Alpha-Noradrenergic Receptors Modulate the Development and Expression of Cocaine Sensitization

CARLOS A. JIMÉNEZ-RIVERA,[a] MONICA FELIU-MOJER,[b] AND RAFAEL VÁZQUEZ-TORRES[a]

[a]*Department of Physiology, University of Puerto Rico, School of Medicine, San Juan, Puerto Rico, 00936-5067*

[b]*Department of Physiology, Universidad Central del Caribe, Bayamón, Puerto Rico, 00956*

ABSTRACT: **The increased activity and stereotyped behaviors that result from repeated administration of cocaine is called cocaine sensitization. This sensitized response has been postulated as one of the basic pathophysiological mechanisms in drug addiction. Recent evidence indicates that noradrenergic neurotransmission might be implicated in some of the behavioral effects of cocaine. The present article examined the role of alpha-adrenergic receptor agonists and antagonists in the development and expression of cocaine sensitization. Rats were injected once per day, for 7 consecutive days, with the alpha-1 receptor antagonist prazosin (0.5 mg/kg, i.p.) 15 min before cocaine administration (15 mg/kg, i.p.). After 8 days, animals received a cocaine challenge (15 mg/kg, i.p.) and were tested for locomotion. Following a 7-day withdrawal period rats received a second cocaine challenge. One day after the last challenge, rats were reinstated to the initial protocol for 1 day. In another set of experiments, rats were injected twice per day with the alpha-2 receptor antagonists yohimbine (5 mg/kg, i.p.), idazoxan (0.25 mg/kg, i.p.), or with the alpha-2 agonist clonidine (0.025 mg/kg, i.p.), followed by cocaine injections (15 mg/kg, i.p.), for 7 consecutive days. Thereafter, the protocol was similar to that following prazosin administration. The results demonstrated that the alpha-1 receptor antagonist prazosin blocked the development and expression of cocaine sensitization. On the other hand, both alpha-2 antagonists failed to inhibit the development or the expression of cocaine sensitization. Instead, they produced an increase in locomotor activity during the first day of experimentation. The alpha-2 agonist clonidine attenuated the acute response to cocaine on day 1 and retarded the increased locomotor activity on the following 2 days. There was a dramatic increase in the level of sensitization after the first cocaine challenge.**

Address for correspondence: C.A. Jimenez-Rivera, Department of Physiology, University of Puerto Rico, School of Medicine, Main Building , Room A-688, Medical Sciences Campus, San Juan, Puerto Rico, 00936-5067. Voice: 787-758-2525; ext.: 1676; fax: 787-753-0120.
e-mail: cajimenez@rcm.upr.edu

Ann. N.Y. Acad. Sci. 1074: 390–402 (2006).
doi: 10.1196/annals.1369.039

However, it inhibited the expression of cocaine sensitization during the reinstatement protocol. These results suggest that alpha adrenoreceptors play an important role in modulating different stages of cocaine sensitization and probably cocaine addiction.

KEYWORDS: **cocaine; norepinephrine; alpha-1 receptors; alpha-2 receptors; clonidine; yohimbine; prazosin; idazoxan**

INTRODUCTION

Cocaine sensitization refers to the increased activity and stereotyped behaviors that result from repeated cocaine administration.[1] This sensitized response can persist for weeks or months following the cessation of drug treatment and has been postulated as one of the basic pathological mechanisms involved in drug addiction.[2–4]

Cocaine-induced sensitization results from neural adaptations in the brain-reward system.[5] One of the most important brain-reward circuits involves dopamine (DA) neurons of the ventral tegmental area (VTA) and its projections to mesolimbic/mesocortical.[6,7] Although extensive evidence indicates that the processes of enhanced locomotion and cocaine sensitization are intimately related with DA transmission, there is compelling data suggesting an important noradrenergic modulatory role in this phenomenon.

The majority of the available data on the role of norepinephrine (NE) in cocaine sensitization deals with alpha-noradrenergic receptors. Recent investigations show that prazosin, an alpha-1 adrenergic receptor antagonist, reduced the acute locomotor effects and blocked behavioral sensitization to both cocaine and amphetamine injections.[8] Additional studies have indicated that stimulation of alpha-1 and alpha-2 adrenergic receptors amplified the DA-mediated locomotor hyperactivity in rats and mice.[9] Furthermore, it was demonstrated that the development of cocaine sensitization was dramatically increased in mice lacking the adrenergic receptor subtype alpha-1b.[10]

In contrast with the aforementioned studies, there are other investigations that suggest that the noradrenergic transmission is not critically involved in the development of cocaine sensitization.[11,12] Therefore, the role of NE transmission in the process of cocaine-induced behavioral sensitization is still equivocal.

