Version 2.0

Abstract

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Grant Number: 1N01DA008806-000
PI Name: CAINE, BARAK S.
PI Email:
PI Title:
Project Title: SCREENING COMPOUNDS UTILITY COCAINE

Abstract: The purpose of this research and development contract is to preclinically determine the effects of compounds in the rat self-administration procedure as a means of evaluating their potential efficacy as cocaine treatment medications. Specifically, this contract is designed to determine the ability of compounds to alter the reinforcing effects of cocaine as assessed by the rat self-administration procedure. Select compounds will also be evaluated for their ability to maintain self-administration behavior in the rat, as a means of determining potential abuse liability. These tests have been selected by NIDA's Division of Treatment Research and Development's (DTR&D) Cocaine Treatment Discovery Program (CTDP) for study because the mechanisms underlying the self-administration of cocaine in animals are thought to be similar to the mechanisms responsible for cocaine abuse in humans. The data generated by this contract will be utilized by the CTDP in the selection of compounds for additional preclinical evaluation. Based on promising findings in the standard studies, additional preclinical studies in rodents may be needed to further characterize the effects of specific compounds. The purpose of these follow-up studies would be to aid the CTDP in the decision of whether to recommend specific compounds as drug development candidates. Insofar as the need for these follow-up studies cannot be accurately predicted, and because the precise experimental design of the studies will depend upon initial compound findings, options are included in this SOW to cover the labor hours which the Contractor may need to devote to this work. Separate options are included to cover the possible need for related animal purchases, laboratory equipment and supplies.

Thesaurus Terms:
cocaine, drug abuse chemotherapy, drug screening /evaluation, narcotic antagonist
self medication
laboratory rat

Institution: MC LEAN HOSPITAL (BELMONT, MA)
115 MILL ST
BELMONT, MA 02178
Fiscal Year: 2000
Department:
Project Start: 30-SEP-2000
Project End: 29-SEP-2005
ICD: NATIONAL INSTITUTE ON DRUG ABUSE
IRG:

Version 2.0

Abstract

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Grant Number: 5R29DA012142-02
PI Name: CAINE, SIMON B.
PI Email:
PI Title:
Project Title: COCAINE SELF ADMINISTRATION IN DOPAMINE KNOCKOUT MICE

Abstract: Studies are proposed to use gene-targeted "knockout" mice to analyze the roles of different dopaminergic systems in the reinforcing effects of cocaine. Compelling pharmacological and neurobiologic evidence suggests that the abuse-related effects of cocaine are mediated by dopaminergic systems, and dopamine-based strategies provide promising avenues for development of new medications to treat cocaine abuse and dependence. The more specific identification of molecular targets for design and synthesis of dopamine-related medications may be greatly assisted by systematic analyses of mechanisms mediating cocaine's reinforcing effects in knockout mice. Although drugs acting at the dopamine transporter or at D1-like or D2- like receptors can modify some abuse-related effects of cocaine, the roles of these proteins in cocaine's effects are not fully understood. Genetic technology in mice that permits the deletion of a single protein by "knockout" of its functional gene provides a highly specific tool that may help to elucidate the roles pharmacologically. For example, the modification of cocaine self-administration by mixed D2/D3 compounds may be due to D2 or D3 actions alone or in combination. Studies in mice that lack the D2 receptor will permit a clearer analysis of the role of the D3 receptor in such effects. The proposed self-administration will: (1) examine the reinforcing effects of cocaine in mice lacking the dopamine transporter or to the D1 or D2 receptor, and (2) use these mice to specify more precisely the receptor mechanisms involved in the modification of cocaine self-administration by non-selective dopaminergic compounds. An important feature of this proposal is that self-administration studies in parental inbred strains and studies of responding maintained by a non-drug reinforcer will be conducted to provide a comprehensive basis for interpreting results of self-administration studies in knockout mice. In addition, studies in male and female mice will allow assessment of gender differences in genetic and pharmacological influences on cocaine self-administration. Overall, this research will increase our understanding of the roles of specific dopaminergic proteins in cocaine's abuse-related effects and help to identify the most appropriate targets for medications development. Moreover, integrating gene-targeting strategies with pharmacological and drug self-administration techniques will provide a framework for future studies using yet more advanced genetic technology to identify molecular mechanisms of cocaine's abuse-related effects.

Thesaurus Terms:
behavioral habituation /sensitization, cocaine, dopamine, dopamine receptor, dopamine transporter, reinforcer, self medication
pharmacogenetics, substance abuse related behavior
behavior test, behavioral /social science research tag, gene targeting, laboratory mouse, transgenic animal

Institution:	MC LEAN HOSPITAL (BELMONT, MA) 115 MILL ST BELMONT, MA 02178
Fiscal Year:	2000
Department:	
Project Start:	12-MAR-1999
Project End:	29-FEB-2004
ICD:	NATIONAL INSTITUTE ON DRUG ABUSE
IRG:	NIDA