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Role of the Inhibitory Adrenergic α_2 and Serotonergic 5-HT_{1A} Components of Cocaine's Actions on the DOI-induced Head-Twitch Response in 5-HT_2-Receptor Supersensitive Mice

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DARMANI, N. A. *Role of the inhibitory adrenergic α_2 and serotonergic 5-HT_{1A} components of cocaine's actions on the DOI-induced head-twitch response in 5-HT_2-receptor supersensitive mice.* PHARMACOL BIOCHEM BEHAV 45(2) 269–274, 1993.—It was recently reported that acute cocaine pretreatment can reduce the (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced 5-hydroxytryptamine$_2$ (5-HT_2)-receptor mediated head-twitch response (HTR) in mice via indirect stimulation of adrenergic α_2- and serotonergic 5-HT_{1A}-receptors. The aim of the present investigation was to determine whether cocaine can alter the DOI-induced HTR in 5-HT_2-receptor supersensitive mice. Supersensitivity was induced by a single injection of DOI 48 h prior to experimentation. These supersensitive mice exhibited a greater frequency of HTR to a challenge dose of DOI 48 h after its initial administration. Cocaine pretreatment dose-dependently reduced the DOI-induced HTR in the supersensitive mice. The stimulant was approximately four times more potent in the 5-HT_2-receptor supersensitive mice relative to its reported effects in normal mice. Receptor blockade studies with yohimbine and alprenolol revealed that both of the inhibitory components of cocaine's actions (i.e., adrenergic α_2- and serotonergic 5-HT_{1A}-receptor effects, respectively) were more efficient in reducing the DOI-induced HTR in supersensitive mice compared to normosensitive animals. The present results further support the previously suggested hypothesis that acute cocaine administration inhibits the 5-HT_2-receptor function by increasing the synaptic concentration of norepinephrine and serotonin via inhibition of their uptake and therefore indirectly stimulating the respective inhibitory adrenergic α_2- and serotonergic 5-HT_{1A}-receptors.

Cocaine DOI Alprenolol Yohimbine 5-HT_2-Receptor 5-HT_{1A}-Receptor α_2-Receptor Head-twitch response

THE stimulant cocaine inhibits the uptake of dopamine and norepinephrine to potentiate the actions of these catecholamines (10,19,27,29). Despite the vast animal and clinical research in the past two decades, the intricate neurochemical mechanisms that maintain cocaine abuse are not well defined (41). It has become more clear that a single neurotransmitter or neuroanatomic system cannot solely account for the complex behavioral, biochemical, and electrophysiological actions of cocaine. Nonetheless, increased dopaminergic activity appears to be the basis of many of its effects (3–5,10,19,29,30). However, a more recent biochemical review suggests that cocaine also exerts a powerful influence over the serotonin neuronal system that is more pronounced than on dopamine and norepinephrine neurochemistry (41). A newly published behavioral study supports this notion because repeated administration of low doses of the stimulant potently enhanced the functional sensitivity of several 5-hydroxytryptamine (5-HT) receptors (14). Moreover, a variety of recent electrophysiological (11,12) neuroendocrine (31), self-administration (7,8,32), and in vivo voltametric neurochemistry combined with behavioral studies (5) strongly indicate the importance of serotonergic components of cocaine's actions.

Biochemical and behavioral studies have characterized up to four different distinct types of receptor sites in the serotonergic superfamily of receptors (21,39). Moreover, some of these receptors (e.g., 5-HT_1) appear to be heterogeneous and consist of a number of subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_{1D}). The 5-HT receptor system is involved in the modulation of important physiological processes such as appetite, blood pressure, sexual behavior and sleep. Disturbance in the function of these receptors has been linked to CNS disorders such as aggression, anxiety, depression, migraine,

and neurodegenerative disorders (21). Although selective radioligands do not exist for many of these receptor sites and some sites are too newly discovered to have had their pharmacology investigated in any detail, a number of behavioral, biochemical, and physiological models have been developed for studying the functional activity of many of these sites (22). The most widely used behavioral model to study changes in the 5-HT_2-receptor function is the head-twitch response (HTR) in rodents. Although the HTR can be produced by different neurotransmitter mechanisms (25), the head-twitch produced by the selective or nonselective (direct and indirect) 5-HT_2-receptor agonists is antagonized by selective 5-HT_2-receptor antagonists (17,34).