The present experiments were designed to investigate the role of alpha adrenoceptors in two distinct processes in cocaine sensitization, initiation and expression. Initiation of sensitization are the immediate molecular and/or cellular effects that induce behavioral sensitization.[13,14] Expression indicates the long-term consequences of these effects. Numerous studies have shown that the VTA is the site where the processes responsible for the initiation of sensitization occur.[15,16] On the other hand, the nucleus accumbens (NAcc) seems to be the anatomical structure more relevant for the expression of sensitization.[14,16–18]

In terms of behavior, the function of noradrenergic neurotransmission in the initiation and expression of cocaine sensitization has been relatively unexplored. We investigated the role of prazosin (an alpha-1 receptor antagonist), yohimbine and idazoxan (alpha-2 receptor antagonists), and clonidine (an alpha-2 agonist) in the development and expression of cocaine sensitization. The results suggest that alpha-adrenergic receptors modulate different stages of cocaine-induced behavioral sensitization.

METHODS

Animal Housing

A total of 76 male Sprague-Dawley rats (250–300 g) were purchased from Taconic Farms (Germantown, NY). They were maintained on a 12-h light/dark cycle. Food and water were available *ad libitum*. All experiments were performed during the light cycle. All procedures were conducted in accordance with approved Institutional Animal Care and Use Committee.

Experimental Design

Prior to injections, and behavioral testing, animals were acclimated to the test cages (AccuScan Instruments Inc., Columbus,OH) for 4 consecutive days.

Alpha-1 Adrenergic Receptors

Behavioral sensitization was induced by once daily administration of saline (1 cc/kg, i.p.), followed by cocaine (15 mg/kg i.p.) or prazosin (0.5 mg/kg, i.p.) for 7 consecutive days. Controls were injected with prazosin (0.5 mg/kg, i.p.) followed by saline (1 cc/kg, i.p.) or with two consecutive saline injections (1 cc/kg, each i.p.). Locomotor activity (counts/60 min) was recorded for all groups on days 1, 3, 5, and 7 of the sensitization protocol. On day 8 all rats received a cocaine challenge (15 mg/kg, i.p.) and locomotor activity was recorded. A 7-day withdrawal period followed, and on day 16 all animals received a second cocaine challenge (15 mg/kg, i.p.) and locomotor activity was recorded. On day 17 all animals were reinstated to the sensitization protocol described above and locomotor activity was measured.

Alpha-2 Adrenergic Receptors

Behavioral sensitization was induced by twice daily administration of saline (1 cc/kg, i.p.), followed by cocaine (15 mg/kg, i.p.) or yohimbine (5 mg/kg, i.p.) for 7 consecutive days. Controls were injected with yohimbine (5 mg/kg, i.p.)

followed by saline (1 cc/kg, i.p.) or with two consecutive saline injections (1 cc/kg each, i.p.) Locomotor activity (counts/60 min) was recorded for all groups on days 1–7 of the sensitization protocol. On day 8 all rats received a cocaine challenge (15 mg/kg, i.p.) and locomotor activity was recorded. A 7-day withdrawal period followed, and on day 16 all animals received a second cocaine challenge (15 mg/kg, i.p.) and locomotor activity was measured. On day 17 all animals were reinstated to the sensitization protocol described above and locomotor activity was measured. The same protocol was used with idazoxan (0.25 mg/kg, i.p.) and clonidine (0.025 mg/kg, i.p.)

Data Analysis

One-way ANOVA followed by the Newman-Kuel's *post hoc* tests were used to analyze the data. A significant level of $P < 0.05$ was employed.

RESULTS

FIGURE 1 illustrates the effects of the alpha-1 receptor antagonist prazosin on the development and expression of cocaine sensitization. Animals pretreated

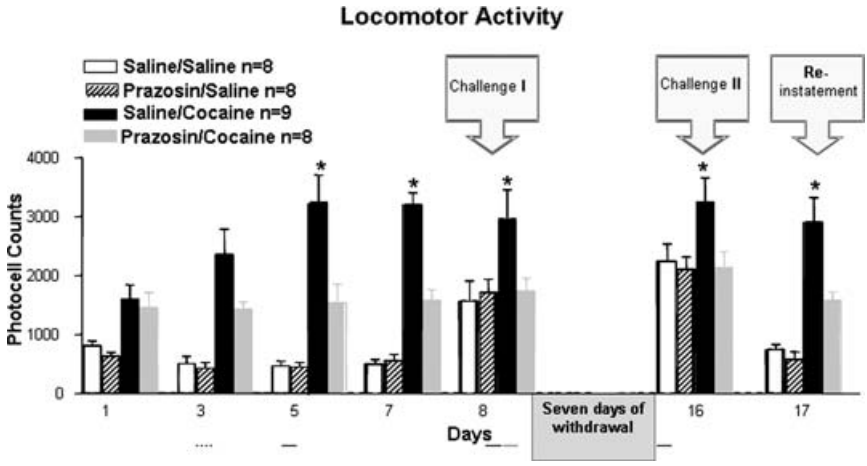

FIGURE 1. The figure illustrates the effects of the alpha-1 receptor antagonist prazosin on the development and expression of cocaine sensitization. Rats that received cocaine alone (saline/cocaine group) were fully sensitized as evidence by their response to a cocaine challenge or a reinstatement protocol (saline/cocaine; $^{*}P < 0.05$, one-way ANOVA followed by Newman-Kuel's test between first day and days 5, 7, 8,16, and 17 of saline/cocaine group). Although there was an enhanced locomotor response after the first cocaine injection (acute response) no significant changes were observed in the prazosin-injected group thereafter. These results demonstrate that the alpha-1 antagonist prazosin blocks the development and expression of cocaine-induced behavioral sensitization. For details see text.

