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National Institute on Alcohol Abuse and Alcoholism (U.S.)

Annual Report of Intramural Research

October 1, 1988
to
September 30, 1989

RC
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1989

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUM

Z01 AA 00257-05 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuroendocrine Studies in Offspring of Familial Alcoholics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. Brown	Unit Chief	LCS, NIAAA
Others:	K. Smith	Senior Staff Fellow	LCS, NIAAA
	M. Linnoila	Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Clinical Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	1.0	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Responses of thyroid stimulating hormone (TSH) to thyrotropin releasing hormone (TRH) have been studied in the offspring of familial alcoholics and age, sex and past alcohol exposure matched control children. Sons but not daughters of familial alcoholics were found to have exacerbated TSH responses to TRH infusions.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00276-01 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychobiology and Behavior of Aggression and Suicide in Adults and Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. Brown	Unit Chief	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	F. Goodwin	Administrator	ADAMHA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Clinical Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.0	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies that relate human aggression (including Disruptive Behavior Disorders in children) and suicide to various behavioral and biological factors have been ongoing. The most significant findings have included pharmacokinetic and metabolic studies of amphetamine administered to hyperactive and conduct disordered children. and a trivariate relationship among a history of aggressive behavior, a history of suicidal behavior, and lower cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5HIAA). More recently, data indicate that certain aggressive, impulsive, and depressive characteristics in childhood are also inversely related to CSF 5HIAA measured during late adolescence; family instability (particularly, alcoholism in a parent) during childhood is also associated with an increased likelihood of aggressive and suicidal behavior in adolescence. These data, along with the work of other investigators studying aggressive and depressive behavior in childhood, indicate the possibility of traits associated with disordered serotonin metabolism; further, the less consistent relationship between lower CSF 5HIAA and suicidal behaviors vs. aggressive behaviors, may indicate that some suicidal behaviors are a self-destructive manifestation of a more basic destructive (aggressive/impulsive) trait.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00277-01 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Non-Human Primate Models of Alcohol Consumption and Aggression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Higley	Staff Fellow	LCS, NIAAA
Others:	M. Hasert	Guest Researcher	LCS, NIAAA
	M. Linnoila	Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*

Laboratory of Comparative Etiology, NICHD (S. Suomi, K. Abbott)

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	1	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

During the past year, three major lines of parallel research have been pursued. Research concerning 1. The effect of peer-only rearing: Our studies demonstrated peer-only reared monkeys were highly anxious. An independent replication demonstrated that they also consume more ethanol than monkeys reared by their mothers. In addition, during the first two years of life they had increased plasma ACTH, cortisol, CSF MHPG, and 5-HIAA. Within group individual differences for these measures were markedly stable across at least the first two years of life. Interestingly, there were genetic effects on CSF 5-HIAA, and HVA. 2. Selective breeding for alcohol consumption and 5-HIAA: A principal part of the past year has involved the development of a major selective breeding program to selectively breed monkeys for high alcohol consumption and CSF 5-HIAA concentration. 3. Treatment of high alcohol consumption in peer-only reared monkeys: A number of studies indicate a relationship between diminished serotonin turnover and -increased alcohol consumption. A study was started to administer sertraline, a potent serotonin reuptake blocker to alcohol consuming monkeys. A second pharmacological study was performed to test the effects of stress on imipramine turnover. Imipramine decreased levels of aggression in the group living subjects. Finally, the MAO-B inhibitor milacemide was tested on 8 monkeys to assess its anxiolytic and antidepressant value. Preliminary findings indicate that it may reduce anxiety as levels of social play increased while the monkeys were together.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00238-07 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

CSF Neuropeptides and Prostaglandins in Alcohol Withdrawal and Brain Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Linnoila	Chief	LCS, NIAAA
Others:	J. Yergey	Senior Staff Fellow	LCS, NIAAA

COOPERATING UNITS *(if any)*

Laboratory of Clinical Neurogenetics, NIMH (W. Berrettini); VA Medical Center, Washington, D.C. (J. Hawley)

LAB/BRANCH

Laboratory of Clinical Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.0	0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Severity of withdrawal symptoms from alcohol was quantified in alcoholics admitted to the Neurology Ward of the Washington, D.C. VA Hospital. Cerebrospinal fluid (CSF) samples were repeatedly obtained early during withdrawal and after all symptoms had subsided. Concentrations of the monoamine neurotransmitter norepinephrine and its major metabolite MHPG were measured at NIH. Significant positive correlations were observed between indices of elevated norepinephrine turnover and several signs of alcohol withdrawal. We are continuing this work trying to identify causes for the noradrenergic dysregulation during alcohol withdrawal. Thus, we are measuring peptides and prostaglandins known to participate in the regulation of the functioning of noradregergic synapses simultaneously with norepinephrine. We are correlating the concentrations of these neuromodulators to concentrations of norepinephrine and MHPG in the CSF and to the severity of withdrawal symptoms in our patients. We are continuing to increase our sample size.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00258-05 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Violent Behavior, Neurotransmitters, Glucose Metabolism and Alcohol Abuse

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Linnoila	Chief	LCS, NIAAA
Others:	D. Goldman	Section Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*

Department of Psychiatry, University Central Hospital, Helsinki, Finland (M. Virkkunen); IRP, NIMH (F. Goodwin)

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have investigated neurotransmitter metabolites and glucose metabolism in incarcerated violent offenders, arsonists and healthy volunteers. We have found that low cerebrospinal fluid (CSF), 5-hydroxyindoleacetic acid (5HIAA) concentrations and hypoglycemia during oral glucose tolerance tests are associated with each other and impulsive violent acts and fire setting. In a follow-up study we found that a low blood glucose nadir and low CSF 5HIAA concentration were powerful predictors of recidivism among impulsive violent offenders and fire setters. We are currently collecting lymphocytes for molecular genetic studies from violent offenders, their family members and appropriate controls.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00270-04 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Impulsivity and Pathologic Gambling

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Roy	Visiting Associate	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	J. DeJong	Staff Fellow	LCS, NIAAA

COOPERATING UNITS *(if any)*

None

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	4	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study was conducted to investigate biological substrates of pathological gambling. We found indices of increased central nervous system noradrenergic activity. Also, depressed gamblers showed evidence of abnormal glucose homeostasis. Furthermore, indices of noradrenergic activity conducted significantly with extraversion scores on the Eysenck personality questionnaire suggesting that biological abnormality in gamblers may manifest itself by an effect on personality. In a study of GABA we found no difference in CSF levels between gamblers and controls or between depressed and non-depressed gamblers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00272-02 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
CSF Monoamine Metabolites in Alcoholic Patients who Attempt Suicide

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Roy	Visiting Associate	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	B. Ravitz	Special Volunteer	LCS, NIAAA
	D. George	Special Expert	LCS, NIAAA
	D. Lamparski	Guest Researcher	LCS, NIAAA
	J. DeJong	Staff Fellow	LCS, NIAAA

COOPERATING UNITS *(if any)*
None

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	4	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Reduced cerebrospinal fluid levels of the serotonin metabolite 5-hydroxyindoleacetic acid have been reported to be commonly associated with suicidal behavior. Alcoholics are known to often manifest suicidal behavior. Therefore, we compared alcoholics who had (N = 18) or had not (N = 132) attempted suicide, and controls (N = 29) on cerebrospinal fluid levels of monoamine metabolites. There were no significant differences among the three groups for cerebrospinal fluid levels of either 5-hydroxyindoleacetic acid, the dopamine metabolite homovanillic acid, norepinephrine, or the norepinephrine metabolite 3-methoxy-4-hydroxypenylglycol. However, in an expanded data set of almost 300 alcoholics there were significant differences for age of onset; alcoholics who attempted had an early age of onset of heavy drinking. They also had significantly more lifetime psychiatric diagnoses of major depression antisocial personality disorder, panic, phobic disorder and more family history of alcoholism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00231-07 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Central and Peripheral Nervous System Function in Abstinent Alcoholics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Eckardt	Section Chief	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	D. Flowers	Special Volunteer	LCS, NIAAA

COOPERATING UNITS *(if any)*

George Washington University (H. Weingartner); Clin. Psychobiol. Br., NIMH (L. Tamarkin); Biol. Psychiat. Br., NIMH (P. Gold).

