Blockade of kappa-opioid receptors attenuates cocaine withdrawal-induced negative affective states

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Drug dependence is characterized by dysregulation of brain reward systems and increased sensitivity to stress. Chronic exposure to drugs of abuse is associated with increased expression of the neuropeptide dynorphin, the endogenous ligand for kappa opioid receptors (KORs). Activation of KORs causes depressive- and aversive-like responses in rodents, raising the possibility that drug-induced upregulation of dynorphin plays a role in dependence-associated negative states. Here we used "binge" exposure to cocaine (3 daily intraperitoneal injections of 15 mg/kg for 14 days) to examine the development of dependence-like behavior in the intracranial self-stimulation (ICSS) test and the forced swim test (FST). When rats were tested immediately before their first scheduled injection of each day—a period of drug withdrawal corresponding to 20 hr after their last injection on the previous day—there were exposure-dependent increases in ICSS thresholds (a putative indicator of anhedonia) and latencies to immobility in the FST (a putative indicator of behavioral despair). Administration of the long-lasting KOR antagonist norBNI (20 µg, intracerebroventricular) before the beginning of the binge regimen attenuated the development of cocaine withdrawal-induced anhedonia in the ICSS test. In contrast, administration of norBNI in the midst of the binge regimen had no effect on expression of cocaine withdrawal-induced anhedonia in the ICSS test, although it did attenuate despair-like behavior in the FST. These data raise the possibility that KOR antagonists may be useful for treating the anhedonia that can promote self-medication with psychostimulants as well as for rehabilitating addicts who are at risk for stress-induced relapse.

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Conflict of interest:
Dr. Carlezon has a patent (US 6,528,518; Assignee: McLean Hospital) related to the use of kappa-opioid antagonists for the treatment of depressive disorders.