with saline (1 cc/kg, i.p. injections) followed 15 min later by cocaine administration (15 mg/kg, i.p.) (saline/cocaine group) were already sensitized at days 5 (one-way ANOVA, $F_{3,28} = 12.61$, $P < 0.0001$; Newman-Kuel's $q = 6.40$, $P < 0.001$, day 5 versus 1) and 7 ($q = 6.24$, $P < 0.001$). The level of sensitization remained the same after the first (day 8, $q = 5.31$, $P < 0.01$) and second (day 16, $q = 6.45$, $P < 0.001$) cocaine challenge and following a reinstatement protocol (day 17, $q = 5.10$, $P < 0.05$). On the contrary, animals that were pretreated with prazosin (0.5 mg/kg, i.p.) 15 min before cocaine administration (prazosin/cocaine) demonstrated an inhibition in the development of cocaine sensitization. On day 1, rats in the prazosin/cocaine group had an increased locomotor response similar to the one present in the saline/cocaine group (acute response). This response remained at the same level with subsequent injections and after the first cocaine challenge. This indicates that no sensitized response was developed ($q = 4.61$, $P < 0.05$ for prazosin/cocaine on day 8 versus saline/cocaine). On the other hand, no changes in locomotion were observed between the saline/saline and prazosin/saline groups throughout the initial 7 days demonstrating that prazosin by itself does not produce any alteration in normal locomotor behavior. After a 7-day withdrawal period, on day 16 (second cocaine challenge) there was no expression of behavioral sensitization in the prazosin/cocaine group ($P > 0.05$ compared to day 1). On the other hand, all three groups (saline/saline, saline/prazosin, and prazosin/saline) demonstrated a similar slight increase in locomotion (although not significant) when compared to the first cocaine challenge. Because at this moment all groups had received two cocaine injections without any pretreatment, this enhancement in locomotion could be due to the beginning of the process of sensitization. On day 17 a reinstatement protocol was introduced. All groups were reinstated to the original sensitization protocol given during the initial 7 days. It was observed that animals in the saline/cocaine group remained sensitized ($q = 5.10, P < 0.05$) whereas the prazosin/cocaine group did not show sensitization ($P > 0.05$ compared to day 1). There was a small but not significant diminution in locomotor response compared to the second cocaine challenge. These results suggest that prazosin administration induces a long-lasting inhibitory effect on both the development and expression of cocaine sensitization.

FIGURE 2 (A and B) illustrates the effects of alpha-2 receptor antagonists on the development and expression of cocaine sensitization. It was observed that animals that were administered saline 15 min before cocaine (saline/cocaine group) developed an enhanced locomotor response already on day 2 of experimentation (one-way ANOVA $F_{3,40} = 10.96, P < 0.0001$; $q = 5.63, P < 0.01$ compared to day 1). The increased locomotion remained at the same level for the rest of the experiment with the exception of day 6 ($P > 0.05$ compared to day 1). This enhanced rate of sensitization could be due to the fact that a protocol of two injections per day was employed. As shown in FIGURE 2 A,

