Stress-induced Reinstatement of Cocaine Seeking: Non-human Primate Model for Relapse to Cocaine Addiction

Buyean Lee

Laboratory of Molecular Neuroimaging, Department of Psychiatry and Biobehavioral Sciences, Neuropsychiatric Institute – UCLA, 760 Westwood Plaza C8-529, Los Angeles, CA 90024

Stress and associated negative mood states have been repeatedly implicated as risk factors in drug addiction and relapse. Although clinical observations suggest that exposure to stress can induce drug craving and relapse in human drug abusers, the mechanisms by which stress triggers renewed drug seeking remain largely unknown. In an effort to better understand the biological basis of stress-induced relapse, recent studies have investigated the effects of stressful interventions using animal models similar to those developed to investigate drug priming- and cue-induced reinstatement of drug seeking. The majority of these studies have employed inescapable foot-shock to induce a presumably stress-like state in rats. The experimental utility of the rodent foot-shock model notwithstanding, however, electric shock is a unique physical stimulus that is not likely to impact relapse in human drug abusers. Several laboratories are attempting to develop models of stress that do not rely solely on electric shock and, thus, may be more analogous to the type of stress experienced by people. In our laboratory, we systemically investigated the impacts on reinstatement of drug seeking of pharmacological modulations of stress-related physiological systems in squirrel monkeys.

Study 1. An important physiological system activated by stress is the hypothalamic-pituitary-adrenal (HPA) axis; however, evidence for a role of HPA axis activation in cocaine relapse has been contradictory. This study examined the effects of pharmacological stimulation of the HPA axis on reinstatement of drug-seeking behavior and salivary cortisol levels in a nonhuman primate model of cocaine relapse. In addition, the effect of corticotropin releasing hormone type 1 receptor (CRH-R1) blockade on cocaine priming-induced reinstatement was investigated. Squirrel monkeys were trained to self-administer cocaine under a second-order schedule in which behavior was maintained by i.v. drug injections and a drug-paired visual stimulus. A period of extinction was then imposed during which saline was substituted for cocaine and the stimulus was omitted. Subsequently, monkeys were tested for reinstatement of cocaine seeking following priming injections of drugs. During reinstatement tests, the drug-paired stimulus was restored. Salivary cortisol levels were

determined to measure the effects of drug treatments on the HPA axis activity. Priming with corticotropin releasing hormone (10 and 50 mg/kg), adrenocorticotropic hormone (1 mg/kg), or cortisol (1-10 mg/kg) did not induce significant reinstatement of cocaine seeking. All of these treatments, however, resulted in a significant increase in salivary cortisol. In contrast, priming injections of cocaine (0.1-1.0 mg/kg) dose-dependently induced reinstatement of drug seeking, but did not increase salivary cortisol. The CRH-R1 antagonist CP-154,526 (10 mg/kg, i.v.) did not modulate cocaine priming-induced reinstatement of drug seeking, but attenuated CRH-induced increases in salivary cortisol. In summary, the results suggest that activation of the HPA axis is neither necessary nor sufficient for reinstatement of cocaine-seeking behavior in this nonhuman primate model of cocaine relapse.

Study 2. Converging evidence suggests a role for noradrenergic mechanisms in stress-induced reinstatement of cocaine seeking in animals. Yohimbine, an a_2-adrenoceptor antagonist, is known to be anxiogenic and induce stress-related responses in humans and animals. Here, we tested the ability of yohimbine to reinstate cocaine-seeking behavior and induce behavioral and physiological signs characteristic of stress in squirrel monkeys. Monkeys were trained to self-administer cocaine under a second-order schedule of intravenous drug injection. Drug seeking subsequently was extinguished by substituting saline for cocaine injections and omitting the cocaine-paired stimulus. The ability of yohimbine and the structurally distinct a_2-adrenoceptor antagonist RS-79948 to reinstate cocaine-seeking behavior was assessed by administering priming injections immediately before test sessions in which the cocaine-paired stimulus was either present or absent. Priming injections of yohimbine (0.1-0.56 mg/kg, i.m.) or RS-79948 (0.01-0.1 mg/kg, i.m.) induced dose-related reinstatement of cocaine-seeking behavior. The magnitude of yohimbine-induced reinstatement was similar regardless of the presence or absence of the cocaine-paired stimulus. Yohimbine also significantly increased salivary cortisol levels, a physiological marker of stress, as well as scratching and self-grooming, behavioral markers of stress in nonhuman primates. In drug interaction experiments, pretreatment with the a_2-adrenoceptor agonist clonidine (0.1-0.3 mg/kg, i.m.) dose-dependently inhibited yohimbine-induced reinstatement of cocaine seeking. In contrast, pretreatment with the dopamine receptor antagonist flupenthixol failed to inhibit yohimbine-induced reinstatement of cocaine seeking. The results show that pharmacological blockade of a_2-adrenoceptors can induce reinstatement of cocaine-seeking behavior and characteristic stress responses in squirrel monkeys, providing a potentially useful model of stress-induced relapse to drug seeking.