Pharmacology Biochemistry and Behavior, Vol. 42, pp. 481–486, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Cocaine-Induced Suppression of Renin Secretion Is Partially Mediated by Serotonergic Mechanisms

ANDREW D. LEVY,[1] PETER A. RITTENHOUSE, QIAN LI, JANICE E. KERR, THERESA M. CABRERA, GEORGE BATTAGLIA AND LOUIS D. VAN DE KAR

Department of Pharmacology,
Stritch School of Medicine, Loyola University of Chicago, Maywood IL 60153

Received 24 December 1991

LEVY, A. D., P. A. RITTENHOUSE, Q. LI, J. E. KERR, T. M. CABRERA, G. BATTAGLIA AND L. D. VAN DE KAR. *Cocaine-induced suppression of renin secretion is partially mediated by serotonergic mechanisms.* PHARMACOL BIOCHEM BEHAV **42**(3) 481–486, 1992.—Acute cocaine reduces renin secretion. To determine whether serotonergic neurons mediate this effect, male Sprague-Dawley rats received the serotonin (5-HT) neurotoxin 5,7-dihydroxytryptamine (75 μg/side, ICV) 2 weeks prior to cocaine injections (3.75–15 mg/kg, IP). 5-HT lesions attenuated the cocaine-induced reduction of plasma renin concentration (PRC), suggesting a partial 5-HT role. To determine which receptors mediate this response, rats were pretreated with the partial 5-HT_{1A} agonist 8-[2-[4-(2-methoxyphenyl)-*l*-piperazinyl]ethyl]-8-azaspirol-[4,5]-decane-7,9-dione (BMY 7378) (1 mg/kg, SC), the 5-HT_{1C}/5-HT_2 antagonist ritanserin (0.1 mg/kg, SC), or the α_2/5-HT_{1A} antagonist yohimbine (1 mg/kg, SC) prior to cocaine. None of the antagonists altered the cocaine-induced suppression of PRC, although BMY 7378 and yohimbine elevated PRC. The data suggest that cocaine's effect is partially mediated by a serotonergic mechanism, but do not support a role for 5-HT_{1A} receptors, 5-HT_2/5-HT_{1C} receptors, or α_2-adrenoceptors in mediating the suppressive effect of cocaine on renin secretion.

Cocaine Renin Serotonin Rat 5,7-Dihydroxtryptamine BMY 7378 Yohimbine

IT has recently been determined that acute administration of cocaine reduces secretion of renin (15). The mechanisms by which this action occurs are unknown. Because cocaine inhibits the reuptake of serotonin (5-HT), dopamine (DA), and norepinephrine (NE) (25–27,32), this study was undertaken to evaluate potential neuronal mechanisms underlying this response.

Secretion of renin is influenced by activity of 5-HT and NE neurons. Renin secretion is enhanced by the 5-HT releaser *p*-chloroamphetamine (37), and by various 5-HT agonists (33), via activation of 5-HT_2 receptors. Furthermore, stimulation of α_2-adrenoceptors decreases renin secretion (19), while a role for DA in the regulation of renin secretion has not been demonstrated.

As a consequence of cocaine's inhibition of 5-HT reuptake, acute cocaine increases the concentration of 5-HT in the synapse (11,13). In the dorsal raphe nucleus, the increased concentration of synaptic 5-HT is believed to be responsible for the inhibition of firing of 5-HT neurons by activation of 5-HT_{1A} somatodendritic receptors. Cocaine inhibits the firing of 5-HT neurons in mesencephalic dorsal raphe nucleus in vivo (6,8,14,22) and in vitro (20). The 5-HT_{1A} agonist buspirone also decreases the firing rate of dorsal raphe neurons (40) and decreases plasma renin activity (36). We previously determined that serotonergic neurons mediate the cocaine-induced stimulation of corticotropin (ACTH) and corticosterone secretion (17). Therefore, it was conceivable that serotonergic mechanisms also could mediate the effect of cocaine on renin secretion.

These studies were therefore designed to evaluate the potential neuronal mechanisms underlying the cocaine-induced suppression of renin secretion. Both serotonergic and α_2-adrenergic systems were examined because they have been shown to interact with cocaine and mediate secretion of renin.