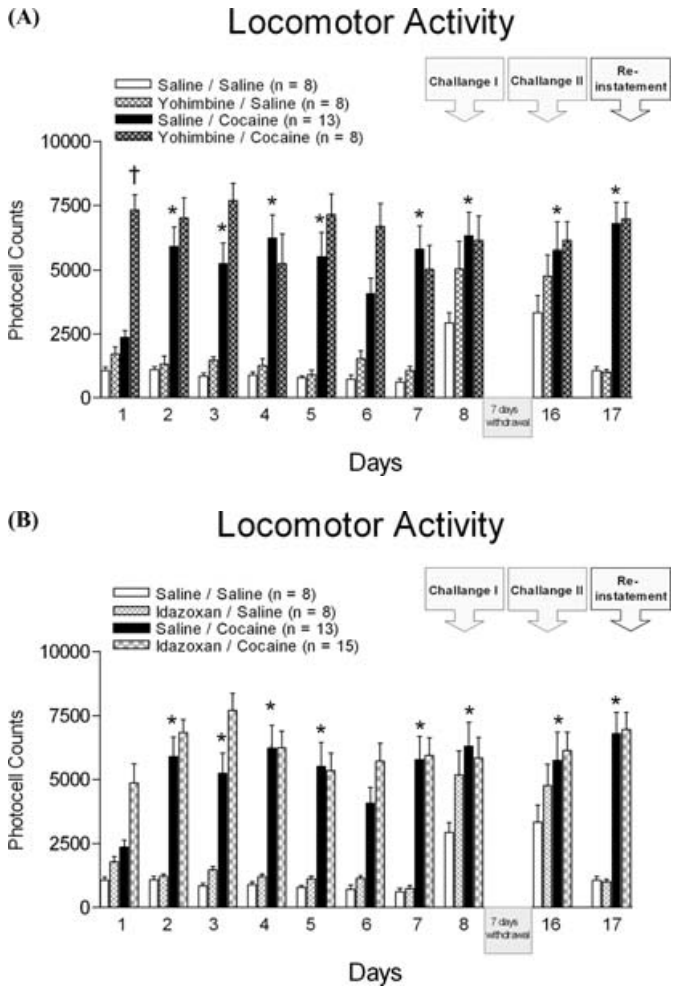

FIGURE 2. The figure (**A** and **B**) illustrates the effects of alpha-2 receptor antagonists on the development and expression of cocaine sensitization. (**A**) Rats that received cocaine (saline/cocaine group) were fully sensitized as evidenced by their response to a cocaine challenge or a reinstatement protocol. Yohimbine (5 mg/kg, i.p.) induced a robust increase in total locomotor activity on day 1 (yohimbine/cocaine; $+P < 0.001$ compared to the saline/cocaine group on day 1, one-way ANOVA followed by Newman-Kuel's test). However, yohimbine administration did not block the development or expression of cocaine-induced sensitization because no significant differences were observed between the yohimbine/cocaine and saline/cocaine groups after a cocaine challenge or a reinstatement protocol. (**B**) The same protocol was used with idazoxan (0.25 mg/kg, i.p.) and similar effects as yohimbine were seen but in lower magnitude. Asterisks denote significant differences ($P < 0.05$, one-way ANOVA followed by Newman-Kuel's test) between the first day and days 2, 3, 4, 5, 7, 8, 16, and 17 of saline/cocaine groups.

animals pretreated with the alpha-2 antagonist yohimbine (5 mg/kg, i.p.), showed a dramatic increase in the acute response to cocaine on day 1 ($q = 6.90$, $P < 0.001$ between saline/cocaine and yohimbine/cocaine groups). There were no significant differences between the yohimbine/cocaine and saline/cocaine groups thereafter. No significant differences were observed within the yohimbine/cocaine group on day 1 versus any other day, including cocaine challenges and the reinstatement period. In addition, no significant changes were seen between the saline/saline and saline/yohimbine groups throughout the initial 7 days of experimentation suggesting that yohimbine by itself did not have any effects on normal locomotor behavior. After the first (day 8) and second (day 16) cocaine challenges there was a tendency for the saline/yohimbine group to show an increase in locomotor behavior when compared to day 1, although it did not reach significance. FIGURE 2 B shows the effects of the alpha-2 antagonist's idazoxan (0.25 mg/kg, i.p.) on the development and expression of cocaine sensitization. It can be observed that on day 1, similar to yohimbine administration, the idaxozan/cocaine group had a tendency to show an increased acute locomotor response, although in this case, it did not reach significance ($P > 0.05$). No differences were observed at any other days, including the two cocaine challenges and during the reinstatement protocol. Therefore, it seems that the alpha-2 antagonists enhance the locomotor response to cocaine during the first day (acute response) of experimentation but failed to inhibit the development or the expression of cocaine sensitization.

FIGURE 3 illustrates the effects of the alpha-2 agonist clonidine (0.025 mg/kg, i.p.) on the development and expression of cocaine sensitization. It can be observed that clonidine administration attenuated the acute response to cocaine on day 1. There was a diminution in locomotion on days 2 and 3 when compared to the saline/cocaine group reaching significance on day 3 (one-way ANOVA $F_{3,40} = 15.11$, $P < 0.0001$; $q = 4.99$, $P < 0.05$). However for days 4–7 there were no significant differences between the clonidine/cocaine and saline/cocaine groups. As a matter of fact, on day 7 both groups were behaviorally sensitized in comparison to their respective day 1 ($q = 6.48$, $P < 0.01$ for clonidine/cocaine and $q = 6.21$, $P < 0.01$ for saline/cocaine). At the time of the first challenge the clonidine/cocaine group demonstrated a dramatic increase in the level of sensitization when compared to the response of the saline/cocaine group ($q = 9.19$, $P < 0.001$). Following the withdrawal period, the clonidine/cocaine group showed an enhanced behavioral response ($q = 8.35$, $P < 0.001$ compared to day 1) during the second cocaine challenge although it was greatly diminished compared to the sensitization demonstrated during the first challenge ($q = 6.12$, $P < 0.001$ for clonidine/cocaine day 16 versus day 8). Clonidine was able to block the expression of cocaine sensitization during the reinstatement protocol ($q = 7.67$, $P < 0.001$ for clonidine/cocaine at day 17 compared to saline/cocaine day 17).

