ELSEVIER

European Journal of Pharmacology 331 (1997) R1–R3

ejp

Rapid communication

Repeated administration of 3,4-methylenedioxymethamphetamine augments cocaine's action on dopamine in the nucleus accumbens: A microdialysis study

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Received 22 May 1997; accepted 23 May 1997

Abstract

In this study, we examined the ability of a single injection of cocaine (20 mg/kg, i.p.) to augment extracellular dopamine levels in the nucleus accumbens two weeks after pretreating rats with either saline (1 ml/kg, i.p.) or the serotonin neurotoxin 3,4-methylenedioxymethamphetamine (20 mg/kg, s.c., twice daily for 4 days). The level of dopamine in the nucleus accumbens was measured using in vivo microdialysis. Cocaine produced a 400% increase in extracellular nucleus accumbens dopamine levels in control rats, whereas in 3,4-methylenedioxymethamphetamine treated rats the increase produced by cocaine was 800%, which was significantly different from controls. This suggests that 3,4-methylenedioxymethamphetamine, a relatively common drug of abuse, may alter subsequent vulnerability to cocaine dependence and abuse. © 1997 Elsevier Science B.V.

Keywords: MDMA (3,4-methylenedioxymethamphetamine); Dopamine; Cocaine

It has been reported that reduction of brain serotonin levels can alter the behavioral response of animals to various dopaminergic drugs. For example, pretreatment of rats with *p*-chlorophenylalanine, a depletor of brain serotonin, can potentiate the behavioral effects of *d*-amphetamine (Mabry and Campbell, 1973). Serotonergic lesions produced by the intracerebroventricular injection of the neurotoxin 5,7-dihydroxytryptamine produces an increase in self-administration of *d*-amphetamine (Lecesse and Lyness, 1984) and appears to increase the motivation for animals to self-administer cocaine (Loh and Roberts, 1990).

The recreationally abused drug 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') has been shown to produce a destruction of serotonin neurons and a decrease in serotonin levels in the brains of various mammalian species (Battaglia et al., 1988; Insel et al., 1989). Given the evidence suggesting that serotonin depletion may augment responsiveness to dopaminergic drugs and that 3,4-methylenedioxymethamphetamine is a commonly abused drug, we examined the effect of systemic cocaine administration on extracellular dopamine levels in the nucleus accumbens in rats pretreated with 3,4-methylenedioxymethamphetamine.

Adult male Sprague–Dawley rats (200–300 g, Taconic Farms, NY) were randomly assigned to two treatment groups ($n = 8$ per group) and received either saline (1 ml/kg, s.c.) or 3,4-methylenedioxymethamphetamine (20 mg/kg, s.c.) twice a day for four consecutive days. Thirteen days after the last saline or 3,4-methylenedioxymethamphetamine injection, animals were anesthetized with chloral hydrate (400 mg/kg, i.p.), placed in a stereotaxic instrument and guide cannulae were implanted into the right nucleus accumbens (1.5–2.0 mm anterior and 1.0 mm lateral to bregma, and 7.0 mm ventral to the cortical surface). The night before the study, animals were placed into test chambers and a microdialysis probe (2.0 mm) was positioned within the guide cannula and artificial cerebrospinal fluid was perfused through the probe at a flow rate of two μl/min. On the following day, dialysis samples were collected every 20 min throughout the study.

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PII S0014-2999(97)01035-2

The first samples were analyzed to determine baseline stability, which was defined as three successive samples that did not differ by more than 10%. The average value of the first three samples was defined as the control or baseline level. Once a stable baseline was obtained, animals received cocaine (20 mg/kg, i.p.). The determination of nucleus accumbens dopamine levels via HPLC was done as previously described (Dewey et al., 1995).

The data were expressed as % of control, which was calculated by dividing the dopamine concentration (picograms) in the baseline samples by the DA concentration in the sample after the injection of cocaine. The data were analyzed using an analysis of variance.