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SECTION

Section of Clinical Science

INSTITUTE AND LOCATION

NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	2.5	2.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Behavioral deficits in alcoholics have been conceptualized in terms of two neuropathologically distinct syndromes: alcoholic dementia and Korsakoff's psychosis (alcohol amnestic disorder). Alcoholic dementia is characterized by diffuse cortical damage primarily related to the neurotoxicity of alcohol; Korsakoff's psychosis is associated with subcortical lesions due to nutritional (thiamine) deficiency. Severe memory impairment with relative sparing of other intellectual functions distinguishes Korsakoff's psychosis from alcoholic dementia (which may be clinically indistinguishable from the most common cause of dementia, Alzheimer's disease). We have recently found that sleep in Korsakoff patients is characterized by a reduced REM latency compared to normal volunteers, whereas Alzheimer patients have normal latencies. Furthermore, delta sleep is reduced in Alzheimer's disease, but is normal in Korsakoff patients. We have also demonstrated reduced daily excretion of the major urinary metabolite of melatonin, hydroxymelatonin, in patients with Korsakoff's psychosis. This finding is suggestive of impaired pineal function. Genetic differences in thiamine metabolism may predispose patients to develop Korsakoff's psychosis. Most patients with Korsakoff's psychosis whom we have studied have had a transketolase with reduced affinity for thiamine pyrophosphate. The majority of alcoholics with cognitive impairment demonstrate features characteristic of both syndromes. Pharmacologic modulation of neurotransmitter systems may be effective in treatment of the subcortical syndrome, whereas alcoholic dementia may require treatment strategies similar to those in Alzheimer's disease. This protocol is intended to utilize clinical, neuroradiological, physiological, and neuropharmacological tests to differentiate these two pathologic entities, to follow a longitudinal course, and to relate variables in treatment protocols to outcome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00249-06 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pharmacologic Reduction of Alcohol Consumption in Alcoholic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. George	Special Expert	LCS, NIAAA
Others:	M. Eckardt	Section Chief	LCS, NIAAA
	R. Eskay	Research Physiologist	LCS, NIAAA
	M. Linnoila	Chief	LCS, NIAAA
	N. Salem	Section Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*

None

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Laboratory of Clinical Studies

SECTION

Section of Clinical Science

INSTITUTE AND LOCATION

NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Recent studies indicate that alcohol consumption is regulated by several interacting neurotransmitters, including the dopamine and serotonin systems. In a randomized double-blind design, chronic alcoholic outpatients received L-DOPA or L-5-hydroxytrytophan, both with the peripheral decarboxylase inhibitor carbidopa or placebo for a one year period. During this year, alcohol consumption, liver function, craving for alcohol, mental status, psychosocial functioning, and compliance with medication were assessed at regular intervals. Prior to entry into the study, after 3 months, and at one year, the following procedures were conducted to measure drug effects: (1) behavioral evaluation; (2) determination of concentrations of drugs, monoamines, hormones, and peptides in blood and cerebrospinal fluid; (3) orthostatic changes in heart rate, blood pressure, and plasma norepinephrine concentrations; and (4) assessment of plasma vasopressin response to saline infusion. Changes in alcohol consumption will be related to biochemical and behavioral parameters.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00264-04 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Sensitivity to Diazepam in Alcoholics and Children at Risk for Alcoholism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. George	Special Expert	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	M. Eckardt	Section Chief	LCS, NIAAA
	E. Lane	Senior Staff Fellow	LCS, NIAAA
	R. Lister	Visiting Associate	LCS, NIAAA

COOPERATING UNITS *(if any)*

Neuroscience Branch, NIMH (S. Paul); GWU (H. Weingartner)

LAB/BRANCH

Laboratory of Clinical Studies

SECTION

Section of Clinical Science

INSTITUTE AND LOCATION

NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The benzodiazepine-GABA-chloride ionophore receptor complex has been demonstrated to be involved in the physiologic and psychologic effects of ethanol. Diazepam, a benzodiazepine, binds to this receptor complex, and demonstrates a cross-tolerance to ethanol. Recent studies have shown that diazepam-induced alterations in eye movements offer a useful measure of benzodiazepine receptor sensitivity in humans. Preliminary findings at the NIMH and NIAAA suggest an increased sensitivity to the effects of diazepam in alcoholics as measured by saccadic eye movements, in alcoholics. In this study subjects will be administered diazepam and sub- sequently evaluated for changes in EEG, ERP (event-related potentials), body sway, vigilance tracking, memory, mood assessment and expectancy, ACTH, cortisol, prolactin, and growth hormone.

This study has been terminated. The results are being analyzed and will be submitted for publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00265-04 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Alprazolam, Diazepam, Clonidine, and Placebo upon Ethanol Withdrawal

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. George	Special Expert	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	J. Schmitz	Medical Staff Fellow	LCS, NIAAA

COOPERATING UNITS *(if any)*

None

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Laboratory of Clinical Studies

SECTION

Section of Clinical Science

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NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The ethanol withdrawal syndrome, which is characterized by an increased activity of the noradrenergic system, is at present most commonly treated with diazepam or chlordiazepoxide, both conventional benzodiazepines. Alprazolam, a triazolobenzodiazepine, has been demonstrated to be efficacious in the pharmacotherapy of depression and anxiety disorders, in contrast to the conventional benzodiazepines. Alprazolam may have a particularly potent inhibitory action on the noradrenergic system. It can, therefore, be postulated that alprazolam may be an effective and specific treatment for the ethanol withdrawal syndrome. Clonidine, a conventional antihypertensive, has been used to successfully treat withdrawal from the opiates, and most recently, nicotine and alcohol. This study will compare the effects of alprazolam, clonidine, diazepam, and placebo on: 1) the signs and symptoms of the ethanol withdrawal syndrome, and 2) the noradrenergic overactivity of the ethanol withdrawal syndrome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00266-04 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Relationship of Psychobiology to Psychopathology in Alcoholics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. George	Special Expert	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	M. Eckardt	Section Chief	LCS, NIAAA
	D. Goldman	Section Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*

Clinical Psychobiology, NIMH (W. Potter); Biological Psychiatry, NIMH (T. Uhde)

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NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Alcoholism and affective disorders frequently occur in the same individuals and in members of the same family. This association may represent the co-existence of two common disease entities due to chance or due to (a) alcoholism resulting from self-medication of an underlying affective disorder, or (b) depression resulting from toxic effects of alcohol abuse. Studies have shown that alcohol may acutely improve the sense of affective well-being, but with continued intoxication this improvement may be reversed. Also, during chronic experimental intoxication, alcoholics not only become increasingly depressed but also more anxious.

In this protocol we propose to characterize certain biochemical aspects of depression and anxiety as they occur in alcoholic patients. To do this, we will examine cerebrospinal fluid and plasma for norepinephrine (lying and standing), urine for catecholamine-metabolites and employ pharmacological challenge paradigms using lactate, isoproterenol and chlorimipramine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00271-03 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pharmacological Studies in Obese Rodents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. George	Special Expert	LCS, NIAAA
Others:	C. Gleiter	Visiting Fellow	LCS, NIAAA
	M. Linnoila	Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*

None

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The obese rodent provides an interesting experimental model for work in the area of alcoholism, as well as obesity and diabetes in that some strains show increased alcohol preference that appears to be related to their degree of diabetes. We have begun studying several strains of obese mice in order to further characterize the pharmacological defects underlying these observations. In particular, we have investigated the effect of electroconvulsive shock (ECS) on blood sugar levels since this treatment has been reported to improve glucose levels in diabetic humans. It was of interest to see whether ECS would also be an effective antidiabetic agent in this animal model prior to investigating its actions on alcohol intake. Furthermore, since abnormalities of serotonin function have been reported in alcoholics as well as in mice made diabetic by destruction of pancreatic islet cells we plan to study the actions of serotonin active drugs (eg. uptake blockers and agonists) on control of diabetes, on glucose metabolism, body weight and body temperature in these animals. These peripheral measures will be correlated with indices of central serotonin functions.

This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00273-01 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Serotonergic Activity on Neuroendocrine & Behavioral Measures

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. George	Special Expert	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*

Laboratory of Clinical Studies, NIMH (D. Murphy)

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Section of Clinical Science

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NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several studies suggest possible serotonergic involvement in the neurobiology of alcoholism and panic disorder. To evaluate this possibility we administered the serotonin agonist m-chlorophenyl piperazine (m-CPP) to alcoholics, alcoholics with panic disorder and controls. By observing the drug-induced behavioral effects and measuring changes in prolactin, cortisol and ACTH we hope to make inferences about post-synaptic serotonin function in these patient populations.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00274-01 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Intravenous Procaine in Alcoholics and Adult Children of Alcoholics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. George	Special Expert	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*

Biological Psychiatry, NIMH (R. Post); Laboratory of Psychology, NIMH (R. Coppola)

LAB/BRANCH
Laboratory of Clinical Studies

SECTION
Section of Clinical Science

INSTITUTE AND LOCATION
NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Intravenous procaine hydrochloride has been administered to a number of subjects with affective disorders and borderline personality disorder at NIMH. Subjects have uniformly experienced dose-related increases in psychosensory symptoms. Mood changes have been diverse, ranging from euphoria to dysphoria. Bipolar patients tended to experience more physical symptoms, while patients with borderline personality showed dysphoria both at baseline and after procaine. Procaine also increased plasma ACTH, cortisol and prolactin, but not growth hormone. Because procaine selectively stimulates the temporal lobes of the brain, these findings suggest that the mood changes may originate in this area of the brain. These studies have also shown that the procedure is safe and satisfactory to patients. The present application is for an additional study in alcoholics, children of alcoholics and normal controls. In addition, the patient groups will be separated into those with and without panic attacks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00260-05 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of Social Drinking on Blood Pressure

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. Ravitz	Special Volunteer	LCS, NIAAA
Others:	R. Eskay	Research Physiologist	LCS, NIAAA
	J. Karanian	Senior Staff Fellow	LCS, NIAAA
	M. Linnoila	Chief	LCS, NIAAA
	N. Salem	Section Chief	LCS, NIAAA
	G. Bone	Guest Researcher	LCS, NIAAA

COOPERATING UNITS *(if any)*

Hypertension-Endocrine Branch, NHLBI (H. Keiser)

LAB/BRANCH

Laboratory of Clinical Studies

SECTION

Section of Clinical Science

INSTITUTE AND LOCATION

NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Hypertension is common in the adult population of the United States. It has been demonstrated to be associated with increased cardiovascular morbidity and mortality. Alcohol consumption is also prevalent and may play an important causative or contributory role to elevate blood pressure in up to one-third of all hypertensives. The association between hypertension and alcohol consumption awaits causative explanation. Elucidation of the pathophysiology of the alcohol associated increment in blood pressure is the purpose of this study. Blood pressure is measured using a 24-hour ambulatory monitoring system for several days in normotensive and hypertensive social drinkers during periods of usual alcohol consumption and abstinence. Blood and urine samples are obtained to measure neurotransmitters, neuromodulators, and electrolytes involved in blood pressure regulation.