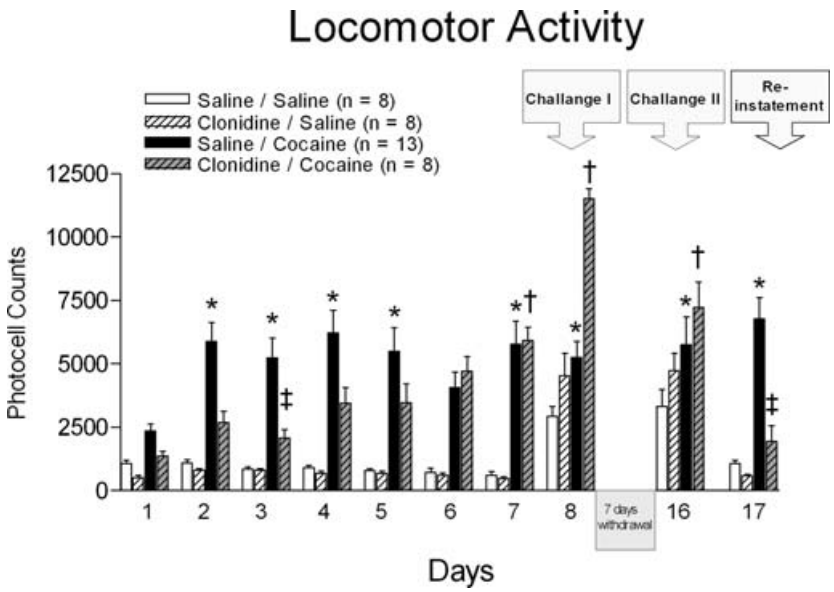

FIGURE 3. The figure illustrates the effects of the alpha-2 agonist clonidine (0.025 mg/kg, i.p.) on the development and expression of cocaine sensitization. Rats that received cocaine alone (saline/cocaine group) were fully sensitized as evidence by their response to a cocaine challenge or a reinstatement protocol. Clonidine attenuated the acute response of cocaine on day 1 and retarded the increase in locomotor activity on the following 2 days (clonidine/cocaine; ‡$P < 0.05$ compared to saline/cocaine on days 3 and 17 one-way ANOVA followed by Newman-Kuel's test) but did not block the development of cocaine sensitization during day 7, or challenges I and II. Clonidine was able to block the expression of cocaine sensitization during the reinstatement protocol (clonidine/cocaine; ‡$P < 0.001$ compared to saline/cocaine on reinstatement protocol, one-way ANOVA, Newman-Kuel's test). Asterisks denote significant differences ($P < 0.05$, one-way ANOVA, Newman-Kuel's test) between the first day and days 2, 3, 4, 5, 7, 8, 16, and 17 of saline/cocaine groups. †denotes a significant difference ($P < 0.05$, one-way ANOVA and Newman-Kuel's test) between first day and days 7, 8, and 16 of clonidine/cocaine groups.

DISCUSSION

The goal of the present experiment was to investigate the role of the alpha-adrenergic receptors in the initiation and expression of cocaine sensitization. The results revealed that the pretreatment with the alpha-1 antagonist prazosin blocked not only the initiation but also the expression of cocaine-induced behavioral sensitization. On the contrary, both alpha-2 antagonists' yohimbine and idazoxan, seemed to affect only the acute response to cocaine by increasing it during the first day of treatment. The administration of clonidine, an alpha-2 receptor agonist, attenuated the acute response to cocaine on experimental

day 1 and retarded the increased locomotor activity on the following 2 days. However, it was unable to fully block the development of cocaine sensitization. After clonidine's pretreatment there was a dramatic enhancement of locomotor activity during the first cocaine challenge. Nevertheless, clonidine inhibited the expression of cocaine sensitization during the reinstatement protocol. The data is consistent with the notion that alpha-adrenergic receptors have the capacity to modulate the initiation and expression of cocaine-induced behavioral sensitization. The results also suggest that NE transmission could be an important factor in the development and expression of cocaine sensitization.

Initial studies on the induction of sensitization have implicated alterations in the functioning of DA neurons in the VTA. Changes in D2 autoreceptor sensitivity[19–21] and DA neuronal firing[19] have been correlated with the development of cocaine sensitization. More recent studies suggest that alterations in VTA D1 receptors might be the most important dopaminergic adaptation in the development of sensitization.[22–24] However, there is contrasting information demonstrating that DA receptors might not play a critical role in the induction of behavioral sensitization.[25,26] On the other hand, changes in the spontaneous activity of DA neurons and D_1 receptor-mediated augmentation of γ-aminobutyric acid (GABA) $_B$- mediated inhibitory postsynaptic potentials have been shown to occur with the expression of cocaine sensitization.[27]

It is well known that the VTA and NAcc receive innervation from other catecholaminergic nuclei that release NE and serotonin onto them.[28–30] Because the reuptake mechanisms of these neurotransmitter systems are equally affected by cocaine,[31,32] their role in the initiation and expression of behavioral sensitization should not be overlooked.