METHOD

Animals

Male Sprague-Dawley rats (225–275 g) were purchased from Sasco-King Animal Laboratories (Oregon, WI). Rats were housed two per cage (unless specified otherwise) in a temperature-, humidity-, and illumination (12 L : 12 D cycle,

[1] Requests for reprints should be addressed to Andrew D. Levy, Ph.D., Department of Pharmacology, Stritch School of Medicine, Loyola University of Chicago, 2160 S. First Avenue, Maywood, IL 60153.

lights on at 7 a.m.)-controlled room. Water and food (Wayne Lab Blox, Lab Mills Inc., Chicago, IL) were available ad lib. Rats were randomly divided into groups of eight (unless specified otherwise) for each experiment. All experiments were conducted early in the light cycle (approximately 10:45 a.m.-1:30 p.m.). All procedures were approved by the Loyola University Animal Care and Use Committee and were conducted in accordance with the *NIH Guide for the Care and Use of Laboratory Animals.*

Blood Collection

Rats were killed by decapitation 15 min following cocaine injections in an area outside the animal room. The maximal renin response to cocaine occurs approximately 15 min postinjection (15). Trunk blood was collected into centrifuge tubes containing 0.5 ml 0.3 M EDTA (pH 7.4) for assay of plasma renin concentration (PRC).

Drugs

All drug solutions were made immediately before injections. Cocaine HCl was obtained from Sigma Chemical Co. (St. Louis, MO) and was dissolved in physiological saline. 5,7-Dihydroxytryptamine (5,7-DHT) was obtained from Sigma and dissolved in saline containing 0.1% ascorbic acid. 8-[2-[4-(2-Methoxyphenyl)-*l*-piperazinyl]ethyl]-8-azaspirol-[4,5]-decane-7,9-dione (BMY 7378), donated by Bristol-Meyers (Wallingford, CT) was dissolved in saline and pH adjusted to 6.0. Ritanserin (Janssen Pharmaceuticals, Beerse, Belgium) was dissolved in ethanol and adjusted with saline to a 10% v/v ethanol solution. Yohimbine was purchased from Sigma and dissolved in distilled water. All drugs (except for 5,7-DHT) and their respective vehicles were injected in volumes of 1 ml/kg and were administered either IP (cocaine) or SC (BMY 7378, ritanserin, and yohimbine) and injected SC in a volume of 1 ml/kg. All drug doses were determined by the salt form of each drug.

Procedures

Effect of ICV injection of 5,7-DHT on cocaine-induced reduction of PRC. Serotonergic neurons were destroyed by stereotaxic ICV injections of 5,7-DHT (4,5) under pentobarbital anesthesia (50 mg/kg, IP). All rats were pretreated with ampicillin (50 mg/kg, IM) and atropine methylbromide (0.2 mg/kg, IP). To prevent damage to dopaminergic or noradrenergic neurons, rats also received 15 mg/kg IP of the dopamine and norepinephrine uptake inhibitor nomifensine 20 min prior to ICV injections of 5,7-DHT. Hamilton 25-μl syringes were lowered into the lateral cerebral ventricles (A -0.5; L 1.4; H -4.6 from bregma), and 75 μg/10 μl 5,7-DHT or vehicle were infused bilaterally over 1 min. After recovery from surgery (2-3 weeks), rats (n = 10 for the 5,7-DHT-injected groups and n = 8 for vehicle-injected rats) received injections of cocaine (0, 3.75, 7.5, or 15 mg/kg, IP) and were decapitated 15 min later. To confirm the loss of 5-HT nerve terminals induced by 5,7-DHT, brains were rapidly removed and cerebral cortex was dissected and frozen at -70°C. The extent of the lesion was determined by measuring [^{3}H]citalopram binding to the 5-HT uptake sites in rat cortex (3).

Effect of the partial 5-HT$_{1A}$ agonist BMY 7378 on cocaine-induced reduction of PRC. Rats received injections of 1 mg/kg (SC) BMY 7378 (29) or vehicle, followed 15 min later by injections of cocaine HCl or saline. Cocaine was administered in doses of 0, 3.75, 7.5, or 15 mg/kg IP.