This protocol has been terminated. The results are being prepared for publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00233-07 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Family Studies of Alcoholism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. George	Special Expert	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	D. Lamparski	Guest Researcher	LCS, NIAAA
	V. Moore	Social Worker	LCS, NIAAA
	D. Garnett	Social Worker	LCS, NIAAA
	A. Roy	Visiting Associate	LCS, NIAAA
	D. Goldman	Section Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*
Social Work Department, Clinical Center, NIH (D. Rooney)

LAB/BRANCH
Laboratory of Clinical Studies

SECTION
Section of Clinical Science, Unit of Family Studies

INSTITUTE AND LOCATION
NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	4.0	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Unit of Family Studies has two major functions (1) to recruit and assess alcoholics, controls and their families, for various investigators within the Laboratory of Clinical Studies; and (2) to conduct psychosocial studies of alcoholic families and their individual members. In the current year, Unit staff have focused on coding and entering onto a computer the data collected since the inception of the Laboratory. A series of correlational studies comparing suicidal versus non-suicidal alcoholics on clinical, psychosocial and family variables has been carried out. In addition, the Unit has begun a study examining middle class black alcoholic families. Unit staff has also been collaborating with the Unit on Genetic Studies in identifying and phenotyping several pedigrees for linkage analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00234-07 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Genetic Studies on Alcoholism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Goldman	Section Chief	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	J. Stoll	Staff Fellow	LCS, NIAAA
	W. Chen	Senior Staff Fellow	LCS, NIAAA
	R. Haber	NRC Fellow	LCS, NIAAA
	A. Bolos	Visiting Fellow	LCS, NIAAA
	B. Giblin	NRC Fellow	LCS, NIAAA
	M. Enoch	Visiting Fellow	LCS, NIAAA

COOPERATING UNITS *(if any)*
Laboratory of Viral Carcinogenesis, NCI (S. O'Brien); VA Medical Center, Portland, OR (J. Crabbe); Program Resources, Inc., Frederick, MD (M. Dean)

LAB/BRANCH
Laboratory of Clinical Studies

SECTION
Section on Genetic Studies

INSTITUTE AND LOCATION
NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10	6	4

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To identify unknown genetic loci determining alcoholism, we are testing for linkage or association between genetic markers and behavioral phenotypes. Our strategy has been to: 1) focus on alcoholism with impulsivity/aggressivity as a prominent accompanying behavioral trait, 2) utilize mouse genetic models, 3) use very large panels of DNA and protein polymorphisms, and 4) study in detail candidate genetic loci including tryptophan hydroxylase, the alcohol dehydrogenases and Y chromosome loci. Human linkage markers include >1000 DNA probes of which we are currently typing 150, and also include 25 polymorphic protein markers detectable by two-dimensional electrophoresis (2DE) of lymphocytes and serum. These polymorphisms are being typed in large families with alcoholism, including American Indian families. After cloning the human class III alcohol dehydrogenase, we demonstrated that it is part of an ADH gene complex by comparatively mapping the gene in mouse and man. After cloning tryptophan hydroxylase from mouse mastocytoma, we showed that this cDNA recognizes a brainstem mRNA for this rate-limiting enzyme of serotonin synthesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00239-06 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Alcoholism-Associated Cognitive Impairment and Organic Brain Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Eckardt	Section Chief	LCS, NIAAA
Others:	R. Lister	Visiting Associate	LCS, NIAAA
	R. Rawlings	Mathematical Statistician	DBE, NIAAA

COOPERATING UNITS *(if any)*
United States Soldiers' and Airmen's Home, Washington, D. C. (N. Keller, A. Law); GWU (H. Weingartner)

LAB/BRANCH
Laboratory of Clinical Studies

SECTION
Section of Clinical Brain Research

INSTITUTE AND LOCATION
NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to examine the neuropsychological performance of several clinically defined populations of detoxified male alcoholics. Comparisons will be made among detoxified alcoholics with clinically defined chronic organic brain syndromes, dementia or amnestic syndrome; less cognitively impaired alcoholics who are in alcoholism treatment programs; and nonalcoholic controls.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00240-10 LCS

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Cognitive Function in Male Alcoholics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Eckardt	Section Chief	LCS, NIAAA
Others:	R. Rawlings	Mathematical Statistician	DBE, NIAAA

COOPERATING UNITS *(if any)*: Department of Psychiatry and Human Behavior, University of California, Irvine (L. Gottschalk)

LAB/BRANCH: Laboratory of Clinical Studies

SECTION: Section of Clinical Brain Research

INSTITUTE AND LOCATION: NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This series of studies is concerned with cognitive function in detoxified male alcoholics. Recent and chronic alcohol consumption variables were found to interact with each other and with age and education in a non-linear fashion in predicting neuropsychological performance. Increased consumption predicted decreased performance, even on tests whose mean scores were in the normal range. Little or no improvement in performance was demonstrable with short-term abstinence (14 - 20 days), although long-term abstinence (7 months) was associated with improvement. Similarly, hepatic and hematologic characteristics of long-term abstainers improved, whereas these systems functioned abnormally in people who continued to consume alcoholic beverages, albeit at significantly reduced levels. Relationships between various pretreatment prediction variables and subsequent outcome are also being studied. Increased risk of relapse was associated with excessive drinkers who were relatively early in their alcoholic careers as assessed by years of abusive drinking and accumulated lifetime exposure to alcohol. Although statistically significant relationships were observed between scores on certain neuropsychological tests and posttreatment alcohol consumption, neurospychological evaluation was determined to be of limited clinical utility.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00267-04 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Imaging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Eckardt	Section Chief	LCS, NIAAA
Others:	M. Linnoila	Chief	LCS, NIAAA
	R. Rawlings	Mathematical Statistician	DBE, NIAAA
	D. Rio	Physicist	LCS, NIAAA
	J. Rohrbaugh	Research Psychologist	LCS, NIAAA

COOPERATING UNITS *(if any)*

Radiation Oncology Branch, NCI (Lamoreau)

LAB/BRANCH

Laboratory of Clinical Studies

SECTION

Section of Clinical Brain Research

INSTITUTE AND LOCATION

NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	3.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Various clinical imaging methods are being used to study the brain in vivo. These techniques enable comparisons of gross anatomy (CAT - Computed Axial Tomography; MRI - Magnetic Resonance Imaging) of the brain with electrical activity (EEG - electroencephalography; ERPs - Event-Related Potentials) and rate of glucose utilization in specific regions (PET - Positron Emission Tomography). From a clinical perspective, these techniques, in association with other diagnostic tests, enable qualitative judgments to be made as to the anatomic and physiologic integrity of the brain. In order to quantitatively analyze image data, the imaging techniques themselves are being investigated, as well as the effects of the associated mathematical models and subjective inputs on the reconstruction of the brain image. Moreover, mathematical and statistical methods for evaluating and relating these various sources of multivariate data are being developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00268-04 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Behavioral Effects of Ethanol and Other Psychotropic Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. Lister	Visiting Associate	LCS, NIAAA
Others:	M. Durcan	Visiting Fellow	LCS, NIAAA
	M. Eckardt	Section Chief	LCS, NIAAA
	D. Goldman	Section Chief	LCS, NIAAA
	L. Hilakivi	Visiting Fellow	LCS, NIAAA
	M. Linnoila	Chief	LCS, NIAAA
	M. Ota	Visiting Fellow	LCS, NIAAA

COOPERATING UNITS *(if any)*
George Washington University (H. Weingartner); VA Medical Center, Portland, OR (J. Crabbe); United States Soldiers' and Airmen's Home, Washington, DC

LAB/BRANCH
Laboratory of Clinical Studies

SECTION
Section of Clinical Brain Research

INSTITUTE AND LOCATION
NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	1.4	0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Pharmacologic and genetic methods are being used to determine the psychobiological mechanisms underlying various behavioral processes. The current research is focusing on the neurobiology of anxiety, impulsivity and aggression in mice and on learning and memory processes in humans. The effects of ethanol and of drugs with known and specific mechanisms of action are being investigated.

In mice, isolation has been found not only to increase aggressive behavior, but also to increase motor activity and decrease directed exploration. A sub-population of aggressive NIH Swiss mice were found to spend less time immobile in Porsolt's swim test than nonaggressive controls. No differences were found in the concentrations of 5-HT or its metabolite 5-HIAA in four brain areas of these two groups. The effects of ethanol on aggressive behavior were found to depend on the basal levels of aggressivity.

