Version 2.0

Abstract

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Grant Number: 5R01DA012891-02
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PI Title:
Project Title: GENETIC ANALYSIS OF NICOTINE ADAPTATION IN C ELEGANS

Abstract: Tobacco use has been implicated in a wide range of human diseases, including heart disease, emphysema, and cancer, which together result in millions of premature deaths each year. The addictive properties of nicotine are a major cause of persistent and compulsive tobacco use. Nicotine addiction is thought to result from long-term adaptive changes in the activity and expression of nicotinic acetylcholine receptors in the brain. However, the molecular and neuronal mechanisms that underlie these adaptive processes remain poorly understood. The goal of this research is to use genetic analysis in a simple animal model, the nematode Caenorhabditis elegans, to investigate the molecular basis of nicotine adaptation. C. elegans is highly amenable to molecular analysis of nervous system function: it has a simple and well characterized nervous system, and its short generation time, small and largely sequenced genome, and accessibility to germline transformation make it ideal for classical and molecular genetic studies. C. elegans exhibits a striking and easily measurable response to nicotine, and long- term nicotine exposure leads to nicotine tolerance and dependence with respect to behaviors controlled by both neuromuscular and neuronal nicotinic receptors. In this project, genes required for nicotine adaptation in nematodes will be identified by screening for adaptation-defective mutants. Two nicotine adaptation genes identified in earlier screens will be cloned to determine their molecular functions, and to characterize the cellular pathways in which they function. The possibility, suggested by studies of protein kinase C-defective mutants, that PKC phosphorylation of nicotinic receptor subunits is a mechanism for nicotine adaptation will be tested through the analysis of transgenic worms expressing mutant receptors. The ultimate goal of this work is to provide a model for the general molecular mechanisms underlying nicotine adaptation in neurons, and to identify new proteins that participate in nicotine addiction in other animals, including vertebrates.

Thesaurus Terms:
drug addiction, molecular genetics, nicotine, nicotinic receptor
gene expression, genetic mapping, phosphorylation, protein kinase C, tobacco abuse
Caenorhabditis elegans, biological model, molecular cloning, mutant

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Fiscal Year: 2001
Department: BIOLOGY
Project Start: 01-FEB-2000
Project End: 31-DEC-2004
ICD: NATIONAL INSTITUTE ON DRUG ABUSE
IRG: ZRG1