It has been known for more than a decade that stimulation of the noradrenergic receptor system can modulate the HTR induced by 5-HT agonists [for a review, see (25)]. In particular, excitation of noradrenergic α_2-receptors dose-dependently attenuate the 5-HT_2-receptor-induced HTR. These inhibitory α_2-adrenoceptors appear to be postsynaptic because clonidine suppression of 5-hydroxytryptophan-induced HTR was not reduced by 6-hydroxydopamine pretreatment (26). Activation of either adrenergic β_1- or β_2-receptors do not produce the HTR; however, their stimulation can enhance the frequency of serotonergically induced HTR [for a review, see (25)]. Moreover, the β-receptor antagonists (selective and nonselective) do not affect the HTR produced by the 5-HT_2-receptor agonists. Thus, β-adrenoceptor effects appear to be purely facilitatory (25). More recently, several investigators have shown that a functional interaction exists between 5-HT_{1A} and 5-HT_2-receptors such that simultaneous costimulation of 5-HT_{1A} receptors is inhibitory to 5-HT_2-induced HTR (1,17). Further, Darmani et al. (14,18) have reported that acute cocaine administration dose-dependently attenuates the HTR induced by the "selective" and nonselective 5-HT_2-receptor agonists. This inhibition in the 5-HT_2-receptor function appears to be due to indirect stimulation of the inhibitory adrenergic α_2- and serotonergic 5-HT_{1A}-receptors via the inhibition of uptake of endogenous norepinephrine and serotonin by cocaine.

To further characterize the contribution of the indirect inhibitory components of cocaine's acute actions on the HTR, one can selectively induce supersensitivity in 5-HT_2-receptor function prior to administration of the stimulant. In a recent study, it was shown that a single injection of the 5-$HT_{2/1C}$ agonist, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl [(±)-DOI], can induce tolerance at 24 h but supersensitivity at 48 h prior to a challenge dose of DOI (15). This supersensitivity persisted up to 6 days following the initial DOI administration. Thus, the purpose of this investigation was to evaluate the acute inhibitory effects of cocaine on the DOI-induced HTR 48 h following an initial injection of DOI.

METHOD

Animals and Drugs

Male albino mice of the ICR strain, bred in the animal facilities of the Kirksville College of Osteopathic Medicine, were used throughout the study. At the time of experiments, animals weighed 18–22 g and were housed in groups of six on a 12 L : 12 D cycle at a room temperature of 22 ± 1°C with ad lib supply of food and water. All experiments were performed between 8:00 a.m. and 5:00 p.m. The following drugs were obtained from Sigma Chemical Co. (St. Louis, MO): alprenolol tartrate and yohimbine HCl. DOI was purchased from Research Biochemicals, Inc. (Natick, MA). Cocaine HCl was obtained from the National Institute on Drug Abuse.

Experimental Protocols

The dose–response effects of acute administration of cocaine on DOI-induced HTR in normosensitive mice has already been published (18). To determine the inhibitory dose–response effects of the stimulant on DOI-induced HTR in 5-HT_2-receptor supersensitive mice, two groups of animals were initially injected with either distilled water (n = 7, IP) or 2.5 mg/kg DOI (n = 35, IP). DOI-treated animals were then randomly divided into five different groups (n = 6–7). Forty-eight hours following the initial injection, each animal was randomly transferred to a 40 × 25 × 16-cm plastic cage lined with wood chippings. Animals were allowed 10 min to acclimate to the test environment. The water-pretreated group (normosensitive control) received a second injection of distilled water 10 min prior to administration of a 2.5-mg/kg dose of DOI. Immediately following DOI injection, the HTR frequency was scored at 2-min intervals for the next 20 min. Mean scores (± SEM) for every 2-min time period were calculated. The DOI-pretreated groups received either water (supersensitive control, n = 6) or different doses of cocaine (0.5, 2.5, 10, and 20 mg/kg, IP, n = 7) following the acclimation period. Ten minutes later, these animals were injected with a second dose of DOI (2.5 mg/kg) and the induced HTR was scored as described earlier. Stimulation of serotonergic 5-HT_{1A}- and adrenergic α_2-receptors can attenuate the DOI-induced HTR in normosensitive mice (see the introductory section). Thus, their corresponding antagonists, alprenolol and yohimbine, were used for the determination of the indirect inhibitory actions of cocaine (via inhibition of uptake of serotonin and norepinephrine) in 5-HT_2-receptor supersensitive mice. Therefore, a large group of mice were made supersensitive by a 48 h prior treatment with a single injection of DOI (2.5 mg/kg, IP). These animals were then randomly divided into seven groups. Forty-eight hours following the initial DOI injection, each animal was allowed to acclimate to the test environment 10 min prior to the initiation of drug interaction studies. The control mice (group 1, n = 6) received an IP injection of distilled water following the acclimation period and 10 min later each control mouse was injected with a 2.5-mg/kg dose of DOI. The DOI-induced HTR was scored for 20 min as described for the dose–response studies. Yohimbine-treated mice received either yohimbine alone (0.1 mg/kg, n = 6) (group 2) or a mixture of 0.5 mg/kg cocaine plus 0.1 mg/kg yohimbine (group 3, n = 6) or a mixture of 20 mg/kg cocaine plus 0.1 mg/kg yohimbine (group 4, n = 5). Ten minutes later, each mouse received an IP injection of DOI (2.5 mg/kg) and the induced HTR was scored as described for control mice. The remainder of the 5-HT_2-receptor supersensitive mice received alprenolol (10 mg/kg, IP) following habituation to the test environment. Twenty minutes later, group 5 (n = 6) received an injection of distilled water whereas groups 6 (n = 6) and 7 (n = 6) were treated with either a 0.5- or a 20-mg/kg dose of cocaine (IP). Ten minutes later, each animal received DOI (2.5 mg/kg, IP) and the induced behavior was scored for the next 20 min as described earlier. The dose and dosing schedules are based upon our previous findings (13,14,17,18).