In normal human volunteers, ethanol impaired the ability of subjects to learn material when memory was tested explicitly, but no impairments for the same material were found when implicit tests of memory were used.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00275-01 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Psychomotor and Cognitive Aspects of Alcoholism

PRINCIPAL INVESTIGATOR *(List other professional personnal below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Moran	Staff Fellow	LCS, NIAAA
Others:	M. Eckardt	Section Chief	LCS, NIAAA
	D. Garnett	Social Worker	LCS, NIAAA
	D. George	Special Expert	LCS, NIAAA
	M. Linnoila	Chief	LCS, NIAAA
	J. Rohrbaugh	Research Psychologist	LCS, NIAAA
	K. Smith	Senior Staff Fellow	LCS, NIAAA

COOPERATING UNITS *(if any)*
Georgetown University, Washington, D.C. (S. Gilson); VAMC, Charleston, S.C. (B. Adinoff)

LAB/BRANCH
Laboratory of Clinical Studies

SECTION
Section of Clinical Brain Research

INSTITUTE AND LOCATION
NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	2.2	0.6

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This series of studies is designed to investigate the neuroanatomical and neurochemical pathways underlying impaired cognitive and psychomotor functions in detoxified adult alcoholics and their offspring. We have demonstrated that long-term alcohol abuse is associated with unusual saccadic eye movements in about half the alcoholics studied. Low doses of diazepam administered i.v. to these alcoholics reduce the number of unusual eye movements. It is anticipated that studies on the children of alcoholics will clarify whether these unusual eye movements predate the onset of excessive alcohol consumption.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00250-06 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Electrophysiological Studies of Acute and Chronic Alcohol Consumption

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Rohrbaugh	Research Psychologist	LCS, NIAAA
Others:	M. Eckardt	Section Chief	LCS, NIAAA
	M. Linnoila	Chief	LCS, NIAAA
	D. Rio	Physicist	LCS, NIAAA
	J. Moran	Staff Fellow	LCS, NIAAA
	M. Enoch	Visiting Fellow	LCS, NIAAA

COOPERATING UNITS *(if any)*
Department of Psychology, Catholic University (R. Parasuraman); Department of Electrical Engineering, University of Nebraska (J. Varner)

LAB/BRANCH
Laboratory of Clinical Studies

SECTION
Section of Clinical Brain Research

INSTITUTE AND LOCATION
NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.2	1.2	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The aim of this research is to study the covert brain processes that underlie cognition and performance in human subjects, and the acute and chronic effects of ethanol upon such processes. Included is an extensive study in which we are examining brain processes in individuals with different family histories of alcoholism. A principal focus of these studies is the measurement of brain electrical potentials, which provide information regarding the timing and character of the constituent sensory, cognitive and motor elements that are the mechanisms underlying observable behavior. The study of brain potentials also allows inference of the specific brain regions affected by ethanol. The brain electrical potentials are studied within a broad context provided by performance and psychometric data, and measurement within other psychophysiological response systems.

We have obtained data which document a large number of acute and chronic effects on specific brain functions, ranging from sensory input to motor control functions. Of particular interest is a finding that brain electrical and autonomic signs of alerting and orienting are enhanced by ethanol, in contrast to its depressant effect on most other functions. A similar effect was observed in a sample of chronic alcoholic organic brain disease patients. Such findings suggest that ethanol intoxication and alcoholic organic brain disease may be associated with a disinhibition or deregulation of orienting processes. The attendant fragmentation of behavior may account for at least some of the cognitive impairment associated with alcohol.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00237-07 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Individual Variability in Drug Metabolism by Carbon Dioxide Breath Tests

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Lalka	Special Expert	LCS, NIAAA
Others:	M. Towle	Chemist	LCS, NIAAA

COOPERATING UNITS *(if any)*
Epilepsy Branch, NINCDS (R. Porter); Nursing Department, NINCDS (I. Naveau)

LAB/BRANCH
Laboratory of Clinical Studies

SECTION
Section of Clinical Biochemistry and Pharmacology

INSTITUTE AND LOCATION
NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	0.8	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Preliminary testing of the prediction that caffeine, a low extraction ratio drug (0.1) should be a more sensitive probe of enzyme induction than methacetin, a high extraction ratio drug (0.9), when excretion of a metabolite (CO_2) is measured, has been carried out. A single dose of each was administered to 8 healthy volunteers and 9 epilepsy patients treated with phenytoin, carbamazepine and/or phenobarbital. The 13C carbon dioxide in expired breath was measured by isotope ratio mass spectrometry. The percentages of the dose excreted as CO_2 in 2 hr. were compared: $3.22\% \pm 0.86$ and $5.54\% \pm 1.59$ caffeine was excreted by controls and patients, respectively, compared with $28.6\% \pm 5.8$ and $40.0\% \pm 4.2$ methacetin. The results in the 2 subject groups were significantly different for both probes ($p<.05$). These data do not support the theoretical prediction that the extraction ratio of a drug has a critical effect upon its usefulness in detection of induction of oxidative metabolism via the carbon dioxide breath test. In addition, preliminary data illustrate the potential usefulness of this test to follow the time course of changes in drug metabolism/liver function of an alcoholic patient when he stops drinking.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00235-07 LCS

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 chererers or less. Title must fit on one line between the borders.)
Metabolic and Structural Studies of Polyunsaturated Lipids in Cell Membranes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	N. Salem, Jr.	Section Chief	LCS, NIAAA
Others:	H. Kim	Senior Staff Fellow	LCS, NIAAA
	J. Yergey	Senior Staff Fellow	LCS, NIAAA
	J. Karanian	Senior Staff Fellow	LCS, NIAAA
	T. Shingu	Visiting Fellow	LCS, NIAAA
	F. Hullin	Visiting Fellow	LCS, NIAAA
	M. Bossant	Visiting Fellow	LCS, NIAAA
	S. Sawazaki	Visiting Fellow	LCS, NIAAA
	A. Yoffe	Chemist	LCS, NIAAA

COOPERATING UNITS (if any)

Department of Clinical Pharmacology, Vanderbilt University (H. Knapp)

LAB/BRANCH: Laboratory of Clinical Studies

SECTION: Section of Analytical Chemistry

INSTITUTE AND LOCATION: NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.5	4.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The principal objective of this study is to elucidate the structural and metabolic functions of polyunsaturated fatty acids and phospholipids with particular reference to their modulation by ethanol. Several approaches to this problem were taken, including studies of cellular lipid composition, membrane asymmetry, fatty acid oxygenation and dietary supplementation. In particular, these studies focused on the major polyunsaturate of brain, docosahexaenoate (C22:6w3) and, to a lesser extent, on arachidonate (C20:4w6).

Progress has been made in the development of a covalent labelling technique that allows the study of aminophospholipid molecular species composition and membrane topology. Data for reference purposes has been obtained for more than 50 species in the human erythrocyte. Generally, the phenomenon of molecular species asymmetry has been confirmed, i.e. polyunsaturates are selectively localized on the cytoplasmic leaflet of the plasma membrane. Dietary supplementation with w-3 fatty acids leads to replacement primarily of alkenyl-20:4w6 phosphatidylethanolamines (PE) with the corresponding 20:5w3 or 22:6w3 species. The eicosanoid profile is shifted towards w-3 products in this case as there is an increase in platelet 12-lipoxygenase products of 20:5w3 and 22:6w3 and decreased 18:2w6 and 20:4w6 products relative to an w-6 supplemented group. Urinary PGI_3 metabolites are also increased but there was no evidence of a decrease in PGI_2 metabolism.

Hydroxy-docosahexaenoates (HDHE) have been biosynthesized for pharmacological experiments in which it was observed that they have a weak contractile action on smooth muscle and can also antagonize thromboxane-induced contractility. Platelet HDHEs were steroselectively formed but the brain products appear to be racemic mixtures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00262-05 LCS

PERIOD COVERED

October 1, 1988 to June 9, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characterization of Oxygenated Fatty Acid Metabolites by Capillary GC/MS

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Yergey	Senior Staff Fellow	LCS, NIAAA
Others:	N. Salem, Jr.	Section Chief	LCS, NIAAA
	H. Kim	Senior Staff Fellow	LCS, NIAAA
	M. Linnoila	Chief	LCS, NIAAA

COOPERATING UNITS *(if any)*

Department of Neurology Services, Veterans Administration Hospital, Washington, D.C. (J. Hawley); Laboratory of Clinical Science, NIMH (M. Heyes)