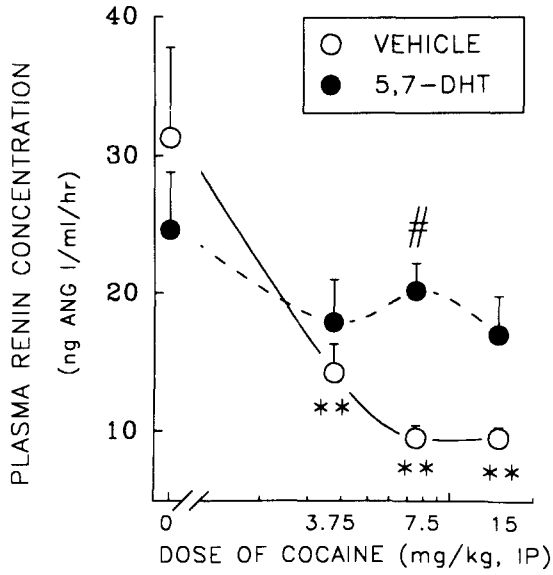

FIG. 1. Destruction of 5-HT neurons inhibits cocaine-induced reduction of PRC. Rats received ICV injections of 5,7-DHT (75 μg/side) or vehicle 2-3 weeks prior to cocaine injections (0, 3.75, 7.5, or 15 mg/kg). Mean ± SEM for each group is presented (n = 8 in vehicle-pretreated groups, n = 10 in 5,7-DHT-pretreated groups). Main effect of 5,7-DHT: $F(1, 60) = 2.57$, NS; main effect of cocaine: $F(3, 60) = 8.08$, $p < 0.001$. The two-way interaction approached statistical significance, $F(3, 60) = 2.55$, $p < 0.065$. **$p < 0.01$ from the respective 0 dose of cocaine (i.e., saline) group (Newman-Keuls test). #$p < 0.05$ from corresponding vehicle-pretreated group.

Effect of the 5-HT$_{1C}$/5-HT$_2$ antagonist ritanserin on cocaine-induced reduction of PRC. Rats received 0.1 mg/kg (SC) ritanserin (28,39) or vehicle 60 min prior to cocaine administration (0, 3.75, 7.5, or 15 mg/kg, IP). This dose of ritanserin was found to completely block the effect of RU 24969 (34) and DOI (24) on renin secretion.

Effect of the α_2 antagonist yohimbine on cocaine-induced reduction of PRC. Rats received injections of 1 mg/kg yohimbine (SC) or vehicle (distilled water) followed 2 h later by injections of cocaine HCl or saline. Yohimbine was previously shown to increase renin secretion up to 2 h after (SC) injection (21). However, the effects of yohimbine on blood pressure and heart rate subsided within 1 h after injection (21). Cocaine was administered in doses of 0, 3.75, 7.5, or 15 mg/kg IP.

Biochemical Determinations

PRC. In this assay, a saturating concentration of renin substrate is added to the plasma to allow generation of angiotensin I (ANG I) at maximal velocity. Thus, this assay reflects the total concentration of the enzyme renin in plasma, independent of the concentration of renin substrate. In the PRC assay, renin substrate is obtained from plasma of rats that were nephrectomized and received a dexamethasone injection (0.2 mg/rat) 24 h before sacrifice. The details of this assay were described by us elsewhere (23). The radioimmunoassay of ANG I was performed with antiserum at a dilution of 1 : 16,000 and a total binding of 30% as previously described (23). The data were analyzed by a computer program (RIA-AID, Robert Maciel Associates, Arlington, MA). The sensitiv-

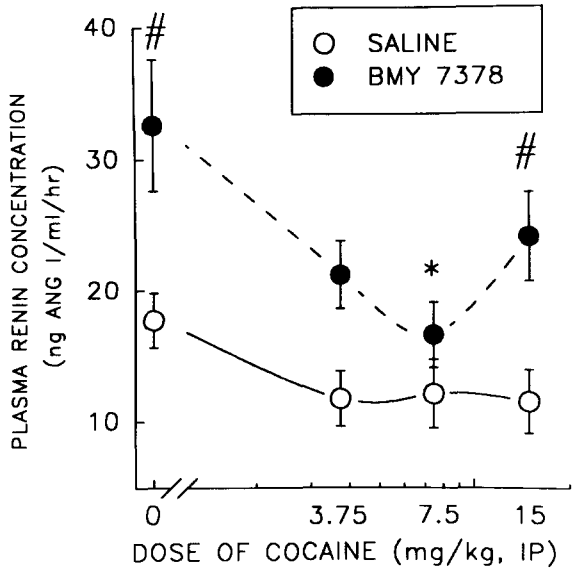

FIG. 2. BMY 7378 does not influence cocaine-induced reduction of PRC. Rats were injected with BMY 7378 (1 mg/kg, SC) 15 min prior to cocaine administration. Mean ± SEM for each group (n = 8) is presented. Main effect of cocaine: $F(3, 55) = 4.889$, $p < 0.004$; cocaine × BMY 7378 interaction: $F(3, 55) = 1.12$, NS. *$p < 0.05$ for both saline- and BMY 7378-pretreated groups compared to non-cocaine-injected groups (Newman-Keuls test). #Significant difference from saline (0 dose of BMY 7378)-pretreated rats, $p < 0.05$ (Newman-Keuls test).

ity limit of the radioimmunoassay (RIA) was 10 pg ANG I per tube and the intraassay variability was 4.4%. The interassay variability was 12.6%.