RESULTS

A 2.5-mg/kg dose of DOI produced 31 ± 3 head-twitches in the 20-min observation period in normosensitive control

mice that had received an injection of distilled water 48 h prior to the DOI injection (Fig. 1). A challenge dose of DOI (2.5 mg/kg) in supersensitive mice (i.e., mice pretreated with the same DOI dose 48 h earlier) produced a 97% increase in the HTR frequency (61 ± 5) for the same observation period (Fig. 1). Relative to the normosensitive group, the cumulative HTR score in supersensitive mice exhibited significant increases ($p < 0.05$) as early as the eighth minute of the observation period and persisted throughout the experiment. Cocaine by itself did not produce head-twitch but dose-dependently attenuated (ID_{50} = 3.3 mg/kg; 95% confidence limit 1.6–6.7 mg/kg) the HTR in supersensitive mice (Fig. 1). The lowest cocaine dose tested (0.5 mg/kg) significantly reduced the total HTR score in supersensitive mice (61 ± 5) by 33% (41 ± 3) in the 20-min observation period. In these mice, the cumulative HTR frequency exhibited significant decreases ($p < 0.05$) from the supersensitive control group from the eighth-minute observation time interval and persisted throughout the experiment. The 2.5-mg/kg cocaine-dose reduced the total HTR score by 44% ($p < 0.05$) and the significance of difference was apparent from the 6-min observation interval. The 10- and 20-mg/kg cocaine doses further reduced the HTR score by 75 and 84%, respectively. The significance of differences were apparent from the 2-min time period for each case.

A dose of 0.1 mg/kg yohimbine had no significant effect (63 ± 5) on the DOI-induced HTR frequency in supersensitive mice (61 ± 5) (Fig. 2). A combination of 0.5 mg/kg cocaine plus 0.1 mg/kg yohimbine also failed to modify the induced head-twitch score (Fig. 3). However, a dose of 20 mg/kg cocaine plus 0.1 mg/kg yohimbine significantly reduced the DOI-induced HTR by 84% (Fig 3). The significance of difference was apparent as early as the fourth minute of observation. The extent of total reduction in the HTR frequency was the same as that produced by the 20-mg/kg cocaine dose when the effect of the stimulant by itself was investigated on the DOI-induced HTR (e.g., Fig. 1).