LAB/BRANCH

Laboratory of Clinical Studies

SECTION

Section of Analytical Chemistry

INSTITUTE AND LOCATION

NIAAA, 9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It has been hypothesized that part of the etiology of alcoholism may be linked to aberrant fatty acid and prostaglandin metabolism, based primarily upon the finding that behavioral effects of ethanol can be modulated by preadministration of prostaglandin synthetase inhibitors. Direct evidence for ethanol induced changes in CNS prostaglandins has been contradictory. Therefore, we developed a sensitive and specific assay based on selected-ionmonitoring, electron-capture negative ionization GC/MS detection of the N-methyl methoxime, pentafluorobenzyl ester, tris-trimethylsilyl ether derivatives of PGE_2, PGE_1, PGF_{1a}, and 6-keto-PGF_{1a}. We previously reported significant improvements in the assay procedure and results which indicated that the concentrations of PGE_2, PGE_1, PGF_{2a}, and 6-keto-PGF_{1a} were below 15 pg/mL in lumbar CSF of healthy humans and abstinent alcoholics. In order to investigate other means of measuring CNS prostaglandins, we explored both in vivo microdialysis techniques and in vitro tissue slice techniques. Extracellular fluid concentrations of PGE_2, PGD_{2a}, 6-keto-PGF_{1a} and TXB_2 were sampled from rat brain in vivo using microdialysis. The lowest levels measured may represent baseline in vivo production of eicosanoids in the central nervous system, whereas the higher levels present in the initial sampling period were believed to be due to the acute penetration injury of the microdialysis probe. Extension of the methodology to unanesthetized animals may provide a useful model for measuring in vivo effects of ethanol on eicosanoid production in the central nervous system. Results with in vitro tissue slice preparations of rat frontal cortex, showing no significant difference in eicosanoid production between control and ethanol exposed tissues, must be rationalized with behavioral studies showing significant attenuation of ethanol's central nervous system effects following administration of eicosanoid synthesis inhibitors. The tissue slice data indicate that a simple enzymatic stimulation of eicosanoid production by ethanol does not occur, in vitro.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00035-03 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Ethanol and its Metabolites on Metabolism and Inorganic Ion Balance

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	W.L. Gitomer	Chemist	LMMB, NIAAA
Others:	R.L. Veech	Chief	LMMB, NIAAA

COOPERATING UNITS *(if any)*

LCBG, NIDDK (R.L. Ornberg); DRS BEI, (R.D. Leapman)

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Metabolic Control

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Ave., Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It was observed that the treatment of 48hr. starved rats with acetate, propionate or butyrate results in large increases in the hepatic Ca2+, Mg2+ and inorganic pyrophosphate (PPi) content apparantly due to the formation of calcium and magnesium PPi precipitates within the mitochondrial matrix. The increase in mitochondrial calcium and magnesium was shown to occur using electron probe x-ray microanalysis. Assuming that the free matrix [Mg2+]=1 mM and using the magnesium PPi and calcium PPi solubility products, the free mitochondrial [Ca2+] in the liver was calculated to be 1.2 mM after treatment with short chain fatty acids. This observation was then expanded to all metabolic states and it was concluded that under all in vivo conditions thus far studied that, in the in vivo rat liver, calcium and magnesium PPi precipitates are present in the mitochondrial matrix and the free mitochondrial matrix [Ca2+] is about 1mM. This value is three orders of magnitude greater than values estimated for the free mitochondrial matrix [Ca2+] using isolated mitochondria.

This project has been terminated.

Gitomer WL, Veech RL. The estimation of the in vivo mitochondrial Ca^{2+} concentration. In: Lemasters JL, Hackenbrock CR, Thurman RG, Westerhoff HV eds. Integration of Mitochondrial Function. New York: Plenum Publishing Corporation, 1988;551-8.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 00001-04 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Ethanol on Gastrointestinal Biochemistry and Physiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M.-T. Huang	Chemist	LMMB, NIAAA
Other:	R.L. Veech	Chief	LMMB, NIAAA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Metabolism and Metabolic Biology

SECTION

Metabolic Control

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A surgical method was developed to cannulate chronically both the portal and hepatic veins of laboratory rats. This experimental system is useful for studies on intestinal absorption and hepatic extractions of nutrients. With this experimental system, the following objectives can be determined (1) the effect of ethanol on GI absorption and liver metabolism and (2) glucose paradox. In the first study, the rate of ethanol elimination will be determined in rats meal-fed with diet containing glucose, fructose, mixture of glucose and fructose, and sucrose to determine the importance of alcohol dehydrogenase and redox state in liver on the metabolism of ethanol in vivo. In the second study, portal-hepatic difference of glucose and gluconeogenetic precursors will be determined in order to resolve the paradox that liver can not utilize glucose efficiently. Our results, in the latter subject, show that liver can utilize exogenous glucose and can synthesize glycogen directly from exogenous glucose directly. Recent theory on the pathway of glycogen synthesize in liver (Glucose-C3-G6P-Glucogen) was found to be based on questionable data and inadequate method of calculation.

This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00024-11 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Genetic and Metabolic Studies of Human Alcoholics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R.L. Veech	Chief	LMMB, NIAAA
Others:	J.P. Casazza	Chemist	LMMB, NIAAA

COOPERATING UNITS *(if any)*

Department of Academic Medicine, London, England (M. Morgan)

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Metabolic Control

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	0.6	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In three separate studies involving three different sets of collaborators, elevated levels of 2,3-butanediol have been found in the blood of 80% of chronic alcoholics, but not social drinkers consuming distilled spirits. Two separate methods of gas chromatographic analysis of diols have been developed. One method involving formation of the bromophenylboronate derivative can accurately measure to D-L, or *meso*-2,3-butanediol to 5 uM.

In the rat, two pathways of butanediol formation have been demonstrated. The first (Veech RL, et al. Curr Top Cell Regul 1981;18:151-179) involves elevated blood acetaldehyde entering the brain with an active pyruvate dehydrogenase multi-enzyme complex where it condenses with hydroxyethyl thiamine pyrophosphate to form acetoin. The acetoin is subsequently converted in liver to 2,3-butanediol. In a second animal model, 2,3-butanediol in the rat is produced by acetone feeding. Prolonged fasting in man, however, produces only 1,2-propanediol. Whether D/L-2,3-butanediol production is due to expression of an aberrant gene product or is due to some other metabolic change caused by chronic ethanol consumption is not known, but the presence of this compound in approximately 40% of all alcoholics prior to the onset of alcoholic liver disease during periods of ethanol ingestion, and in approximately 25% of all alcoholics with alcoholic cirrhosis in the absence of recent ingestion of ethanol make this compound a useful indicator of alcoholic liver disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00033-06 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Metabolic Effects of Growth Factors and Growth Hormone

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	B.Y. Reed	Senior Staff Fellow	LMMB, NIAAA
Others:	M.J. Gerhart	Chemist	LMMB, NIAAA
	M.T. King	Chemist	LMMB, NIAAA
	R.L. Veech	Chief	LMMB, NIAAA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Molecular Genetics

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.1	1.1	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

An important effect of ethanol is to disrupt cellular growth. Specifically ethanol has been shown to inhibit hepatocyte DNA synthesis by a number of agents including epidermal growth factor (EGF)(Carter EA, Wands JR, Biochem Biophys Res Commun 1985;128:767-774). In an attempt to understand the mechanism by which ethanol interferes with the normal processes of growth and development we studied the early metabolite changes induced by EGF, platelet derived growth factor (PDGF) and angiotensin in rat liver in vivo (Reed BY, King MT, Gitomer WL, Veech RL, J Biol Chem 1987;262:8712-8715; Reed BY, King MT, Gerhart MJ, Veech RL, Biochem Soc Trans 1988;16:636-637). Elucidation of the metabolic changes induced enabled us to identify 2 enzymes affected by the actions of EGF and PDGF respectively. We have subsequently demonstrated a direct effect of ethanol on the normal metabolic action of EGF in vivo (Gerhart MJ, Reed BY, Veech RL, Alcoholism: Clin and Exp Res 1988;12:116-118) and further shown that the apparent modulation of the action of EGF by ethanol occurs at an intracellular site as ethanol does not interfere with the binding of the growth factor to its receptor (Gerhart MJ, Reed BY, Veech RL, In: Advances in Alcohol and Substance Abuse. 1988; in press). Currently further studies are in progress to elucidate the role of PDGF in alcoholic liver disease.

This project has been terminated.

Gerhart MJ, Reed BY, Veech RL. Ethanol inhibits some of the early effects of epidermal growth factor in vivo. Alcoholism: Clinical and Experimental Research 12:116-118, 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00036-03 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structure and regulation of ethanol-inducible cytochrome P450 gene (II)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	B.J. Song	Senior Staff Fellow	LMMB, NIAAA
Others:	R.L. Veech	Chief	LMMB, NIAAA
	Y.P. Yun	Visiting Fellow	LMMB, NIAAA

COOPERATING UNITS *(if any)*

Laboratory of Molecular Carcinogenesis, National Cancer Institute (F.J. Gonzalez)

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Molecular Genetics

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The elevated levels of 1,2-propanediol found in the sera of alcoholics is probably produced by the reaction of microsomal enzyme that is induced by ethanol feeding. We have identified and determined the structures of the ethanol-inducible cytochrome P450 (P450IIE1) of both rat and human. We have also demonstrated three different types of regulation of P450 IIE1 in rat: transcriptional activation during development; mRNA stabilization in diabetes and starvation; and post-transcription activation by various inducers such as ethanol, acetone, and pyrazole derivatives all of which elevate the levels of P450IIE1 in liver, lung, and kidney tissues. By measuring the turnover rates of P450IIE1 from untreated control rats and acetone-treated rats using radiolabeled amino acid precursors, we further demonstrated that the post-transcriptional activation by various exogenous inducers is due to specific P450IIE1 protein stabilization without any changes in the rate of synthesis.