Verification of 5,7-DHT-induced lesions. Verification of the magnitude of the lesions produced by 5,7-DHT was examined by determination of the density of 5-HT uptake sites in cerebral cortex. This method has been shown to provide a good index for drug-induced neurodegeneration of 5-HT axons and nerve terminals (3). [^{3}H]Citalopram-labeled 5-HT uptake sites were determined according to D'Amato et al. (9).

Statistics

The data are presented as the group means and the SEM. Statistical analysis of the data was performed by two-way analysis of variance (ANOVA), and individual group means were compared by Newman-Keuls test (30). All tests were performed using a computer program (NWA STATPAK, Portland, OR).

RESULTS

Studies were conducted to examine whether serotonergic neurons mediate the suppressive effect of cocaine on renin secretion. First, serotonergic neurons were destroyed by ICV injection of 5,7-DHT. 5-HT lesions inhibited the cocaine-induced reduction of renin secretion (Fig. 1). Posthoc Newman-Keuls test indicates that the cocaine-induced suppression of PRC was attenuated in 5,7-DHT-pretreated rats ($p < 0.05$). Destruction of 5-HT neurons was verified by determining the density of 5-HT uptake sites ([^{3}H]citalopram binding) in the cortex (3). A 90% reduction in the density of 5-HT uptake sites was observed in the cortex of rats treated with 5,7-DHT [control = 12.1 ± 0.3 fmol/mg tissue (n = 30); 5,7-DHT = 1.0 ± 0.1 fmol/mg tissue; 8.3% of control values (n = 38)]. These data suggest a nearly complete destruction of the serotonergic nerve terminals.

Injection of the partial 5-HT$_{1A}$ agonist BMY 7378 (Fig. 2) alone significantly increased PRC, $F(1, 55) = 24.2$, $p < 0.001$. However, BMY 7378 did not prevent the cocaine-induced decrease in PRC. Also, the 5-HT$_{1C}$/5-HT$_2$ antagonist ritanserin did not inhibit the cocaine-induced decrease in PRC (Fig. 3).

Finally, we tested whether pretreatment with the α_2-adrenoceptor antagonist yohimbine would prevent the cocaine-induced decrease in PRC. Yohimbine significantly increased PRC, $F(1, 45) = 132.72$, $p < 0.01$. Although cocaine produced a significant reduction in PRC, $F(3, 45) = 3.465$, $p < 0.03$, there was no statistically significant interaction between yohimbine and cocaine treatments (Fig. 4).

DISCUSSION

The data indicate that acute cocaine reduces secretion of renin partially through a serotonergic mechanism. Destruction of serotonergic neurons by ICV injection of 5,7-DHT inhibited, but did not completely block, the cocaine-induced decrease in PRC. The magnitude of the lesion in serotonergic neurons was verified by measuring the reduction in the density of cortical 5-HT uptake sites using [^{3}H]citalopram. 5-HT uptake sites in the forebrain are primarily localized on serotonergic nerve terminals, and these sites are not subject to regulation. Therefore, reduction in their number provides a valid index to quantify the degeneration of serotonergic nerve terminals (3). These data agree well with previous observations that the same dose of 5,7-DHT caused 87% loss of the 5-HT concentration in the hypothalamus and a 52.3% loss of 5-HT concentration in the midbrain without affecting hypothalamic

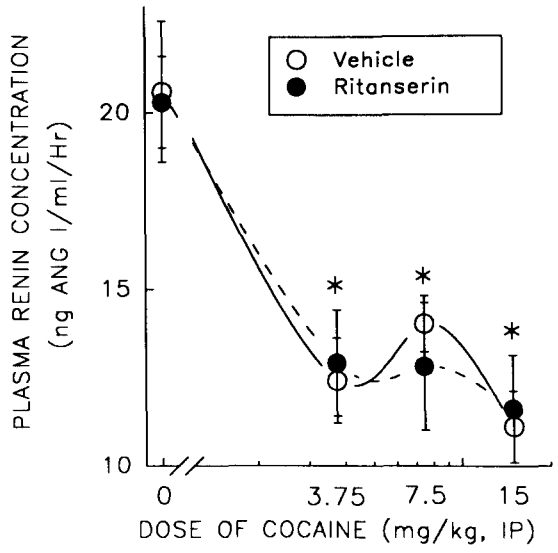

FIG. 3. The 5-HT$_2$/5-HT$_{1C}$ antagonist ritanserin does not inhibit cocaine-induced reduction of PRC. Ritanserin (0.1 mg/kg, SC) was administered 60 min prior to cocaine injections. Mean ± SEM for each group (n = 8) is presented. Main effect of ritanserin: $F(1, 54) = 0.019$, NS; main effect of cocaine: $F(3, 54) = 15.29$, $p < 0.001$; cocaine × ritanserin interaction: $F(3, 54) = 0.17$, NS. *$p < 0.05$ for both vehicle- and ritanserin-pretreated groups compared to saline (0 dose of cocaine)-injected groups (Newman-Keuls test).