Previous behavioral studies have demonstrated that the alpha-1 receptor antagonist prazosin exerted a powerful inhibitory effect on the development of cocaine sensitization.[8] Our results are in agreement with the major finding of the inhibition of the development of cocaine sensitization after prazosin pretreatment. However, we did not find, as the above authors, that prazosin blocked the acute response to cocaine. In our case the acute response remained intact and only the enhanced locomotion, after repeated cocaine administration, was affected. This difference could be due to the cocaine dose of 5 mg/kg, i.p. used in the previous study versus the 15 mg/kg, i.p. employed in our investigation to induce behavioral sensitization. Similar to the above-mentioned study[8] our experiments demonstrated that prazosin administration inhibited the expression of cocaine sensitization. In addition, our results tend to indicate that prazosin might have long-lasting effects on sensitization because the inhibitory actions were clearly present on the reinstatement protocol. However, further studies should be conducted to assess whether prazosin has any effects on the expression of sensitization once it has been developed.

Additional corroboration of the importance of the alpha-1 receptors in the initiation of cocaine sensitization has been demonstrated using alpha-1 receptor knockout mice.[10,33] It was shown that alpha-1b receptors exerted a powerful inhibitory action of the acute and sensitized response to cocaine administra-

tion. The reason why other investigations[11,12] have failed to demonstrate that prazosin had any effects on the development or expression of cocaine sensitization could be related to the different environments or doses used for animal testing. For example, in our experiments as well as in those of Drouin *et al*.[8,10] rats were monitored in the test environment (context dependent) and not in the home cages.

Other experiments have demonstrated that prazosin administration significantly reduce the cocaine-induced hypophagia and hyperlocomotion in rats.[34] Prazosin pretreatment was also revealed to significantly reduce the locomotor hyperactivity and striatal Fos expression induced by amphetamine injections.[35] More recently, it was shown that prazosin administration attenuated the cocaine-induced reinstatement of drug-seeking behavior.[36] Therefore, the majority of the recent evidence demonstrates an important role of alpha-adrenergic receptors in long-term behavioral adaptations including psychostimulant-induced behavioral sensitization.

Additional studies have shown that stimulation of alpha-1 and alpha-2 receptors amplified the DA-mediated locomotor activity in rats and mice. An important role of postsynaptic alpha-2 receptors in the induction of locomotor hyperactivity was suggested.[9] Other studies demonstrated that alpha-2 receptor antagonists, like idazoxan and efaroxan, enhanced the circling behavior induced by either methylphenidate or apomorphine.[37] Our studies provide support to this notion because it was demonstrated that with alpha-2 receptor blockers the acute response to cocaine was enhanced whereas with an alpha-2 agonist it was attenuated. As no changes were observed with yohimbine alone, the antagonist-induced enhanced locomotion can not be attributed to the yohimbine's anxiogenic effects or the production of behavioral sensitization with this drug reported by others.[38]

The present investigation demonstrated that alpha-2 receptor blockade was not sufficient to prevent the development or the expression of cocaine sensitization. To our knowledge, studies looking at the role of alpha-2 receptor antagonists on cocaine sensitization are lacking. Other studies have indicated that pharmacological inhibition of alpha-2 receptors triggers a reinstatement of cocaine-seeking behavior in squirrel monkeys.[39] Priming injections of yohimbine or RS-79948 produced a dose-related reinstatement of cocaine-seeking behavior.

On the other hand, the results with the alpha-2 receptor agonist clonidine tend to indicate that alpha-2 receptors can modulate cocaine sensitization. The administration of clonidine was able to retard the development of cocaine sensitization although it was not capable to fully block this process. Again, the differences observed with other studies[11] could be attributed to the doses and variations in protocols used. An interesting finding observed with clonidine administration was the enhanced level of sensitization reached after the first cocaine challenge. It has been demonstrated that repeated cocaine administration alters the sensitivity of alpha-2 receptors in different brain areas.[40,41] It is possible that after prolonged agonist-induced activation of alpha-2 receptors there

is a downregulation of this receptor type. Therefore, this apparent enhanced sensitization observed after the first cocaine challenge could be due to a combined effect of a decreased sensitivity and downregulation of alpha-2 receptors. However, whatever the mechanism is present, it is not permanent because this enhanced sensitization returned to normal levels after a withdrawal period. Moreover, clonidine was able to affect the expression of sensitization during the reinstatement protocol suggesting that the receptor regains functionality after a prolonged withdrawal episode. Further studies should investigate if a downregulation of alpha-2 receptors occurs after cocaine sensitization and for how long can clonidine modulate the expression of behavioral sensitization.

Finally, a clear notion of the function of alpha receptors in cocaine sensitization will further add to our knowledge of the specific mechanism of the noradrenergic system in cocaine addictive processes. In addition, it might suggest possible avenues for therapeutic pharmacological interventions.