The level of P450IIE1 in easily obtainable human tissues was also examined. P450IIE1 can be easily detected by specific antibody to P450IIE1 in peripheral lymphocytes from poorly controlled diabetic children whose levels are elevated four to ten fold over the levels of corresponding control subjects. The induced levels of P450IIE1 determined by the density of immunoblot analysis highly correlated with the levels of hemoglobin Alc which is metabolic indicator of these individuals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00037-03 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular cloning of pyruvate dehydrogenase gene (II)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

P.I.	B.J. Song	Senior Staff Fellow	LMMB, NIAAA
Others:	R.L. Veech	Chief	LMMB, NIAAA
	T.L. Huh	Visiting Fellow	LMMB, NIAAA
	Y.T. Chi	Visiting Fellow	LMMB, NIAAA
	J.W. Huh	Visiting Fellow	LMMB, NIAAA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Molecular Genetics

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Recent studies from our laboratory indicate that 2,3-butanediol, one of two unusual metabolites found in human alcoholic blood, is predominantly associated with human subjects who suffer alcoholic hepatitis or alcoholic cirrhosis (Casazza, et al., Alcohol and Alcoholism 1987;(suppl 1):607-609). Although the exact mechanism of 2,3-butanediol formation is not known, Veech and his associates have postulated that it could be generated by the side reaction of pyruvate dehydrogenase that are found in brain and testis (Curr Top Cell Regulation 1981;18:151-179). Based on this hypothesis, we have started to clone genes encoding for every component of the pyruvate dehydrogenase complex. Using synthesized oligodeoxynucleotide probes we have identified full-length cDNA clones for pyruvate dehydrogenase (PDH) E1A, E1B, and E3 subunits whose genes are located in chromosome X, 3, and 7, respectively. The brain PDHE1A sequence was determined to be identical with that of liver indicating that the differences in the production of 2,3-butanediol in brain and liver may not be due to a structural difference in PDH E1A but rather due to tissue-specific differential regulation of PDH by PDH specific kinase and phosphatase as well as metabolic intermediates. Two different types of cDNA clones for PDH E1B were identified: one of which had an unusual polyadenylation signal on its 3' untranslated region immediately following the termination codon. The full-length cDNAs for each PDH subunit were inserted into plasmids for expressing these enzymes for further biochemical and immunological analyses.

PDH specific protein kinase and phosphatase have been purified according to the published procedures. These proteins are now subjected to amino acid sequence analysis in order to clone the genes coding for PDH kinase and phosphatase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00043-01 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Effects of Ethanol on Isolated Cerebral Arteries

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: E. Dora	Visiting Scientist	LMMB, NIAAA
Others: A. C. McLaughlin	Section Chief	LMMB, NIAAA

COOPERATING UNITS *(if any)*

Experimental Research Department, Second Institute of Physiology, Semmelweis Medical University, Budapest, Hungary (Farago, M)

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Physical Chemistry

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.20	0.20	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The acute administration of ethanol decreases cerebral blood flow in the intact animal (see accompanying Project Report "Cerebral Blood Flow and Metabolism in the Rat"). The in vivo effects of ethanol can be studied in more detail with the isolated artery preparation. Studies with isolated arteries have shown:

(1) Ethanol induces contractions in isolated arteries, and facilitates the vasoconstrictory effects of norepinephrine.

(2) The effects of ethanol appear to be specific for cerebral arteries.

(3) Preliminary results suggest that ethanol may interfere with the endothelium-mediated regulation of cerebral vascular smooth muscle tone.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00038-02 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cerebral Blood Flow and Energy Metabolism in the Cat

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	A. C. McLaughlin	Section Chief	LMMB, NIAAA
Others:	L. Ligeti	Visiting Scientist	LMMB, NIAAA
	T. Sinnwell	Technician	LMMB, NIAAA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Physical Chemistry

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.60	0.40	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study was undertaken to assess a new method for the non-invasive determination of regional cerebral blood flow without the use of radioactive tracers. Specifically, we investigated a new 19F NMR technique that has been used to measure the clearance of a fluorinated inert gas, CHF3, from the brain of a cat. In the previous year, we used this new technique to obtain cerebral wash-out curves on animals with different arterial CO2 levels, and performed a preliminary analysis of the data. During the current year, we obtained the ancillary data necessary to perform a full analysis of the cerebral wash-out curves, i.e., the arterial wash-out curves and the brain/blood partition coefficient, and completed the analysis of the cerebral wash-out curves obtained previously.

The full analysis of the cerebral wash-out curves allowed us to test the new technique by comparing the cerebral blood flow values determined by 19F NMR with cerebral blood flow values determined simultaneously by radioactive microsphere techniques. The cerebral blood flow values determined by 19F NMR and radioactive microsphere techniques agreed reasonably well, and showed the same response to variations in the arterial CO2 level. We conclude that 19F NMR technique gives a quantitative measure of cerebral blood flow.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 0039-02 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cerebral Blood Flow and Energy Metabolism in the Rat

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	A. C. McLaughlin	Section Chief	LMMB, NIAAA
Others:	E. Dora	Visiting Scientist	LMMB, NIAAA
	L. Ligeti	Visiting Scientist	LMMB, NIAAA
	K. Hines	Technician	LMMB, NIAAA
	T. Sinnwell	Technician	LMMB, NIAAA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Physical Chemistry

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.20	1.6	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In the previous year, we developed a new technique for measuring cortical cerebral blood flow in the rat. We have now combined the blood flow measurements with arterial/venous differences for oxygen and glucose to calculate the cerebral oxygen consumption (CMR_{O2}) and the cerebral glucose consumption (CMR_{glu}), and used this technique to study two problems:

(1) Most studies on the acute effects of alcohol on cerebral blood flow and metabolic rate have been performed on restrained or anesthized animals, where it is difficult to separate the effects of stress and anesthesia from the effects of alcohol. We have studied the acute effects of alcohol on cerebral blood flow and metabolism in the unrestrained, conscious, rat under normocapnic and hypercapnic conditions.

(2) The role of humoral and neuronal factors in the control of cerebral blood flow and metabolism is controversial. We have studied the role of the adrenal/hypophysis axis and the role of sympathetic activation on cerebral blood flow and metabolism under normocapnic and hypercapnic conditions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00040-02 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Electrostatic Properties of Membranes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	A.C. McLaughlin	Section Chief	LMMB, NIAAA
Other:	K. Hines	Technician	LMMB, NIAAA
	T. Sinnwell	Technician	LMMB, NIAAA

COOPERATING UNITS *(if any)*

Physiology Department, State University of New York, Stonybrook, New York (S. McLaughlin); Biochemistry Department, University of Pennsylvania, Philadelphia, PA (J.R. Williamson).

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Physical Chemistry

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.2	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The surface potential of cellular membranes is an important determinant in the physiological function of the cell. We have investigated a number of factors that affect the surface potential of membranes. We have also modified the theory that has been used to calculate the surface potential, the Gouy-Chapman theory, to account for these factors.

Triphosphoinositide lipids in plasma membranes could have up to five negative charges. We have investigated the interaction of calcium, magnesium, potassium, protons and other cations with triphosphoinositides, and determined the number of cations bound to the lipid under physiologically-relevent conditions. The proton titration curves of the lipid demonstrate that there is a cooperative interaction between the two monoester groups in the inositol headgroup. This interaction has important consequences in terms of the net charge on the triphosphoinositide lipid under physiological conditions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00041-02 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*

Determination of Plasma Free Magnesium Concentration by Ion-Selective Electrodes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

P.I.:	A. C. McLaughlin	Section Chief	LMMB, NIAAA
Other:	K. Hines	Technician	LMMB, NIAAA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Physical Chemistry

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.50	0.20	0.30

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

An ion-selective technique has been developed for the determination of free serum magnesium levels. A number of major technical difficulties have been overcome, but further studies to determine the accuracy of the technique are necessary.