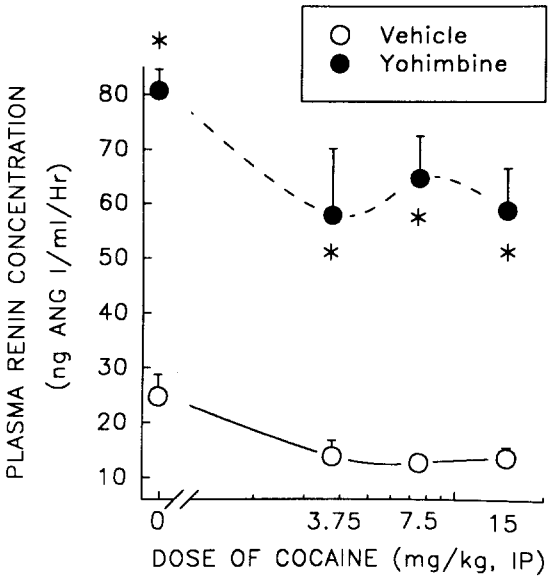

FIG. 4. The α_2/5-HT_{1A} antagonist yohimbine does not inhibit cocaine-induced reduction of PRC. Yohimbine (1 mg/kg, SC) was administered 2 h prior to cocaine injections. Mean ± SEM for each group (n = 8) is presented. Main effect of yohimbine: $F(1, 48)$ = 130.4, $p < 0.001$; main effect of cocaine: $F(3, 48) = 3.42$, $p < 0.05$; cocaine × yohimbine interaction: $F(3, 48) = 0.43$, NS. *$p < 0.05$ compared with vehicle (0 dose of yohimbine)-pretreated groups (Newman-Keuls test).

DA and NE concentrations (37). The lack of a complete blockade of cocaine's actions by 5,7-DHT suggests that other mechanisms contribute to the cocaine-induced inhibition of renin release.

We also attempted to establish the 5-HT receptor subtype that could mediate the cocaine-induced reduction in renin secretion. Previous data suggest that disruption of serotonergic activity in the dorsal raphe nucleus leads to a small but significant decrease in renin secretion under basal conditions and an inhibition of stress-induced elevation of renin secretion (35,37,38). Moreover, the 5-HT_{1A} agonist buspirone decreases plasma renin activity (36) and also decreases the firing of serotonergic neurons in the dorsal raphe nucleus (40). Thus, cocaine could conceivably decrease renin secretion by activating these 5-HT_{1A} receptors in the dorsal raphe nucleus. The lack of inhibition, by BMY 7378, of the suppressive effect of cocaine does not support this hypothesis. However, BMY 7378 is a partial 5-HT_{1A} agonist. BMY 7378 can antagonize some actions of 5-HT_{1A} agonists, such as 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) (29,42), particularly the suppressive effect of 8-OH-DPAT on the firing rate of dorsal raphe neurons (7). However, BMY 7378 did not prevent the suppressive effect of microiotophoretically applied 5-HT on cells in the dorsal raphe nucleus (7). The dose of BMY 7378 used by us (1 mg/kg, SC) was found by Sharp et al. (29) to inhibit the effects of the 5-HT_{1A} agonist 8-OH-DPAT on head-weaving and forepaw-treading. A higher dose (5 mg/kg) also was effective but it inhibited the sterotypy and hyperactivity produced by the DA agonist apomorphine, while the dose of 1 mg/kg (used by us) did not. Thus, the dose for BMY 7378 was judged by us to be in the "selective" range. When administered alone, BMY 7378 can produce actions that are similar to those of classical 5-HT_{1A} agonists (43). Since no full 5-HT_{1A} antagonists are presently available, the data cannot conclusively rule out a role for 5-HT_{1A} receptors in mediating the effect of cocaine on renin secretion. It should be noted that BMY 7378 increased renin secretion. This effect could be due to hypotensive actions (31), mediated through α_1- (41) or 5-HT_{1A} receptors. A reduction in blood pressure can stimulate renin secretion by activating renal baroreceptor mechanisms (10).