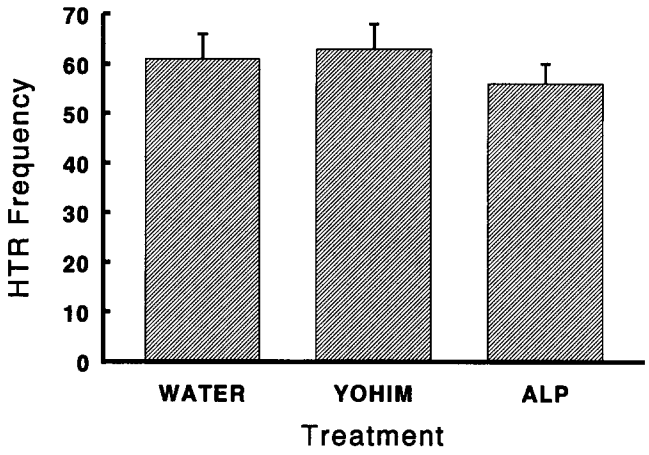

FIG. 2. Effects of either vehicle (water), yohimbine (0.1 mg/kg), or alprenolol (10 mg/kg) pretreatment on the (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (2.5 mg/kg)-induced head-twitch response (HTR) in 5-hydroxytryptamine$_2$ (5-HT$_2$)-receptor supersensitive mice. Alprenolol was administered 30 min whereas water or yohimbine 10 min prior to DOI administration. The data are presented as mean (±SEM) for the 20-min observation period. Supersensitivity was induced by a single administration of a 2.5-mg/kg dose of DOI 48 h prior to the day of experimentation (n = 6 per group).

The 5-HT$_1$ antagonist alprenolol (10 mg/kg) by itself had no significant effect on the DOI-induced HTR in supersensitive mice (Fig. 2). However, a combination of 0.5 mg/kg cocaine plus 10 mg/kg alprenolol reduced the total HTR frequency by 35% ($p < 0.05$) (Fig. 4). The cumulative HTR frequency exhibited significant differences from the eighth minute of observation and persisted throughout the experiment. When the dose of cocaine was increased to 20 mg/kg

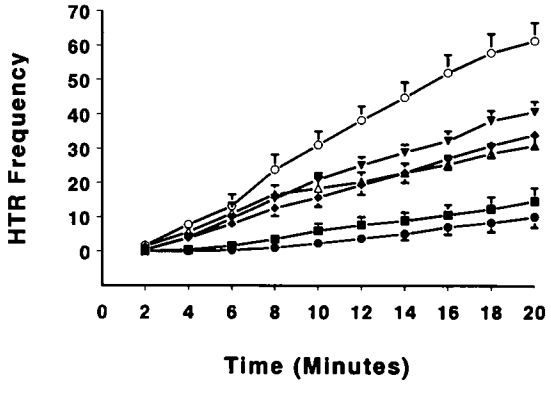

FIG. 1. Dose-dependent inhibitory effects of either cocaine [0.5 (▼), 2.5 (♦), 10 (■), and 20 (●) mg/kg] or water (○) pretreatment onthe mean (±SEM) cumulative head-twitch response (HTR) frequency observed at 2-min intervals following IP injection of a 2.5-mg/kg dose of (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) in 5-hydroxytryptamine$_2$ (5-HT$_2$)-receptor supersensitive mice. Cocaine or its vehicle (water) was administered 10 min prior to DOI injection. The cumulative effects of a 2.5-mg/kg dose of DOI in normosensitive mice is presented by △. Supersensitivity was induced by a single administration of DOI (2.5 mg/kg) 48 h prior to the day of experimentation. The statistical differences are described in the Results section (n = 6 at each dose).

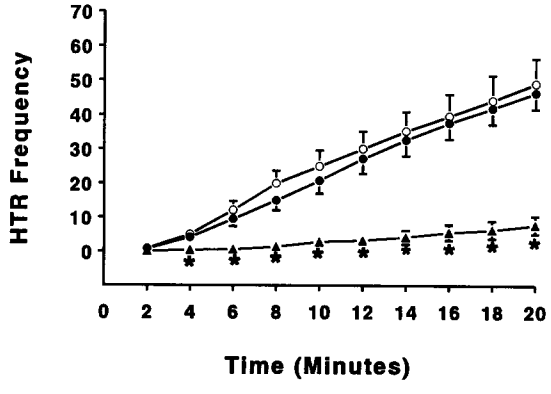

FIG. 3. Effects of prior administration of either water (○), a dose of 0.5 mg/kg cocaine plus 0.1 mg/kg yohimbine (●), or a 20-mg/kg dose of cocaine plus 0.1 mg/kg yohimbine (▲) on the cumulative mean (±SEM) head-twitch frequency, observed at 2-min intervals following a 2.5-mg/kg dose of (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) in 5-hydroxytryptamine$_2$ (5-HT$_2$)-receptor supersensitive mice. Cocaine and yohimbine solutions were mixed and injected as a single injection 10 min prior to DOI administration. Supersensitivity was induced by a single administration of a 2.5-mg/kg dose of DOI 48 h prior to the day of experimentation. *Significantly different from vehicle control at $p < 0.05$, n = 5–6 per group.