PHS 6040 (Rev. 12/84)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00042-01 LMMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Multiple Quantum NMR Studies of Sodium and Potassium in the Rat Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	A. C. McLaughlin	Section Chief	LMMB, NIAAA
Others:	R. Lyon	Staff Fellow	LMMB, NIAAA

COOPERATING UNITS *(if any)*

Biomedical Engineering and Instrumentation Branch, NIH, Bethesda, MD (Pekar J, Moonen CT)

LAB/BRANCH

Laboratory of Metabolism and Molecular Biology

SECTION

Physical Chemistry

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.20	1.20	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have developed a new approach for studying trans-membrane ion gradients in the intact brain utilizing the different NMR relaxation times of intracellular and extracellular ions. Double quantum NMR spectra are much more sensitive than conventional single quantum NMR spectra to changes in relaxation times. Double quantum and single quantum 23Na and 39K NMR spectra were obtaimed from rat brain in vivo. Upon death, the double quantum 23Na NMR signal increased by a factor of five, while the single quantum signal decreased by 20%. The results are consistent with the well-known influx of sodium ions into the cell, and suggest that double quantum sodium and potassium NMR may be useful in visualizing compromised regions of the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00406-01 LPPS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Noradrenergic Neurotransmission and Actions of Ethanol

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E. Ishac	Visiting Associate	LPPS, NIAAA
Others:	G. Kunos	Laboratory Chief	LPPS, NIAAA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Physiologic and Pharmacologic Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Neurotransmitter release is triggered by an elevated level of free calcium and thus represents a crucial event in synaptic transmission. However the biochemical processes involved in calcium influx and calcium-dependent transmitter release are not known. Ethanol can alter the mobilization of calcium in a number of cells systems including synaptic transmission. The calcium/phospholipid-dependent protein kinase, protein kinase C, is highly localized in neuronal tissue and in particular presynaptic nerve terminals. I have examined the role of activation or inhibition of protein kinase C on the release of noradrenaline from rat isolated atria preloaded with [3-H]-noradrenaline. It was found that activation of protein kinase C by phorbol 12-myristate 13-acetate caused a concentration-dependent enhancement of membrane depolarization induced (electrical field stimulation or high potassium) release of noradrenaline. Whereas polymyxin B, an inhibitor of protein kinase C reduced noradrenaline release evoked by either electrical field stimulation or high potassium. In contrast, non-exocytotic release of noradrenaline evoked by tyramine was not altered by phorbol 12-myristrate 13-acetate. Polymyxin B only at a high concentration caused a slight reduction in tyramine-induced outflow of radioactivity. The findings suggest that protein kinase C may play a role in the exocytotic release of noradrenaline but not due to displacement. Ongoing studies will examine the effect of acute and chronic ethanol treatment on the calcium/protein kinase systems involved in neurotransmission.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00401-02 LPPS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Interaction Between the Immune System and Adrenergic Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	G. Kunos	Laboratory Chief	LPPS, NIAAA
Others:	M. Virmani	Research Chemist	LPPS, NIAAA
	T. Nakane	Visiting Fellow	LPPS, NIAAA
	T. Szentendrei	Visiting Fellow	LPPS, NIAAA

COOPERATING UNITS *(if any)*
SUNY, Stonybrook, NY (C. Malbon); LMMB, NIAAA (M. McGuire)

LAB/BRANCH
Laboratory of Physiologic and Pharmacologic Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NIAAA, 12501 Washington Avenue, Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.3	3.3	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Earlier studies have demonstrated that cultured human lymphocytes produce protein factors, including interleukin-1 (IL-1), that upregulate beta-adrenergic receptors in cultured human lung tumor cells (A549 cells). In the present studies we further characterized the interactions between IL-1 and beta-adrenergic receptors. Picomolar concentrations of IL-1α, IL-1β and TNFα increase the density of beta-receptors, while a series of other cytokines are inactive. The effect of IL-1 develops over 24 hr, is inhibited by cycloheximide and is supraadditive with the similar effect of cortisol. Various antimitotic agents also upregulate beta-receptors in A549 cells, and IL-1 inhibits DNA synthesis and proliferation and enhances the adhesiveness of A549 cells. This suggests that upregulation of beta-receptors may be linked to the growth inhibitory, differentiating promoting action of IL-1. Analysis of beta-receptor subtypes indicates that A549 cells have both beta1 and beta2 receptors, and the expression of the beta2 but not of the beta1 subtype is regulated by cell density, IL-1 and glucocorticoids. Finally, beta-receptor stimulation in IM9 lymphocytes inhibits the release from these cells of IL-1 and Il-1-like bioactivity. These findings represent reciprocal interactions between the immune system and the sympathoadrenal system involved in stress responses.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00402-02 LPPS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Brainstem Neuromechanisms and Blood Pressure Regulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	G. Kunos	Laboratory Chief	LPPS NIAAA
Others:	J.A. Mastrianni	Staff Fellow	LPPS NIAAA
	A. Florentino	Special Volunteer	LPPS, NIAAA
	A. Hovanessian	Summer Student	LPPS, NIAAA

COOPERATING UNITS *(if any)*
LCB, NIMH (M. Palkovits)

LAB/BRANCH
Laboratory of Physiologic and Pharmacologic Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NIAAA, 12501 Washington Avenue, Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.7	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Interactions between catecholaminergic, endorphinergic and GABAergic neuronal systems at the level of the brainstem are important in the reflex regulation of blood pressure and heart rate. In a recently published study we presented evidence suggesting that endogenous opioid peptides acting on mu-type opiate receptors in the brain of the rat are involved not only in the cardiovascular but also in the analgesic action of the alpha2 adrenergic agonist, clonidine. The opioid-mediated component in cardiovascular depressor effects of clonidine can be localized to the parasympathetic outflow tract to the myocardium, as indicated by the results in another published paper. In a third study, we demonstrated that beta-endorphin-mediated hypotension, bradycardia and potentiation of baroreflex bradycardia can be triggered by activation of a neural pathway projecting from the hypothalamic arcuate nucleus to the nucleus tractus solitarii (NTS) in the dorsal medulla. Finally, we have found that activation of 'postsynaptic'-type GABA-B receptors in the NTS triggers hypertension, tachycardia and inhibition of baroreflex bradycardia, probably through inhibition of the release of the primary baroreflex transmitter. Current work is aimed to identify the nature of this transmitter and the type of receptor it activates by using receptor antagonists of amino acid neurotransmitters and antisera against certain neuropeptides. The above experimental models are also being used to study the mechanism(s) by which ethanol influences baroreflex activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00403-02 LPPS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Inverse Regulation of Hepatic Alphal and Beta-adrenergic Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	G. Kunos	Laboratory Chief	LPPS, NIAAA
Others:	E. Ishac	Visiting Associate	LPPS, NIAAA
	M. Grojec	Visiting Associate	LPPS, NIAAA
	M. Seo	Summer Student	LPPS, NIAAA

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Physiologic and Pharmacologic Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.6	2.6	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Hormones and neurotransmitters usually activate one of two major signal transduction pathways: one that acts through the second messenger cyclic AMP, the other being linked to membrane polyphosphoinositide breakdown and changes in the levels of intracellular calcium. An interesting example of 'crosstalk' between these signal transduction systems is the time-dependent change in the adrenergic activation of glycogenolysis in isolated rat liver cells from a calcium-linked alphal-type response to a cAMP linked beta-receptor-mediated event. Our studies in the last year further explored the mechanisms underlying this change. We have shown that the altered receptor response is evident at the level of the second messengers cAMP and IP3, suggesting that the changes occur at the level of the receptors or their immediate coupling to post-receptor pathways. We have also provided new evidence that supports the involvement of protein kinase C and arachidonic acid in the development of the altered hepatic receptor response. Finally, we found that although ethanol potently increases basal phosphorylase a activity with little or no tolerance developing to this effect, it does not affect the pattern of change in the hormonal stimulation of phosphorylase that is observed during prolonged in vitro incubation of isolated hepatocytes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA 00479-06 LPPS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Synaptic and Neurosecretory Mechanisms and Ethanol Actions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	F.F. Weight	Section Chief	LPPS, NIAAA
Others:	L.G. Aguayo	Staff Fellow	LPPS, NIAAA
	C.S. Rabe	Special Volunteer	USP, NIAAA

COOPERATING UNITS *(if any)*

Howard Hughes Medical Inst., Columbia U. (P. Yavari); Lab. Neurochem., NINDS, NIH (H.D. Pant)

LAB/BRANCH

Laboratory of Physiologic and Pharmacologic Studies

SECTION

Section of Electrophysiology

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Ethanol can alter the release of neurotransmitter from nerve terminals and the secretion of hormones from neuroendocrine cells; however, the cellular and molecular mechanisms involved in these actions have not been established. We have studied neurosecretory mechanisms and the effect of ethanol on those mechanisms in three preparations: (i) pineal cells; (ii) PC12 cells; and (iii) brain synaptosomes and microsomes. Membrane currents were studied in pineal cells acutely dissociated from adult rats using the whole-cell patch-clamp technique. Two distinct potassium currents were found, a transient current similar to the A current in neurons, and a slowly-activating sustained current similar to the delayed rectifier. At normal external calcium concentrations, no calcium currents that might trigger secretion, were observed. The relationship between intracellular calcium and neurosecretion was studied in the rat chromaffin cell line, PC12. The muscarine-stimulated release of catecholamine was found to be associatd with a mobilization of intracellular calcium. Ethanol inhibited both the release of neurotransmitter and increase of intracellular calcium induced by muscarine. In synaptosomes from rat brain, ethanol caused a release of neurotransmitter that was independent of external calcium concentration. The release of calcium from intracellular stores was studied in microsomes from rat brain; these vesicles are derived from endoplasmic reticulum. Ethanol induced a concentration-dependent release of calcium from the microsomes, but did not affect ATP-dependent calcium uptake in the microsomes. The results suggest that ethanol affects neurosecretory mechanisms by altering the release of calcium from intracellular storage sites similar to endoplasmic reticulum.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00480-06 LPPS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Nerve Cell Excitability and Ethanol Actions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

P.I.:	F.F. Weight	Section Chief	LPPS, NIAAA
Others:	J.E. Freedman	Staff Fellow	LPPS, NIAAA
	D.M. Lovinger	Staff Fellow	LPPS, NIAAA
	G.G. White	Staff Fellow	LPPS, NIAAA