These studies also attempted to determine whether 5-HT_2 receptors mediate the effects of cocaine on renin secretion. Since activation of 5-HT_2 receptors stimulates renin secretion (1,2,18,34), we hypothesized that blockade of 5-HT_2 receptors could potentiate the cocaine-induced suppression of renin secretion. Cocaine could reduce renin secretion via suppression of 5-HT neuronal firing. In addition, cocaine increases synaptic concentrations of 5-HT (11,13) that could enhance secretion of renin via activation of postsynaptic 5-HT_2 receptors in then hypothalamus. Serotonergic neurons originating in the dorsal raphe nucleus and terminating in the hypothalamus stimulate renin secretion (33). It was therefore conceivable that administration of a 5-HT_2 antagonist would magnify the suppressive effects of cocaine on renin secretion. However, the inability of ritanserin to alter the cocaine-induced decrease in renin secretion does not support a stimulatory effect of cocaine on renin via activation of 5-HT_{1C}/5-HT_2 receptors. It is interesting to note, however, that ritanserin inhibited cocaine-induced elevation of corticosterone secretion (17).

Activation of brain α_2-receptors decreases renin secretion, probably by reducing sympathetic output (19). There is little evidence for an involvement of dopaminergic neurons in regulating renin secretion. In addition to its actions on 5-HT uptake, cocaine also inhibits NE and DA uptake (25,26,32). The increased concentration of NE in the synapse could activate central α_2-receptors, leading to inhibition of renin secretion. However, the present data do not support this hypothesis since yohimbine did not prevent the effect of cocaine on renin secretion. Yohimbine was previously shown to increase renin secretion up to 2 h after (SC) injection (21). However, the effects of yohimbine on blood pressure and heart rate subsided within 1 h after injection (21). However, the effects of yohimbine 2 h before rats received a cocaine injection and it is clear that yohimbine was still capable of increasing renin secretion at this time point. Thus, the inability of yohimbine to inhibit the effect of cocaine on renin secretion is not likely due to cardiovascular reflex mechanisms. In addition to its actions on α_2-receptors, yohimbine is a 5-HT antagonist (16), probably at the 5-HT_{1A} site (12). Because yohimbine did not antagonize the cocaine-induced reduction of PRC, the data suggest that α_2- and 5-HT_{1A} receptors do not mediate cocaine's action.

In conclusion, the data suggest that cocaine suppresses renin secretion partially via a serotonergic mechanism. The exact 5-HT receptor subtype involved is not known, but seems unlikely to be 5-HT_{1A} or 5-$HT_{1C/2}$. Other neurotransmitters could contribute to the effect of cocaine on renin secretion. However, α_2-receptors are unlikely to be involved in mediating the suppressive effect of cocaine on renin secretion.

ACKNOWLEDGEMENTS

The authors thank Bristol-Myers (Wallingford, CT) for their donations of BMY 7378 and Janssen Pharmaceuticals (Beerse, Belgium) for their donation of ritanserin. They also thank Kayoko Kunimoto and Joseph Yracheta for their excellent technical assistance. This research was supported by USPHS Grants DA04865 and MH45812.