ACKNOWLEDGMENTS

This work was supported by the NINDS and NCRR SNRP # NS39408 and GM-50695 to C.A. Jiménez-Rivera. The authors thank Dr. Guido Santacana for proofreading and Dr. Priscilla Sanabria for figure preparation of the manuscript.

REFERENCES

1. Robinson, T.E. & K.C. Berridge. 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Brain Res. Rev. **18**: 247–291.
2. Koob, G.F. & M. Le Moal. 1997. Drug abuse: hedonic homeostatic dysregulation. Science **278**: 52–58.
3. Robinson, T.E. & K.C. Berridge. 2000. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction **95**(Suppl. 2): S91–S117.
4. Robinson, T.E. & K.C. Berridge. 2003. Addiction. Annu. Rev. Psychol. **54**: 25–53.
5. White, F.J. & P.W. Kalivas. 1998. Neuroad aptations involved in amphetamine and cocaine addiction [review]. Drug Alcohol Depend. **51**: 141–53.
6. Bjorklund, A. & O. Lindvall. 1984. Dopamine-containing systems in the CNS. *In* Handbook of Chemical Neuroanatomy, Vol. 2. Classical Transmitters in the CNS, Part 1. Bjorklund, A., Hokfelt, T., Eds.: 55–122. Elsevier. Amsterdam.
7. Wise, R.A. & P.P. Rompre. 1989. Brain dopamine and reward. Annu. Rev. Psychol. **40**: 191–225.
8. Drouin, C., G. Blanc, A.S. Villegier, *et al.* 2002. Critical role of alpha1-adrenergic receptors in acute and sensitized locomotor effects of D-amphetamine, cocaine, and GBR 12783: influence of preexposure conditions and pharmacological characteristics. Synapse **43**: 51–61.
9. Villegier, A.S., C. Drouin, J.C. Bizot, *et al.* 2003. Stimulation of postsynaptic alpha1b- and alpha2-adrenergic receptors amplifies dopamine-mediated locomotor activity in both rats and mice. Synapse **50**: 277–284.

10. DROUIN, C., L. DARRACQ, F. TROVERO, *et al.* 2002. Alpha1b-adrenergic receptors control locomotor and rewarding effects of psychostimulants and opiates. J. Neurosci. **22**: 2873–2884.
11. VANDERSCHUREN, L.J., P. BEEMSTER & A.N. SCHOFFELMEER. 2003. On the role of noradrenaline in psychostimulant-induced psychomotor activity and sensitization. Psychopharmacology (Berl.) **169**: 176–185.
12. FILIP, M., E. NOWAK & I. PAPLA. 2001. On the role of serotonin2A/2C receptors in the sensitization to cocaine. J. Physiol. Pharmacol. **52**:471–81.
13. KALIVAS, P.W. 1995. Interactions between dopamine and excitatory amino acids in behavioral sensitization to psychostimulants [review]. Drug Alcohol Depend. **37**: 95–100.
14. KALIVAS, P.W. 1995. Neuronal basis of behavioral sensitization to cocaine. *In* The Neurobiology of Cocaine; Cellular and Molecular Mechanisms. R.P. Hammer, Jr., Ed.: 81–98. CRC Press, Inc. Boca Raton, FL.
15. KALIVAS, P.W. & J. STEWART. 1991. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. [review]. Brain Res. Brain Res. Rev. **16**: 223–244.
16. VANDERSCHUREN, L.J. & P.W. KALIVAS. 2000. Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. Psychopharmacology (Berl.) **151**: 99–120.
17. CADOR, M., Y. BJIJOU & L. STINUS. 1995. Evidence of a complete independence of the neurobiological substrates for the induction and expression of behavioral sensitization to amphetamine. Neuroscience **65**: 385–395.
18. WANG, X.B., M. FUNADA, Y. IMAI, *et al.* 1997. rGbeta1: a psychostimulant-regulated gene essential for establishing cocaine sensitization. J. Neurosci. **17**: 5993–6000.
19. HENRY, D.J., M.A. GREENE & F.J. WHITE. 1989. Electrophysiological effects of cocaine in the mesoaccumbens dopamine system: repeated administration. J. Pharmacol. Exp. Ther. **251**: 833–839.
20. ACKERMAN, J.M. & F.J. WHITE. 1990. A10 somatodendritic dopamine autoreceptor sensitivity following withdrawal from repeated cocaine treatment. Neurosci. Lett. **117**: 181–187.
21. WOLF, M.E., F.J. WHITE, R. NASSAR, *et al.* 1993. Differential development of autoreceptor subsensitivity and enhanced dopamine release during amphetamine sensitization. J. Pharmacol. Exp. Ther. **264**: 249–255.
22. PIERCE, R.C., B. BORN, M. ADAMS & P.W. KALIVAS. 1996. Repeated intra-ventral tegmental area administration of SKF- 38393 induces behavioral and neurochemical sensitization to a subsequent cocaine challenge. J. Pharmacol. Exp. Ther. **278**: 384–392.
23. BJIJOU, Y., L. STINUS, M. LE MOAL & M. CADOR. 1996. Evidence for selective involvement of dopamine D1 receptors of the ventral tegmental area in the behavioral sensitization induced by intra ventral tegmental area injections of D-amphetamine. J. Pharmacol. Exp. Ther. **277**: 1177–1187.
24. VEZINA, P. 1996. D1 dopamine receptor activation is necessary for the induction of sensitization by amphetamine in the ventral tegmental area. J. Neurosci. **16**: 2411–2420.
25. MATTINGLY, B.A., T.C. HART, K. LIM & C. PERKINS. 1994. Selective antagonism of dopamine D1 and D2 receptors does not block the development of behavioral sensitization to cocaine. Psychopharmacology (Berl.) **114**: 239–242.

