Cocaine Alters Rates of Regional Protein Synthesis in the Rat Brain.
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Administration of cocaine induces long-term behavioral and biochemical effects. Neurochemical changes involve mechanisms of post-receptor signal transduction and gene expression (Nestler, E.J., *J Neurosci* 12:2439,1992). In the present study we sought to determine whether single or repeated treatment with or withdrawal from cocaine (15 mg/kg, i.p.) modify rates of local cerebral protein synthesis ($lCPS_{leu}$) as measured with the [1-^{14}C]leucine method (Smith et al., *PNAS* 85:9341, 1988) in the adult, male, Sprague Dawley rat. Three sets of paired experiments were carried out and results were analyzed by statistical methods for paired data. In the first set, eight pairs of rats were treated with normal saline, i.p., for seven days and either normal saline or cocaine on the eighth day, 30 min prior to the initiation of the measurement of $lCPS_{leu}$ with a bolus injection of [^{14}C]leucine. In this set $lCPS_{leu}$ was reduced by about 10% throughout the brain in the cocaine-treated rats; reductions were highly statistically significant in the shell of the nucleus accumbens ($P=0.0003$) and in some other limbic areas ($P\leq0.007$). The second set of seven pairs was similar to the first except that rats received cocaine for seven days and either normal saline or cocaine on the eighth day. There were no statistically significant differences in $lCPS_{leu}$ found in these pairs. In the third set, eight pairs of rats were injected with either normal saline or cocaine for eight days and determinations of $lCPS_{leu}$ were carried out on the 15th day. The results of these delayed experiments showed increases of about 10% in $lCPS_{leu}$ in selective brain regions, i.e., prefrontal and primary olfactory cortex ($P\leq0.006$), hippocampus, and thalamic nuclei ($P\leq0.05$). Nucleus accumbens and the septal nuclei were not affected. Our results suggest that acute cocaine treatment and withdrawal from chronic cocaine treatment both alter rates of protein synthesis in distinctly different ways and in different brain regions.

DOPAMINE DIRECTLY ACTIVATES HUMAN 5-HT_{1C} RECEPTORS EXPRESSED IN *XENOPUS* OOCYTES.
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The activation of human 5-HT_{1C} receptors by dopamine was studied in *Xenopus* oocytes voltage clamped at -70 mV. 5-HT_{1C} receptors were expressed by microinjection of human cRNA transcripts (*Biochem. Biophys. Res. Comm.* 181:1469-1478, 1991) and allowing 2 to 4 days for expession. The application of 1 μM 5-HT or 1 mM dopamine did not cause any detectable current in 32 uninjected oocytes from 4 different frogs. On the other hand, the application of 5-HT or dopamine activated current responses in 20 cRNA injected oocytes from 3 different frogs. The activation of current by 5-HT or dopamine was concentration-dependent, having EC_{50} values of 6.2 nM and 67.7 μM, respectively. Although the EC_{50} value for dopamine was higher than 5-HT, the maximal current activated by dopamine was the same as the maximal current activated by 5-HT. Both 5-HT- (0.1 μM) and dopamine- (100 μM) activated currents were completly blocked by the 5-HT_{1C} antagonist, 1-(1-Naphtyl)piperazine, (1 μM). The results suggest that dopamine directly activates human 5-HT_{1C} receptors expressed in *Xenopus* oocytes.

EFFECT OF COCAINE ON 5-HT_3 RECEPTOR-MEDIATED ION CURRENT IN *XENOPUS* OOCYTES

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The 5-HT_3 receptor, a ligand-gated ion channel, has been proposed to be involved in brain mechanisms associated with drug abuse (Costall et al., *Pharmac. Ther.* 47: 181, 1990). In the present study, the effect of cocaine on the activation of 5-HT_3 receptors expressed in *Xenopus* oocytes was investigated. *Xenopus* oocytes were injected with the mRNA transcripts from the cloned 5-HT_3 receptor (Maricq et al., 254: 432, *Science* 1991) and voltage-clamped at -70 mV. 5-HT and the selective 5-HT_3 receptor agonists, 2-methyl-5-HT and m-chloro-phenylbiguanide activated a fast inward current which was blocked by the specific 5-HT_3 receptor antagonist LY278584. Cocaine (0.1 to 10 μM) inhibited the current activated by 1 μM 5-HT in a concentration-dependent manner. The IC_{50} value is 0.5 μM and the apparent Hill coefficient is 1.42. This action of cocaine could be overcome by increasing 5-HT concentration, suggesting a competitive inhibition of 5-HT by cocaine. The results are similar to previous observations suggesting that cocaine competitively antagonizes the action of 5-HT at neuronal 5-HT_3 receptors (Fan et al., *Soc. Neurosci. Abst.* 18: 800, 1992)

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The activation of 5-HT_3 receptors by dopamine was studied in *Xenopus* oocytes voltage clamped at -70 mV. 5-HT_3 receptors were expressed by the microinjection of cRNA transcripts from the cloned 5-HT_3 receptor (*Science*, 254:432, 1991) and allowing 1 to 3 days for expression. The application of either the selective 5-HT_3 agonist, 2-methyl-5-HT (100 μM), or dopamine (100 μM) did not induce a current in 12 uninjected oocytes from 3 different frogs. On the other hand, the application of 2-methyl-5-HT or dopamine induced a rapidly activating current in 10 cRNA injected oocytes from 3 different frogs. Currents activated by both agonists had the same reversal potential of -10 mV, and both currents were reversibly inhibited by the application of the selective 5-HT_3 antagonist LY-278584 (1 μM). At a concentration of 100 μM, the selective D_1 and D_2 agonists, SKF-38393 and PPHT, respectively, failed to induce a current in 12 oocytes tested. The selective D_1 and D_2 antagonists, SCH-23390 and spiperone, respectively, up to a concentration of 10 μM, failed to inhibit the currents activated by 2-methyl-5-HT and dopamine. The results suggest that dopamine directly activates 5-HT_3 receptors expressed in *Xenopus* oocytes.