REFERENCES

1. Alper, R. H. Hemodynamic and renin response to (+)-DOI, a selective 5-HT2 receptor agonist, in conscious rats. Eur. J. Pharmacol. 175:323-332; 1990.
2. Alper, R. H.; Snider, J. M. Activation of serotonin2 (5-HT2) receptors by quipazine increases arterial pressure and renin secretion in conscious rats. J. Pharmacol. Exp. Ther. 243:829-833; 1987.
3. Battaglia, G. Criteria for assessing drug-induced biochemical alterations and degeneration of serotonergic neurons. In: Paoletti, R.; Vanhoutte, P. M.; Bruenllo, N.; and Maggi, F. M. eds. Serotonin: From cell biology to pharmacology and therapeutics. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1990:p. 651-660.
4. Baumgarten, H. G.; Bjorklund, A.; Lachenmayer, L.; Nobin, A. Evaluation of the effect of 5,7-dihydroxytryptamine on serotonin and catecholamine neurons in the rat CNS. Acta Physiol. Scand. 391 (suppl.): 1-17; 1973.
5. Bjorklund, A.; Baumgarten, H. G.; Rensch, A. 5,7-Dihydroxytryptamine: Improvement of its selectivity for serotonin neurons in the CNS by pretreatment with desipramine. J. Neurochem. 24: 833-835; 1975.
6. Black, E. W.; Lakoski, J. M. In vitro electrophysiology of dorsal raphe serotonergic neurons in subchronic cocaine treated rats: Development of tolerance to acute cocaine administration. Mol. Cell. Neurosci. 1:84-91; 1990.
7. Chaput, Y.; de Montigny, C. Effects of the 5-hydroxytryptaminel receptor antagonist, BMY 7378, on 5-hydroxytryptamine neurotransmission: Electrophysiological studies in the rat central nervous system. J. Pharmacol. Exp. Ther. 246:359-370; 1988.
8. Cunningham, K. A.; Lakoski, J. M. Electrophysiological effects of cocaine and procaine on dorsal raphe serotonin neurons. Eur. J. Pharmacol. 148:457-462; 1988.
9. D'Amato, R. J.; Largent, B. L.; Snowman, A. M.; Snyder, S. H. Selective labeling of serotonin uptake sites in rat brain by [^{3}H]citalopram contrasted to labeling of multiple sites by [^{3}H]imipramine. J. Pharmacol. Exp. Ther. 242:364-371; 1987.
10. Hackenthal, E.; Paul, M.; Ganten, D.; Taugner, R. Morphology, physiology, and molecular biology of renin secretion. Physiol. Rev. 70:1067-1116; 1990.
11. Hanson, G. R.; Matsuda, L. A.; Gibb, J. W. Effect of cocaine on metamphetamine-induced neurochemical changes: Characterization of cocaine os a monoamine uptake blocker. J. Pharmacol. Exp. Ther. 242:507-513; 1987.
12. Hoyer, D. Functional correlates of serotonin 5-HT$_1$ recognition sites. J. Receptor. Res. 8:59-81; 1988.
13. Koe, B. K. Molecular geometry of inhibitors of the uptake of catecholamines and serotonin in synaptosomal preparation of rat brian. J. Pharmacol. Exp. Ther. 199:649-661; 1976.
14. Lakoski, J. M.; Cunningham, K. A. Cocaine interaction with central monoaminergic systems: Electrophysiological approaches. Trends Pharmacol. Sci. 9:177-180; 1988.
15. Lakoski, J. M.; Rittenhouse, P. A.; Bonadonna, A. M.; Van de Kar, L. D. Acute, but not repeated, cocaine administration decreases renin secretion in the conscious male rat. Neurosci. Lett. 127:181-184; 1991.
16. Lambert, G. A.; Lang, W. J.; Friedman, E.; Meller, E.; Gershon, S. Pharmacological and biochemical properties of isomeric yohimbine alkaloids. Eur. J. Pharmacol. 49:39-48; 1978.
17. Levy, A. D.; Li, Q.; Kerr, J. E.; Rittenhouse, P. A.; Milonas, G.; Cabrera, T. M.; Battaglia, G.; Alvarez Sanz, M. C.; Van de Kar, L. D. Cocaine-induced elevation of plasma adrenocorticotropin hormone and corticosterone is mediated by serotonergic neurons. J. Pharmacol. Exp. Ther. 259:495-500; 1991.
18. Lorens, S. A.; Van de Kar, L. D. Differential effects of serotonin (5-HT1A and 5-HT2) agonists and antagonists on renin and corticosterone secretion. Neuroendocrinology 45:305-310; 1987.
19. Nolan, P. C.; Reid, I. A. Mechanism of suppression of renin secretion by clonidine in the dog. Cir. Res. 42:206-211; 1978.
20. Pan, Z. Z.; Williams, J. T. Differential actions of cocaine and amphetamine on dorsal raphe neurons *in vitro*. J. Pharmacol. Exp. Ther. 251:56-62; 1989.
21. Pfister, S. L.; Keeton, T. K. Yohimbine induces sympathetically mediated renin release in the conscious rat. Eur. J. Pharmacol. 97:247-255; 1984.
22. Pitts, D. K.; Marwah, J. Electrophysiological effects of cocaine on central monoaminergic neurons. Eur. J. Pharmacol. 131:95-98; 1986.