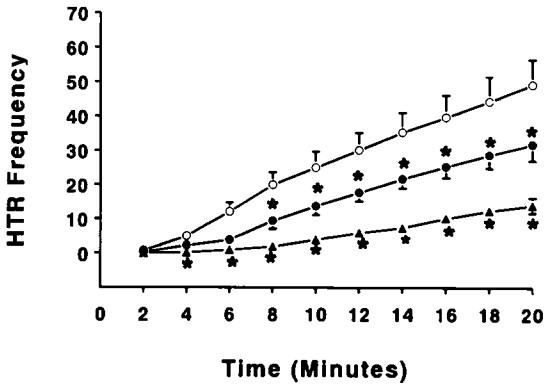

FIG. 4. Effects of prior administration of either water (○), a dose of 0.5 mg/kg cocaine plus 10 mg/kg alprenolol (●), or a dose of 20 mg/kg cocaine plus 10 mg/kg alprenolol (▲) on the mean cumulative head-twitch response (HTR) score observed at 2-min intervals following administration of a 2.5-mg/kg dose of (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) in 5-hydroxytryptamine$_2$ (5-HT$_2$)-receptor supersensitive mice. For details regarding drug administration schedules, see the Method section. Supersensitivity was induced by a single administration of a 2.5-mg/kg dose of DOI 48 h prior to the experimentation. *Significantly different from vehicle control, n = 6 per each group.

(plus 10 mg/kg alprenolol), the total HTR score was further attenuated by 71% ($p < 0.05$). In the latter case, the cumulative HTR score attained significance from the fourth-minute observation interval.

DISCUSSION

Although initial cocaine use can produce a feeling of well being and a decrease in anxiety (20), chronic abuse or administration of high doses of the stimulant can induce clinical anxiety as well as other psychiatric problems (33). Such anxiogenic effects are also evident in rodents following acute and chronic cocaine exposure (38,42). The anxiolytic effects of serotonergic 5-HT$_2$-receptor antagonists have been demonstrated both in animals (2,40) and man (9,37). Moreover, it has been suggested that 5-HT$_2$-receptors play a permissive role in anxiety-like behaviors and downregulation of these receptors consistently results in anxiolytic effects (38). In addition, the 5-HT$_{1A}$ agonists that possess anxiolytic activity can attenuate 5-HT$_2$-receptor function in rodents (1,17). Thus, investigation of the acute and chronic effects of cocaine on the serotonergic receptor systems can help to delineate the possible mechanisms through which the cocaine-induced animal and clinical anxieties are expressed.

Acute cocaine pretreatment has been shown to dose-dependently attenuate the HTR in mice when the behavior was produced by either selective or nonselective 5-HT$_2$-receptor agonists (14,18). This attenuation in the induced behavior appears to be due to functional interactions between: a) adrenergic α_2- and serotonergic 5-HT$_2$-receptors; b) serotonergic 5-HT$_{1A}$- and 5-HT$_2$-receptors. Cocaine causes indirect stimulation of the inhibitory adrenergic α_2- and serotonergic 5-HT$_{1A}$-receptors by increasing the synaptic concentrations of these bioamines (18). The increase in synaptic dopamine level does not affect the HTR score because dopamine receptors are not involved in the modulation of the head-twitch behavior (25). Darmani and coworkers (14) have further shown that chronic administration of low doses of the stimulant enhances the 5-HT$_2$-receptor-induced head-twitch frequency, probably via a persistent decrease in synaptic concentration of 5-HT. Repeated cocaine administration has the potential to alter the functional capacity of many receptor systems (14,23,24). Thus, to characterize the acute effects of cocaine on the head-twitch behavior in 5-HT$_2$-receptor supersensitive animals and reduce the possibility of altering the functional sensitivity of other receptor systems, the 5-HT$_2$-receptor was selectively sensitized by pretreating test animals with a single injection of the 5-HT$_{2/1C}$ agonist DOI 48 h prior to actual experimentation (15). In such treated animals, a challenge dose of DOI produced a greater frequency of the HTR. Several investigators (6,16,36) have previously reported that acute administration of a moderate dose of DOI does not alter the 5-HT$_2$-receptor density or affinity 24–48 h following its injection. Further, even chronic administration of DOI does not alter the adrenergic α_2- and serotonergic 5-HT$_{1A}$-receptors (6). It seems that the induced increase in the HTR frequency to a challenge dose of DOI is probably due to a specific alteration in the sensitivity of the 5-HT$_2$-receptor signal transduction mechanisms (13,15). Similar to published studies (13), the present results show that a challenge dose of DOI 48 h following its initial administration caused a significant increase (97%) in the frequency of the HTR. In such supersensitive mice, acute cocaine pretreatment dose-dependently reduced the DOI-induced HTR score. Cocaine is 3.6 times more potent in inhibiting the induced behavior in 5-HT$_2$-receptor supersensitive mice (ID_{50} = 3.3 mg/kg) relative to the normosensitive group [ID_{50} = 11.8 mg/kg; (18)].

