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Grant Number:	1K02DA000436-01
PI Name:	PICCIOTTO, MARINA R.
PI Email:	marina.picciotto@yale.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	ROLE OF THE HIGH AFFINITY NICOTINE RECEPTOR IN ADDICTION

Abstract: The primary goal of this proposal is to organize a laboratory that can study complex neurobiological problems at levels ranging from the molecular to the behavioral. In addition, this Career Development Award would free up time to learn about self-administration and electrophysiology so that these techniques can ultimately be performed in this laboratory rather than in collaboration. Another important goal of this application is to allow for time to improve conditional knock-out studies, so that ultimately gene expression can be controlled both temporally and spatially in brain areas of transgenic mice. The studies proposed therefore involve traditional pharmacological, biochemical, and behavioral experiments, as well as use of transgenic and knock-out technology. The career development plan involves attendance at physiology seminars and hands on work with faculty members whose expertise is in mammalian electrophysiology. In addition, I will do experiments with behavioral neuroscientists studying self-administration and other mouse behaviors. Hands on work will be supplemented with seminars in this area and a class in statistical analysis of behavioral data. Finally, this proposal will allow time for attendance at meetings on the latest conditional technologies in the mouse, as well as the time to perform experiments in the laboratory to optimize this technology. The Specific Aims of this project are to use these new techniques to determine the molecular events underlying nicotine addiction, to determine how nicotine affects responses to other drugs of abuse, to examine the role of the high affinity receptor for nicotine in learning and memory, and to develop new tools to examine the role of nicotinic receptors in specific brain areas and at specific times in development. These Aims will be achieved using wild-type mice, traditional knock-out mice that lack expression of the beta2 subunit of the neuronal nicotinic receptor throughout development in all tissues, and mice that conditionally express this subunit only in particular brain areas under the control of the tetracycline-regulated promoter. Together these different approaches will build a bridge between molecular biological data on nicotinic receptor subtypes and the large body of behavioral pharmacological literature on the actions of nicotine in vivo.

Thesaurus Terms:
drug addiction, drug receptor, nicotine, nicotinic receptor

developmental neurobiology, dopamine, gene expression, learning, memory, neuroanatomy, protein isoform, reinforcer
behavior test, laboratory mouse, transgenic animal

Institution:	YALE UNIVERSITY NEW HAVEN, CT 06520
Fiscal Year:	1999
Department:	PSYCHIATRY
Project Start:	05-SEP-1999
Project End:	31-JUL-2004
ICD:	NATIONAL INSTITUTE ON DRUG ABUSE
IRG:	ZDA1

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Grant Number:	5P01MH025642-259007
PI Name:	PICCIOTTO, MARINA R.
PI Email:	marina.picciotto@yale.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	CORE--TRANSGENIC MOUSE FACILITY

Abstract: This new Facility will enable a more accurate evaluation of the role of identified genes in regulating the biochemical pathways relevant to physiology, behavior, and response to drug treatment. The transgenic and knock out methodologies are necessary to complement the other molecular methodologies used in this Program Grant. This Core will provide support for breeding and selection, genotyping, and behavioral assays of the mice for the studies proposed in Projects 1-3. Coordination of this work under the Transgenic Core will also make these studies far more cost- effective. Initially, behavioral and physiologic evaluation will be conducted on four available gene knock out strains: 1) GAP-43, a protein important in synapse formation; these mice will be used to examine the role of GAP-43 and behavioral and cellular responses to antidepressant treatments (Project 2); 2) b2 subunit of the nicotinic acetylcholine receptor, which is important in modulating the reward characteristics of nicotine in the brain; these mice will be used to examine the role of the nicotinic receptor in models of anxiety (Project 3); 3) cAMP response element binding protein (CREB) and FosB, important transcription factors involved in many aspects of neuronal function; these mice will be used to study the role of these proteins in antipsychotic (Project 1) and antidepressant (Project 2) drug actions, as well as in models of anxiety (Project 3); 4) BDNF, a neurotrophic factor important for the survival and function of many neurons in brain. We have found that expression of BDNF, as well as its receptor, TrkB, is increased by chronic antidepressant treatments; these mice will be used to determine the functional consequences of the up-regulated BDNF response (Project 2). Another specific aim of this Core (5) is to generate new conditional CREB and delta FosB transgenic mice to further evaluate the role of these transcription factors in the actions of antipsychotic and antidepressant treatments (Projects 1 and 2), as well as in fear potentiated startle (Project 3). The conditional transgenics will provide a method for time-dependent and tissue-specific expression of CREB and delta FosB so that the direct effects, not secondary adaptations, of the transgenes can be determined. Finally, this facility will generate additional knock out and conditional transgenic mice of specific interest to investigators in the Program.