23. Richardson Morton, K. D.; Van de Kar, L. D.; Brownfield, M. S.; Bethea, C. L. Neuronal cell bodies in the hypothalamic paraventricular nucleus mediate stress-induced renin and corticosterone secretion. Neuroendocrinology 50:73-80; 1989.
24. Rittenhouse, P. A.; Bakkum, E.; Van de Kar, L. D. Evidence that the serotonine agonist, DOI, increases renin secretion and blood pressure through both central and peripheral 5-HT2 receptors. J. Pharmacol. Exp. Ther. 259:58-65; 1991.
25. Ross, S. B.; Renyi, A. L. Uptake of some tritiated sympathomimetic amines by mouse brain cortex slices in vitro. Acta Pharmacol. Toxicol. 24:297-309; 1966.
26. Ross, S. B.; Renyi, A. L. Inhibition of the uptake of tritiated catecholamines by antidepressant and related agents. Eur. J. Pharmacol. 2:181-186; 1967.
27. Ross, S. B.; Renyi, A. L. Inhibition of the neuronal uptake of 5-hydroxytryptamine and noradrenaline in rat brain by (Z)- and (E)-3-(4-bromophenyl)-*N*-*N*-dimethyl-3-(3-pyridyl)allylamines and their secondary analogues. Neuropharmacology 16:57-63; 1977.
28. Schotte, A.; De Bruyckere, K.; Janssen, P. F. M.; Leysen, J. E. Receptor occupancy by ritanserin and risperidone measured using ex vivo autoradiography. Brain Res. 500:295-301; 1989.
29. Sharp, T.; Backus, L. I.; Hjorth, S.; Bramwell, S. R.; Grahame-Smith, D. G. Further investigation of the in vivo pharmacological properties of the putative 5-HT1A antagonist BMY 7378. Eur. J. Pharmacol. 176:331-340; 1990.
30. Steel, R. G. D.; Torrie, J. H. Principles and procedures of statistics with special reference to the biological sciences. New York: McGraw-Hill; 1960.
31. Stubbs, C. M.; Connor, H. E.; Feniuk, W. BMY 7378 is an agonist at 5-HT$_{1A}$ receptors mediating hypotension and renal sympatho-inhibition in anesthetised cats. Eur. J. Pharmacol. 197: 113-116; 1991.
32. Taylor, D.; Ho, B. T. Comparison of inhibition of monoamine uptake by cocaine methylphenidate and amphetamine. Res. Comm. Chem. Pathol. Pharmacol. 21:67-75; 1978.
33. Van de Kar, L. D. Neuroendocrine pharmacology of serotonergic (5-HT) neurons. Annu. Rev. Pharmacol. Toxicol. 31:289-320; 1991.
34. Van de Kar, L. D.; Carnes, M.; Maslowski, R. J.; Bonadonna, A. M.; Rittenhouse, P. A.; Kunimoto, K.; Piechowski, R. A.; Bethea, C. L. Neuroendocrine evidence for denervation supersensitivity of serotonin receptors: Effects of the 5-HT agonist RU 24969 on corticotropin, corticosterone, prolactin and renin secretion. J. Pharmacol. Exp. Ther. 251:428-434; 1989.
35. Van de Kar, L. D.; Lorens, S. A.; McWillims, C. R.; Kunimoto, K.; Urban, J. H. Role of midbrain raphe in stress-induced renin and prolactin secretion. Brain Res. 311:333-341; 1984.
36. Van de Kar, L. D.; Urban, J. H.; Lorens, S. A.; Richardson, K. D. The non-benzodiazepine anxiolytic buspirone inhibits stress-induced renin secretion and lowers heart rate. Life Sci. 36:1149-1155; 1985.
37. Van de Kar, L. D.; Wilkinson, C. W.; Ganong, W. F. Pharmacological evidence for a role of brain serotonin in the maintenance of plasma renin activity in unanesthetized rats. J. Pharmacol. Exp. Ther. 219:85-94; 1981.
38. Van de Kar, L. D.; Wilkinson, C. W.; Skrobik, Y.; Brownfield, M. S. Ganong, W. F. Evidence that serotonergic neurons in the dorsal raphe nucleus exert a stimulatory effect on the secretion of renin but not of corticosterone. Brain Res. 235:233-243; 1982.
39. Van Nueten, J. M.; Schuurkes, J. A. J.; De Ridder, W. J. E.; Kuyps, J. J. M. D.; Janssens, W. J. Comparative pharmacologi-

cal profile of ritanserin and ketanserin. Drug Dev. Res. 8:187–195; 1986.
40. VanderMaelen, C. P.; Matheson, G. K.; Wilderman, R. C.; Patterson, L. A. Inhibition of serotonergic dorsal raphe neurons by systemic and iontophoretic administration of buspirone, a non-benzodiazepine anxiolytic drug. Eur. J. Pharmacol. 129:123–130; 1986.
41. Yocca, F. D.; Hyslop, D. K.; Smith, D. W.; Maayani, S. BMY 7378, a buspirone analog with high affinity, selectivity, and low intrinsic activity at the 5-HT1A receptor in rat and guinea pig hippocampal membranes. Eur. J. Pharmacol. 137:293–294; 1987.
42. Yocca, F. D.; Maayani, S. 5-HT receptors linked to adenyl cyclase activity in mammalian brain. Ann NY Acad. Sci. 600:212–223; 1990.
43. Zemlan, F. P.; Zieleniewski-Murphy, A.; Murphy, R. M.; Behbehani, M. M. BMY 7378: Partial agonist at spinal cord 5-HT_{1A} receptors. Neurochem. Int. 16:515–522; 1990.