Pretreatment with the adrenergic α_2-receptor antagonist, yohimbine (0.1 mg/kg), was shown to prevent the cocaine (20 mg/kg)-induced attenuation of HTR in normosensitive mice (18). Similar to the latter report, in this study yohimbine pretreatment by itself failed to affect the DOI-induced HTR. In the present investigation, however, yohimbine under the same experimental conditions failed to antagonize the effects of a 20-mg/kg cocaine dose on the DOI-induced HTR in supersensitive mice. Indeed, a similar degree of attenuation (84%) was observed in cocaine-only-treated (control) supersensitive mice. However, yohimbine did prevent the 35% inhibitory effects of a smaller dose of cocaine (0.5 mg/kg) on the DOI-induced behavior. These results indicate that in the presence of α_2-receptor blockade in 5-HT$_2$-receptor supersensitive mice, the inhibitory 5-HT$_{1A}$ component of cocaine's actions has a more prominent role in the attenuation of DOI-induced HTR relative to its minor role in normosensitive mice.

In normosensitive mice, the 5-HT$_1$-receptor antagonist alprenolol (10 mg/kg) was shown to partially prevent the inhibitory effects of a 20-mg/kg dose of cocaine on the DOI-induced HTR (18). Presently, in supersensitive mice alprenolol (10 mg/kg) failed to prevent the inhibitory component of cocaine's (20 mg/kg) effects. Moreover, even the low dose of cocaine (0.5 mg/kg) in the presence of alprenolol reduced the DOI-induced HTR frequency by a similar degree to that observed in cocaine-only-pretreated animals. These data suggest that relative to normosensitive animals, 5-HT$_2$-receptor supersensitive mice are also more responsive to the adrenergic α_2-receptor inhibitory component of cocaine's actions. Moreover, it appears that the inhibitory adrenergic α_2-receptor effect of acute cocaine administration is more prominent than its serotonergic 5-HT$_{1A}$ actions both in normo- and supersensitive mice. Further, these inhibitory effects appear not to be additive because cocaine-only-treated animals do not produce a greater degree of attenuation than those observed in the presence of yohimbine or alprenolol.

In summary, the present results indicate that 5-HT_2-receptor supersensitive mice are more sensitive to the inhibitory influence of cocaine via stimulation of the inhibitory serotonergic 5-HT_{1A}- and adrenergic α_2-receptors. Cocaine may also affect the head-twitch frequency via various receptor systems (25) by altering other neuronal mechanisms such as those of benzodiazepine-(35) and GABA-(28) receptors at high doses. Thus, a better understanding of such receptor interactions can lead to the development of new therapeutic agents to combat cocaine-induced psychiatric problems.