Thesaurus Terms:
animal breeding, antipsychotic agent, biomedical facility, gene targeting, laboratory mouse,

mental disorder, neuropharmacology, transgenic animal
drug screening /evaluation, genotype
behavior test

Institution:	YALE UNIVERSITY NEW HAVEN, CT 06520
Fiscal Year:	1999
Department:	
Project Start:	
Project End:	
ICD:	NATIONAL INSTITUTE OF MENTAL HEALTH
IRG:	

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Grant Number:	3P01MH025642-25S19007
PI Name:	PICCIOTTO, MARINA R.
PI Email:	marina.picciotto@yale.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	CORE--TRANSGENIC MOUSE FACILITY

Abstract: This new Facility will enable a more accurate evaluation of the role of identified genes in regulating the biochemical pathways relevant to physiology, behavior, and response to drug treatment. The transgenic and knock out methodologies are necessary to complement the other molecular methodologies used in this Program Grant. This Core will provide support for breeding and selection, genotyping, and behavioral assays of the mice for the studies proposed in Projects 1-3. Coordination of this work under the Transgenic Core will also make these studies far more cost- effective. Initially, behavioral and physiologic evaluation will be conducted on four available gene knock out strains: 1) GAP-43, a protein important in synapse formation; these mice will be used to examine the role of GAP-43 and behavioral and cellular responses to antidepressant treatments (Project 2); 2) b2 subunit of the nicotinic acetylcholine receptor, which is important in modulating the reward characteristics of nicotine in the brain; these mice will be used to examine the role of the nicotinic receptor in models of anxiety (Project 3); 3) cAMP response element binding protein (CREB) and FosB, important transcription factors involved in many aspects of neuronal function; these mice will be used to study the role of these proteins in antipsychotic (Project 1) and antidepressant (Project 2) drug actions, as well as in models of anxiety (Project 3); 4) BDNF, a neurotrophic factor important for the survival and function of many neurons in brain. We have found that expression of BDNF, as well as its receptor, TrkB, is increased by chronic antidepressant treatments; these mice will be used to determine the functional consequences of the up-regulated BDNF response (Project 2). Another specific aim of this Core (5) is to generate new conditional CREB and delta FosB transgenic mice to further evaluate the role of these transcription factors in the actions of antipsychotic and antidepressant treatments (Projects 1 and 2), as well as in fear potentiated startle (Project 3). The conditional transgenics will provide a method for time-dependent and tissue-specific expression of CREB and delta FosB so that the direct effects, not secondary adaptations, of the transgenes can be determined. Finally, this facility will generate additional knock out and conditional transgenic mice of specific interest to investigators in the Program.

