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Abstract

Back to Hit List

Grant Number:	1R29DA010460-01
PI Name:	SELF, DAVID W.
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PI Title:	ASSOCIATE PROFESSOR
Project Title:	INTRACELLULAR MECHANISMS OF DRUG REWARD AND ADDICTION

Abstract: DESCRIPTION: (Applicant's Abstract) All of the reward-related dopamine and opiate receptors are coupled to the cAMP second messenger system, which is up-regulated in the nucleus accumbens (NAc) following chronic drug exposure. Recently, studies from our laboratory have suggested that the NAc-cAMP system modulates drug reinforcement mechanisms. These studies directly tested the role of inhibitory G proteins and cAMP-dependent protein kinase (PKA) in drug reinforcement by infusing agents that modulate these intracellular proteins into the NAc of rats self- administering cocaine or heroin. In addition, our studies also have suggested that PKA in the NAc is involved in drug craving, and relapse of drug-seeking behavior, since NAc infusions of PKA modulators reinstate drug-seeking behavior following extinction from drug self-administration. The present studies will further characterize the intracellular mechanisms of drug reinforcement and addiction. Firstly, the role of excitatory G (Gs) proteins, specific subunits of PKA, and cAMP Response Element Binding (CREB) proteins (a major substrate of PKA), in drug reinforcement and addiction will be studied by infusing agents that modulate these proteins into the NAc of rats during drug self-administration tests. Parallel biochemical experiments will study (and verify) the modulation of intracellular proteins by the NAc infusions. Similarly, intra-accumbens infusions will be used to study the role of PKA in both the positive and the negative motivational aspects of drug addiction and withdrawal by using the conditioned place preference paradigm. Another major focus of this application will study the pharmacological, anatomical, and intracellular substrates of drug craving and relapse by using a drug reinstatement paradigm. With the reinstatement paradigm, we recently found that Dl dopamine receptor agonists will suppress, while D2 receptor agonists will induce, drug-seeking behavior in rats. Thus, Dl and D2 agonists will be used as probes to identify the anatomical loci that mediate these opposing effects on relapse of drug-seeking behavior. The intracellular substrates of drug craving will be studied by infusing PKA modulators into the specific brain sites that mediate the Dl and D2 receptor effects on reinstatement of drug-seeking behavior. Finally, the neural mechanisms through which conditioned cues trigger drug craving will be studied in a cue reinstatement paradigm. The studies in this grant will continue to provide a mechanistic link between the molecular, cellular, and

behavioral aspects of drug abuse, and will seek to identify potential targets for pharmacotherapy.

Thesaurus Terms:
cocaine, drug addiction, neuropharmacology, psychopharmacology, reinforcer
G protein, antisense nucleic acid, avoidance behavior, cholera toxin, dopamine agonist, dopamine receptor, drug withdrawal, motivation, nucleus accumbens, preference, protein kinase A, relapse /recurrence, self medication, transcription factor
behavior test, laboratory rat

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