26. WHITE, F.J., A. JOSHI, T.E. KOELTZOW & X.T. HU 1998. Dopamine receptor antagonists fail to prevent induction of cocaine sensitization. Neuropsychopharmacology **18**: 26–40.
27. WHITE, F.J. & P.W. KALIVAS. 1998. Neuroadaptations involved in amphetamine and cocaine addiction. Drug Alcohol Depend. **51**:141–153
28. OADES, R.D. & G.M. HALLIDAY. 1987. Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity [review]. Brain Res. **434**: 117–165.
29. DELFS, J.M., Y. ZHU, J.P. DRUHAN & G.S. ASTON-JONES. 1998. Origin of noradrenergic afferents to the shell subregion of the nucleus accumbens: anterograde and retrograde tract-tracing studies in the rat. Brain Res. **806**: 127–140.
30. MEJIAS-APONTE, C.A., F. GEORGES, C.A. JIMENEZ-RIVERA & G. ASTON-JONES. Interactions between VTA Dopaminergic and A2 Noradrenergic Neurons. Program No. 113.3. *2003 Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience, 2003. Online www.sfn.org
31. RITZ, M.C., R.J. LAMB, S.R. GOLDBERG & M.J. KUHAR. 1987. Cocaine receptors on dopamine transporters are related to self- administration of cocaine. Science **237**: 1219–1223.
32. KOE, B.K. 1976. Molecular geometry of inhibitors of the uptake of catecholamines and serotonin in synaptosomal preparations of rat brain. J. Pharmacol. Exp. Ther. **199**: 649–661.
33. AUCLAIR, A., C. DROUIN, S. COTECCHIA, *et al.* 2004. 5-HT and alpha1b-adrenergic receptors entirely mediate dopamine release, locomotor response and behavioural sensitization to opiates and psychostimulants. Eur. J. Neurosc. **20**: 3073–3084.
34. WELLMAN, P., D. HO, A. CEPEDA-BENITO, *et al.* 2002. Cocaine-induced hypophagia and hyperlocomotion in rats are attenuated by prazosin. Eur. J. Pharmacol. **455**: 117–126.
35. MUNOZ, A., A. LOPEZ-REAL, J.L. LABANDEIRA-GARCIA & M.J. GUERRA. 2003. Interaction between the noradrenergic and serotonergic systems in locomotor hyperactivity and striatal expression of Fos induced by amphetamine in rats. Exp. Brain Res. **153**: 92–99.
36. ZHANG, X.Y. & T.A. KOSTEN. 2005. Prazosin, an alpha-1 adrenergic antagonist, reduces cocaine-induced reinstatement of drug-seeking. Biol. Psychiatry **57**: 1202–1204.
37. CHOPIN, P., F.C. COLPAERT & M. MARIEN. 1999. Effects of alpha-2 adrenoceptor agonists and antagonists on circling behavior in rats with unilateral 6-hydroxydopamine lesions of the nigrostriatal pathway. J. Pharmacol. Exp. Ther. **288**: 798–804.
38. SCHROEDER, B.E., C.A. SCHILTZ & A.E. KELLEY. 2003. Neural activation profile elicited by cues associated with the anxiogenic drug yohimbine differs from that observed for reward-paired cues. Neuropsychopharmacology **28**: 14–21.
39. LEE, B., S. TIEFENBACHERS, D.M. PLATT & R.D. SPEALMAN. 2004. Pharmacological blockade of alpha-2 adrenoceptors induces reinstatement of cocaine-seeking behavior in squirrel monkeys. Neuropsychopharmacology **29**: 686–93.
40. BAUMANN, M.H., A.B. MILCHANOWSKI & R.B. ROTHMAN. 2004. Evidence for alterations in alpha-2 adrenergic receptor sensitivity in rats exposed to repeated cocaine administration. Neuroscience **125**: 683–90.
41. JIMENEZ-RIVERA, C.A., D. BLOOM, R. CASTRO, *et al.* Decreased Functionality of Alpha-2 Receptors in VTA DA cells after cocaine sensitization. Program No. 688.20. *2004 Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience, 2004. Online. www.sfn.org