Thesaurus Terms:
animal breeding, antipsychotic agent, biomedical facility, gene targeting, laboratory mouse,

mental disorder, neuropharmacology, transgenic animal
drug screening /evaluation, genotype
behavior test

Institution:	YALE UNIVERSITY NEW HAVEN, CT 06520
Fiscal Year:	1999
Department:	
Project Start:	
Project End:	
ICD:	NATIONAL INSTITUTE OF MENTAL HEALTH
IRG:	

Version 2.0

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Grant Number:	1P50DA013334-010001
PI Name:	PICCIOTTO, MARINA R.
PI Email:	marina.picciotto@yale.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	ANIMAL MODELS OF RISK FACTORS FOR RELAPSE TO SMOKING

Abstract: As the overall number of smokers in the American population decreases, many of those that continue to smoke show several risk factors that make smoking cessation more difficult. Some of these risk factors may be environmental while others may have a genetic component. We propose to study the biological basis underlying how risk factors might lead to relapse to smoking. Some major predictors of treatment failure for smoking cessation include depressive symptoms, heavy alcohol use, and female gender. This proposal will use animal models to determine how nicotine affects biological processes related to these risk factors, and will focus on how activation or inhibition of neuronal nicotinic acetylcholine receptors (nAChRs) can affect behavioral and biochemical responses related to these risk factors. These experiments will make use of pharmacological studies in normal mice as well as experiments with transgenic (knock-out) mice lacking the beta2 subunit of the nAChR which have previously been generated. Existing nicotinic agonists cannot distinguish clearly between the various nicotinic subtypes present in the brain; thus these mice will be extremely useful in identifying which receptor subtypes mediate particular pharmacological actions of nicotine. The aims of this project are to determine whether nicotine can act as an antidepressant in the learned helplessness model of depression, to determine whether nicotine withdrawal increases susceptibility to learned helplessness during acute and chronic abstinence, to identify sex- differences in learned helplessness behavior with and without nicotine treatment, to determine the concurrent and independent effects of chronic ethanol and nicotine treatment on biochemical and behavioral responses to stress, and to determine whether chronic nicotine treatment results in changes in levels of second messenger proteins involved in signaling that are associated with motivation and effect. The techniques to be used include neurochemistry, molecular genetics and behavioral paradigms. These approaches should allow an integrated view of how chronic nicotine use and nicotine cessation affect emotional behavior, and how gender differences or alcohol use can modulate that interaction. These experiments will contribute to the scientific background necessary for designing new strategies for treatment of smokers resistant to current cessation methods.

Thesaurus Terms:

chemical stimulation, drug addiction, genetic susceptibility, sex difference, smoking cessation, tobacco abuse
alcoholic beverage consumption, bupropion, depression, drug withdrawal, learned helplessness, motivation, nicotine, nicotinic receptor, receptor expression, second messenger, substance abuse
behavior test, behavioral /social science research tag, densitometry, high performance liquid chromatography, laboratory mouse, neurochemistry, radioimmunoassay, statistics /biometry, transgenic animal

Institution:	YALE UNIVERSITY NEW HAVEN, CT 06520
Fiscal Year:	1999
Department:	
Project Start:	30-SEP-1999
Project End:	31-AUG-2004
ICD:	NATIONAL INSTITUTE ON DRUG ABUSE
IRG:	ZCA1

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Grant Number:	5R03DA011733-02
PI Name:	PICCIOTTO, MARINA R.
PI Email:	marina.picciotto@yale.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	TRANSGENIC APPROACH TO NICOTINES EFFECT ON COGNITION

Abstract: DESCRIPTION: (Applicant's Abstract) Nicotine exerts complex behavioral effects on both humans and animals, and in addition to having reinforcing or rewarding qualities it has also been reported to be anxiolytic, to have effects on arousal and to act as a cognitive enhancer. The goal of this project is to determine where in the brain nicotine acts to exert its cognitive effects. This work will use knock out mice lacking the b2 subunit of the neuronal nicotinic acetylcholine receptor (nAChR) as subjects for neurochemical and behavioral testing. These mice have been shown to be insensitive to the effects of nicotine on the test of passive avoidance, and to perform differently than their wild type siblings on this test even in the absence of pharmacological treatment. We will also generate new lines of transgenic mice in which the b2 subunit is expressed only in specific brain areas. These mice will be used as tools to investigate the anatomical requirements for the high affinity receptor in learning paradigms. The first goal of this project will be to determine whether brain areas are differentially activated in response to avoidance training in b2 mutant and wild type mice in the presence or absence of nicotine treatment. We will also determine whether a7nAChRs or muscarinic receptors are more or less active during passive avoidance training in the absence of the b2 containing high affinity nicotine receptor. Transgenic mice that over express either the beta2 or the beta4 subunit of the nAChR in specific brain regions will be generated and crossed mice lacking the high affinity receptor for nicotine. This will result in lines of mice that express this receptor only in particular brain regions in response to treatment with tetracycline. These experiments will allow a molecular dissection of the effect of nicotine on a cognitive task, and will provide information on both the temporal and anatomical loci of the action of nicotine in the brain.

