding exclusively for cocaine (28). The concurrent access schedule offers a way to demonstrate that an animal maintains the capacity to respond during a period when it declines to respond on the cocaine-reinforced lever. This schedule offers an additional advantage in experiments that require repeated intracerebral injections, in that it allows for the demonstration of the capacity to perform in each animal following every injection. Other alternatives are to assess potentially disruptive effects in a different situation and/or in a separate group of rats; however, because slight variations in cannula placement can have a significant impact on drug effects and the number of intracerebral injections through each guide cannula is limited, these options have their own drawbacks.

It should be emphasized that the concurrent schedule was used here to demonstrate the capacity of treated animals to perform, not as a method to compare the effect of baclofen on food- vs cocaine-reinforced responding. The tendency for animals to respond sequentially on one lever and then the other and the fact that different schedules controlled the delivery of each reinforcer makes comparisons between response rates inappropriate. A number of studies have explicitly examined the effect of baclofen on food-reinforced responding under a variety of experimental conditions including FR, PR, discrete trials, and multiple schedules of reinforcement (27,28,30). These studies have shown that baclofen produces little if any effect on food-reinforced responding at doses that suppress cocaine intake, indicating that the effect is to some degree specific.

Under concurrent access conditions intracerebral injections of baclofen produced a redirection of responding from the cocaine-reinforced lever towards the food-reinforced lever. Stratford and Kelly (32) have reported increased feeding in sated animals following intra-NAC baclofen, raising the possibility that the reduction in cocaine self-administration in the present investigation was an indirect result of an increased motivation to respond for food. However, this seems unlikely, because pilot data collected for these studies showed that baclofen reduced cocaine self-administration in the absence of a concurrently available food-reinforced lever. Furthermore, according to Stratford and Kelly (32), the effect of baclofen on feeding was restricted to the shell of the nucleus accumbens, and the redirection of responding observed in the present investigation was evident in all three groups of rats.

The results of the present investigation demonstrate that microinjection of low doses of baclofen into the VTA attenuates cocaine self-administration, adding to previous reports that $GABA_B$ receptors have the potential to modulate reward processes associated with cocaine use (2–4,27,28,30). GABA terminals are distributed throughout the brain, and it has been suggested that increased GABA levels may play a major role in attenuating centrally mediated reward mechanisms through interactions with the VTA/NAC DA system (18,20,22). Microdialysis studies have confirmed that intra-VTA baclofen decreases extracellular DA in the NAC, and the medial prefrontal cortex (10,35,36,41). This interaction may also play a role in modulating opiate reinforcement. Xi and Stein (40) have recently reported that intra-VTA, but not intra-NAC, baclofen inhibits the development and maintenance of heroin self-administration. Thus, $GABA_B$ receptors within the VTA may have the capacity to modulate the rewarding properties of both stimulants and opiates.

The identification of the neurochemical systems that subserve the reinforcing effects of drug of abuse are an important step in developing therapeutic measures for drug addiction. Ling et al. (19) have reported that in open clinical trials, baclofen attenuated both cocaine use and craving for cocaine, suggesting that baclofen may be useful in preventing relapse to cocaine use in humans. The reductions in cocaine self-administration that are associated with the stimulation of intra-VTA $GABA_B$ receptors suggests that further investigation into GABAergic compounds as potentially therapeutic strategies for cocaine addiction may be warranted.

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