The results are shown in Fig. 1. The administration of 20 mg/kg, i.p., of cocaine produced an increase in extracellular nucleus accumbens dopamine levels in both the 3,4-methylenedioxy-methamphetamine- and saline-treated animals. However, the increase in dopamine levels produced by cocaine in the 3,4-methylenedioxymethamphetamine treated rats was significantly greater than that in the saline treated rats (ANOVA, $F(1,153) = 6.57$, $P < 0.01$). The average value for the greatest percentage increase in dopamine levels produced by cocaine in the 3,4-methylenedioxymethamphetamine- and saline-treated rats were (mean $\pm$ S.E.M.) $396 \pm 24\%$ and $802 \pm 96\%$, respectively.

Thus, the increase in nucleus accumbens dopamine levels produced by cocaine was significantly greater two weeks after pretreatment with 3,4-methylenedioxymethamphetamine compared to saline. It is likely that this effect is due to the depletion of brain serotonin levels by repeated 3,4-methylenedioxymethamphetamine administration, since the 3,4-methylenedioxymethamphetamine regimen used causes a substantial and selective depletion of serotonin levels and serotonin uptake sites in male Sprague–Dawley rats in a number of brain areas (Battaglia et al., 1988). One might argue that since 3,4-methylenedioxymethamphetamine produces dopamine release and behavioral sensitization (Spanos and Yamamoto, 1989), the repeated 3,4-methylenedioxymethamphetamine regimen could produce sensitization to drugs such as cocaine, leading to a greater increase in dopamine levels in these animals compared to saline controls. However, depletion of brain serotonin levels by drugs such as *p*-chlorophenylalanine and 5,7-dihydroxytryptamine, which do not release neuronal dopamine or produce sensitization, clearly augment behavioral responses to cocaine and amphetamine.

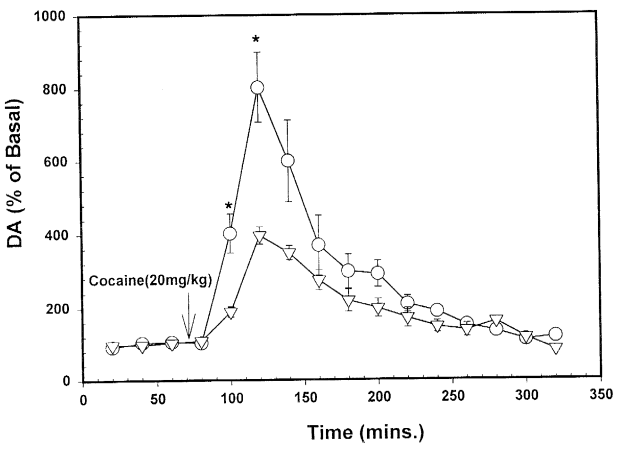

Fig. 1. The effect of a single injection of 20 mg/kg, i.p., of cocaine on extracellular dopamine levels in the nucleus accumbens of rats two weeks after pretreating rats with either 1 ml/kg, s.c., of 0.9% saline (open triangles) or 20 mg/kg, s.c., of MDMA (open circles), twice a day for four consecutive days. Each value represents the mean % increase in extracellular dopamine levels $\pm$ S.E.M. * Significantly greater than saline pretreated rats, $P < 0.01$, ANOVA and Student–Newman–Keuls test.

In conclusion, our results indicate that cocaine produces a significantly greater increase in extracellular nucleus accumbens dopamine levels in rats pretreated with 3,4-methylenedioxymethamphetamine compared to those pretreated with saline. Additional studies using different doses of cocaine, multiple time points beyond two weeks after the last 3,4-methylenedioxymethamphetamine injection and various behavioral paradigms (i.e., self-administration of cocaine) would appear to be warranted. Since 3,4-methylenedioxymethamphetamine is a commonly abused drug and appears to augment the pharmacological actions of cocaine and since cocaine's action on nucleus accumbens dopamine levels appears to underlie its abuse potential, the present findings of this study suggest that 3,4-methylenedioxymethamphetamine abuse may increase the vulnerability to cocaine abuse, although this must be verified using the appropriate paradigms.

Acknowledgements

This research was supported by NIH research grants MH R29 55155 to C.R.A. and MH 49165 to S.L.D. and DOE contract DE-AC02-76CH00016. The authors gratefully acknowledge Dr. Eliot Gardner for his helpful suggestions and discussion regarding this manuscript. The authors also thank David Alexoff and Dr. Andrew Gifford for their technical assistance.

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