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REFERENCES

1. Arnt, J.; Hytell, J. Facilitation of 8-OH-DPAT-induced forepaw treading of rats by the 5-HT_2 agonist DOI. Eur. J. Pharmacol. 161:45–51; 1989.
2. Bennett, D. A.; Sills, M. A.; Williams, M.; Gerber, R.; Amrick, C. L.; Boyar, W. C.; Liebman, J. M.; Lovell, R. A.; Hutchinson, A. J. Pharmacological profile of CGS 18102A, a proposed anxiolytic with 5-HT_{1A} agonist and 5-HT_2 antagonist properties. Soc. Neurosci. Abstr. 15:485.1; 1989.
3. Bradberry, C. W.; Roth, R. H. Cocaine increases extracellular dopamine in rat nucleus accumbens and ventral tegmental area as shown by in vivo microdialysis. Neurosci. Lett. 103:97–102; 1989.
4. Broderick, P. A. Cocaine-on-line analysis of an accumbens amine neuronal basis for psychomotor behavior. Pharmacol. Biochem. Behav. 40:959–968; 1991.
5. Broderick, P. A. Cocaine's colocalized effects on synaptic serotonin and dopamine in ventral tegmentum in a reinforcement paradigm. Pharmacol. Biochem. Behav. 42:889–898; 1992.
6. Buckholtz, N. S.; Zho, D.; Freedman, D. X. Serotonin agonist administration downregulates rat brain serotonin$_2$ receptors. Life Sci. 42:2439–2445; 1988.
7. Carroll, M. E.; Lac, S. T.; Asencio, M.; Kargh, R. Fluoxetine reduces intravenous cocaine self-administration in rats. Pharmacol. Biochem. Behav. 35:237–244; 1990.
8. Carroll, M. E.; Lac, S. T.; Asencio, M.; Kargh, R. Intravenous cocaine self-administration in rats is reduced by dietary tryptophan. Psychopharmacology (Berl.) 100:239–300; 1990.
9. Ceulmans, D. L. S.; Hoppenbroouwers, M. L.; Gelders, Y. G.; Reyntjens, A. J. M. The influence of ritanserin, a serotonin antagonist, in anxiety disorders. A double-blind placebo-controlled study versus lorazepam. Pharmacopsychiatry 18:303–305; 1985.
10. Clouet, D.; Asghar, K.; Brown, R. Mechanisms of cocaine abuse and toxicity. NIDA Monograph 88. Washington, DC: U.S. Government Printing Office; 1988.
11. Cunningham, K. A.; Lakoski, J. M. The interaction of cocaine with serotonin dorsal raphe neurons. Single unit extracellular recording studies. Neuropsychopharmacology 3:41–50; 1990.
12. Cunningham, K. A.; Paris, J. M.; Goeders, N. E. Chronic cocaine enhances serotonin autoregulation and serotonin uptake binding. Synapse 11:112–123; 1992.
13. Darmani, N. A.; Martin, B. R.; Glennon, R. A. Withdrawal from chronic treatment with (±)-DOI causes supersensitivity to 5-HT_2-receptor-induced head-twitch behavior in mice. Eur. J. Pharmacol. 186:115–118; 1990.
14. Darmani, N. A.; Martin, B. R.; Glennon, R. A. Repeated administration of low doses of cocaine enhances the sensitivity of 5-HT_2-receptor function. Pharmacol. Biochem. Behav. 41:519–527; 1992.
15. Darmani, N. A.; Martin, B. R.; Glennon, R. A. Behavioral evidence for differential adaptation of the serotonergic system following acute and chronic treatment with (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-amino-propane (DOI) or ketanserin. J. Pharmacol. Exp. Ther. 262:692–698; 1992.
16. Darmani, N. A.; Martin, B. R.; Miller, K.; Teitler, M.; Glennon, R. A. Single or chronic DOI administration induces supersensitivity to 5-HT_2-receptor function—behavioral and radioligand binding studies. Virg. Acad. Sci. 42:P233; 1991.
17. Darmani, N. A.; Martin, B. R.; Pandey, U.; Glennon, R. A. Do functional relationships exist between 5-HT_{1A} and 5-HT_2-receptors? Pharmacol. Biochem. Behav. 36:901–906; 1990.
18. Darmani, N. A.; Martin, B. R.; Pandey, U.; Glennon, R. A. Inhibition of 5-HT_2-receptor mediated head-twitch response by cocaine via indirect stimulation of adrenergic α_2 and serotonergic 5-HT_{1A} receptors. Pharmacol. Biochem. Behav. 38:353–357; 1991.
19. Galloway, M. P. Neuropharmacology of cocaine: Effects on dopamine and serotonin systems. In: Lakoski, J. M.; Galloway, M. P.; White, F. J., eds. Cocaine. Pharmacology, physiology and clinical strategies. Boca Raton, FL: CRC Press; 1992:163–189.
20. Gawin, F. H.; Ellinwood, E. H. Cocaine dependence. Annu. Rev. Med. 40:149–161; 1989.
21. Glennon, R. A. Serotonin receptors: Clinical implications. Neurosci. Biobehav. Rev. 14:35–47; 1990.
22. Glennon, R. A.; Lucki, I. Behavioral models of serotonin receptor activation. In: Sanders-Bush, E., ed. Serotonin. Clifton Park, NJ: Humana Press; 1989:253–293.
23. Goeders, N. E. Cocaine differentially affects benzodiazepine receptors in discrete regions of the rat brain: Persistence and potential mechanisms mediating these effects. J. Pharmacol. Exp. Ther. 129:543–549; 1991.
24. Goeders, N. E.; Kuhar, M. J. Chronic cocaine administration induces opposite changes in dopamine receptors in the striatum and nucleus accumbens. Alcohol Drug Res. 7:207–216; 1987.
25. Handley, S. L.; Singh, L. Neurotransmitters and shaking behavior: More than a "gut bath" for the brain. Trends Pharmacol. Sci. 7:324–328; 1986.
26. Heal, D. J.; Philpot, J.; O'Shaughnessy, K. M.; Davies, C. L. The influence of central noradrenergic function on 5-HT_2 mediated head-twitch responses in mice: Possible implications for the actions of antidepressant drugs. Psychopharmacology (Berl.) 89: 414–420; 1986.
27. Heikkila, R. E.; Orlanski, H.; Cohen, G. Studies on the distinction between uptake inhibition and release of ^{3}H-dopamine in rat brain tissue slices. Biochemical Pharmacol. 24:847–852; 1975.
28. Ikeda, M.; Dohi, T.; Tsujimoto, A. Inhibition of gamma aminobutyric acid release from synaptosomes by local anesthetics. Anesthesiology 58:495–499; 1983.
29. Johanson, C. E.; Fischman, M. W. The pharmacology of cocaine related to its substance abuse. Pharmacol. Rev. 41:3–52; 1989.
30. Kuhar, M. J.; Ritz, M. C.; Grigoriadis, D.; Lew, R.; Sharkey, J. A cocaine receptor associated with dopamine transport and drug self-administration. In: Lakoski, J. M.; Galloway, M. P.; White, F. J., eds. Cocaine. Pharmacology, physiology and clinical strategies. Boca Raton, FL: CRC Press; 1992:191–201.
31. Levy, A. D.; Li, Q.; Alvarez Sanz, M. C.; Rittenhouse, P. A.; Brownfield, M. S.; Van de Ker, L. D. Repeated cocaine modifies the neuroendocrine responses to the 5-HT_{1C}/5-HT_2-receptor agonist DOI. Eur. J. Pharmacol. 221:121–127; 1992.
32. Loh, E. A.; Roberts, C. S. Break-points on a progressive ratio schedule reinforced by intravenous cocaine increase following depletion of forebrain serotonin. Psychopharmacology (Berl.) 101:262–266; 1990.
33. Lowenstein, D. H.; Massa, S. M.; Rowbotham, M. G.; Collins, S. D.; McKinney, H. E.; Simon, R. P. Acute neurologic and psychiatric complications associated with cocaine abuse. Am. J. Med. 83:841–846; 1987.
34. Lucki, I.; Nobler, M. S.; Frazer, A. Differential actions of serotonin antagonists on two behavioral models of serotonin receptor activation in the rat. J. Pharmacol. Exp. Ther. 228:133–139; 1984.
35. McAllister, J.; Goeders, N.; Dworkin, S. Chronic cocaine modif-