Thesaurus Terms:
avoidance behavior, cognition, nicotine, nicotinic receptor, psychopharmacology
brain mapping, bungarotoxin, muscarinic receptor, receptor expression, tetracycline
animal breeding, behavior test, behavioral /social science research tag, gene targeting, laboratory mouse, transgenic animal

Institution: YALE UNIVERSITY
NEW HAVEN, CT 06520
Fiscal Year: 1999
Department: PSYCHIATRY
Project Start: 20-APR-1998
Project End: 30-APR-2000
ICD: NATIONAL INSTITUTE ON DRUG ABUSE
IRG: ZDA1

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Grant Number:	5R29DA010455-04
PI Name:	PICCIOTTO, MARINA R.
PI Email:	marina.picciotto@yale.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	NICOTINE ADDICTION IN MICE LACKING THE NEURONAL NACHR

Abstract: Nicotine Addiction Is a Serious Health Problem in the United States. Animal Models of Nicotine Addiction. This proposal will make use of transgenic mice lacking the Beta 2 subunit of the neuronal nicotinic acetylcholine receptor (nAChR) that no longer have any high affinity nicotine binding sites in the brain, to determine the role of the high affinity nicotine receptor in nicotine addiction. These studies will help define the precise molecular basis for nicotine addiction, and may provide tools that will allow a pharmacological treatment of this addiction. Three behavioral models of addiction (place preference, selective drinking and locomotor sensitization) will be used to determine whether mice lacking the high affinity nicotine receptors are still sensitive to the addictive effects of nicotine. In addition, the effects of nicotine on anxiety and antinociception will be analyzed in these transgenic animals. We will also attempt to compensate for deficits in animals lacking the Beta 2 subunit of the nAChR by overexpressing the Beta 4 subunit in the brains of these mice, allowing a molecular dissection of the roles of the different subunits of the nAChR in addictive behavior. As nicotine is able to regulate dopamine release in the nucleus accumbens and the ventral tegmental areas, brain area implicated in the addictive properties of several drugs of abuses, the effect of amphetamine, cocaine and ethanol of the behavior of Beta 2 subunit mutant mice will be examined. The specificity of existing nicotinic agonists for the different subtypes of the nAChR will be examined by comparing the binding of these agonists in the brains of wild type and Beta 2 subunit mutant mice. Finally, changes in neurotransmitter systems that can normally be modulated by nicotine treatment will be examined using equilibrium binding studies and essays of choline acetyltransferase assays. These experiments are designed to determine the precise role of a defined subunit of the nAChR in several behaviors that contribute to nicotine addiction in humans, with the goal of defining the molecular substrate of nicotine addiction.

Thesaurus Terms:
cholinergic receptor, drug addiction, neuron, nicotine, protein structure /function
amphetamine, analgesic, choline acetyltransferase, cocaine, enzyme activity, ethanol, psychopharmacology, tranquilizer
behavior test, laboratory mouse, transgenic animal

Institution: YALE UNIVERSITY
NEW HAVEN, CT 06520
Fiscal Year: 1999
Department: PSYCHIATRY
Project Start: 01-SEP-1996
Project End: 31-JUL-2001
ICD: NATIONAL INSTITUTE ON DRUG ABUSE
IRG: NIDA