ies brain benzodiazepine receptor densities. Natl. Inst. Drug Abuse Monogr. Ser. 81:101–108; 1988.
36. McKenna, D. J.; Nazarali, A. J.; Himeno, A.; Saavedra, J. M. Chronic treatment with (±) DOI, a psychotomimetic 5-HT_2 agonist, downregulates 5-HT_2-receptors in rat brain. Neuropsychopharmacology 2:81–87; 1989.
37. Reyntjens, A.; Goeders, Y. G.; Hoppenbrouwers, M. L.; Vann Bussche, G. Thymostenic effects of ritanserin (R55667), a centrally acting serotonin S2 receptor blocker. Drug Dev. Res. 8: 205–211; 1986.
38. Saiff, D. B.; Nevins, T.; Lal, H. Mianserin-induced 5-HT_2-receptor downregulation results in anxiolytic effects in the elevated plus-maze test. Drug Dev. Res. 26:287–297; 1992.
39. Schmidt, A. W.; Peroutka, S. J. 5-Hydroxytryptamine receptor families. FASEB J. 3:2242–2249; 1989.
40. Stutzman, J. M.; Eon, B.; Darche, K.; Lucas, M.; Rataud, J.; Piot, O.; Blanchard, J. C.; Laduron, P. M. Are 5-HT_2 antagonists endowed with anxiolytic properties in rodents? Neurosci. Lett. 128:4–8; 1991.
41. Wolf, W.A.; Kuhn, D.M. Cocaine and serotonin neurochemistry. Neurochem. Int. 18:33–38; 1991.
42. Yang, X.-M.; Gorman, A. L.; Dunn, A. J.; Goeders, N. Anxiogenic effects of acute and chronic cocaine administration: Neurochemical and behavioral studies. Pharmacol. Biochem. Behav. 41:643–650; 1992.