COOPERATING UNITS *(if any)* Dept. of Physiology, Armed Forces Radiobiol. Res. Inst. (K.L. Zbicz); Dept. of Pharmacology, Med. Coll. of Georgia (S.R. Ikeda); Dept. of Physiology, Tulane Univ., Med. Sch. (G.G. Schofield); NINDS, Lab. Neurobiology (P.E. Gallant)

LAB/BRANCH
Laboratory of Physiologic and Pharmacologic Studies

SECTION
Section of Electrophysiology

INSTITUTE AND LOCATION
NIAAA, 12501 Washington Avenue, Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.8	3.8	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Although ethanol is known to affect the excitability of the nervous system, the cellular mechanisms underlying such actions are poorly understood. The objective of this project was to characterize the mechanisms regulating nerve cell excitability and the effects of ethanol on those mechanisms. The membrane ion currents that are involved in the regulation of neuronal excitability were investigated in mammalian neurons from nodose, superior cervical and dorsal root ganglia, and from corpus striatum and hippocampal regions of the CNS. Whole-cell patch-clamp experiments revealed a variety of voltage-activatd ion currents including tetrodotoxin(TTX)-sensitive and TTX-resistant Na currents, a low-threshold transient Ca current (T-type), a high-threshold sustained Ca current (L-type), a transient voltage-activated K current (A current), a sustained voltage-activated K current (delayed rectifier) and a sustained calcium-activated K current (C current). The proportion of these currents varied in different neurons and not all currents were found in all neurons. Ethanol appeared to have little or no effect on these voltage-activated currents in concentrations less than 100 mM. GABA-activated ion current was studied in actuely dissociated adult DRG neurons and found to have all of the pharmacologic properties of a GABA-A type response. Ethanol in concentrations from 10-100 mM had no effect on this GABA-activated current. The NMDA-activated ion current, on the other hand, was found to be inhibited by ethanol. The inhibition increased in a concentration dependent manner over the concentration range 5-50 mM, a range that produces intoxication. The potency for inhibition of the NMDA-activated current by several alcohols was linearly related to their intoxicating potency, suggesting that the alcohol-induced inhibition of responses to NMDA receptor activation may contribute to the neural and cognitive impairments associated with intoxication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA00700-05 LPPS

PERIOD COVERED

October 1, 1988 - September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Ethanol Effects on Membrane-Bound Enzymes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.L. Hoffman	Section Chief	LPPS, NIAAA
	B. Tabakoff	Scientific Director	NIAAA
Others:	F. Moses	Guest Researcher	USP, NIAAA
	J.P. Whelan	Staff Fellow	LPPS, NIAAA
	L. Karrberg	Special Volunteer	USP, NIAAA
	J. Contrera	Special Volunteer	USP, NIAAA

COOPERATING UNITS *(if any)* Karolinska Institute, Sweden (S. Borg); University of Minnesota, Minneapolis (J.A. Halikas); LCS, NIAAA (D. Goldman); Washington Univ., School of Medicine, St. Louis (E. DeVor); VA Med. Ctr., San Diego (M. Schuckit); MDB, NIDDKD (A.M. Spiegel)

LAB/BRANCH

Laboratory of Physiologic and Pharmacologic Studies

SECTION

Section on Receptor Mechanisms

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.2	1.7	2.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It has been hypothesized that the actions of ethanol result from its ability to perturb the structure of neuronal membrane lipids. Changes in the activities of membrane-bound enzymes, which are modulated by the properties of surrounding lipids, may indicate specific sites of action of ethanol within the neuronal membrane, and may persist beyond the time that ethanol is present in tissues, therefore serving as objective measures of alcohol consumption. It has also been postulated that the activities of certain enzymes may be markers of a genetic predisposition to alcoholism. We previously showed that low platelet adenylate cyclase (AC) activity, and an increased sensitivity of platelet monoamine oxidase (MAO) to in vitro inhibition by ethanol, effectively discriminated alcoholic and non-alcoholic individuals. The difference in platelet AC activity was long-lasting and suggested that the properties of Gs, the stimulatory guanine nucleotide binding protein, could be a candidate as a genetic marker. To assess these possibilities, we are currently measuring fluoride-stimulated AC activity in a population of twins, in families with alcoholic and non-alcoholic members, in alcoholics being screened for several other possible genetic markers of alcoholism, and in individuals with positive (FHP) and negative (FHN) family histories of alcoholism. We have also measured Gs-alpha in platelet membranes of a group of alcoholic and non-alcoholic individuals by Western and slot blot analyses, and have found no significant correlation of amount of Gs-alpha with AC activity. These data suggest that the lower AC activity in platelets of alcoholics may arise from a qualitative, rather than quantitative defect in Gs. The studies described will help to determine whether the observed differences in platelet enzyme activities between alcoholics and non-alcoholics are genetically based, and may be a marker for a predisposition to alcoholism, or are a consequence of ethanol consumption.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA00702-05 LPPS

PERIOD COVERED

October 1, 1988 - September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Ethanol Modification on Neurotransmitter Receptor-Effector Coupling

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.L. Hoffman	Section Chief	LPPS, NIAAA
	B. Tabakoff	Scientific Director	NIAAA
Others:	P. Valverius	Visiting Associate	LPPS, NIAAA
	A. Rius	Visiting Fellow	LPPS, NIAAA
	J.P. Whelan	Staff Fellow	LPPS, NIAAA
	J. Dave	Senior Staff Fellow	LPPS, NIAAA
	K. Grant	Staff Fellow	USP, NIAAA

COOPERATING UNITS *(if any)*

Kings College, London (M. Hudspith); Metabolic Disease Branch, NIDDKD (A.M. Spiegel)

LAB/BRANCH

Laboratory of Physiologic and Pharmacologic Studies

SECTION

Section on Receptor Mechanisms

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.4	3.4	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Ethanol selectively alters the function of neurotransmitter and neuromodulator receptors in the CNS, and adaptations in receptor function may be associated with ethanol tolerance and/or physical dependence. Previous work showed decreased stimulation of adenylate cyclase by various agonists and by guanine nucleotides, and decreased high-affinity binding of a beta-adrenergic agonist in certain brain regions of mice fed ethanol chronically. Decreased high-affinity beta-adrenergic agonist binding has now also been found in post-mortem brain tissue of human alcoholics. The data suggested a quantitative or qualitative change in Gs, the stimulatory guanine nucleotide binding protein. This hypothesis was supported by a demonstration of reduced availability for cholera toxin-induced ADP-ribosylation of a protein migrating like Gs-alpha on SDS-polyacrylamide gels. Quantitation of Gs-alpha by Western blot analysis in cerebral cortex of mice fed ethanol chronically shows that the amount of one form of the protein (the 46 kDa form) is increased, while the 52 kDa form, and Gi-alpha, are unchanged. Preliminary studies show a decrease in Gs-alpha mRNA in brains of these mice. These data suggest decreased turnover of Gs in brains of ethanol-fed mice. The altered ribosylation and "heterologous desensitization" of adenylate cyclase, however, suggest a functional change in Gs. Another receptor system that changes in mice fed ethanol chronically is the NMDA receptor. There is an increase in NMDA receptors, measured by 3H-MK-801 binding, in hippocampus and cerebellum, but not cortex. This up-regulation of receptors may reflect an adaptation to the acute inhibitory effects of ethanol (see AA0705), and may be associated with the appearance of ethanol withdrawal seizures. One consequence of such seizures, possibly related to the increase in NMDA receptors and consequent calcium influx, is a large increase in brain levels of mRNA for the proto-oncogene, c-fos. This oncogene is believed to affect CNS plasticity, and its activation after ethanol withdrawal seizures may lead to long-term changes in CNS function.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA00703-05 LPPS

PERIOD COVERED

October 1, 1988 - September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurohypophyseal Peptides and Ethanol Tolerance

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.L. Hoffman	Section Chief	LPPS, NIAAA
Others:	L. Liu	Guest Researcher	USP, NIAAA
	J.R. Dave	Senior Staff Fellow	LPPS, NIAAA
	P. Rathna Giri	Visiting Associate	LPPS, NIAAA
	K. Gulya	Visiting Associate	LPPS, NIAAA

COOPERATING UNITS *(if any)*

LCB, NIMH (S. Young); LCS, NIAAA (J. Karanian)

LAB/BRANCH

Laboratory of Physiologic and Pharmacologic Studies

SECTION

Section on Receptor Mechanisms

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	2.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Arginine vasopressin (AVP) and related peptides, when administered exogenously, prolong the duration of tolerance to ethanol. We have characterized the receptors in mouse brain that mediate this effect as V-1 receptors. Autoradiographic studies revealed a high density of receptors in lateral septum, with lower densities in other limbic areas. The lateral septal receptors were characterized as V-1, and studies with the neurotoxin 6-hydroxydopamine suggested that a portion of these receptors is localized on presynaptic terminals of noradrenergic and/or dopaminergic neurons. Thus, AVP may modulate tolerance by influencing neurotransmitter release. Another possible (postsynaptic) action of AVP is stimulation of the expression of the proto-oncogene, c-fos, which is postulated to play a role in learning or memory. AVP, acting at V-1 receptors, increased levels of c-fos mRNA in mouse septum and hippocampus, but not cerebral cortex, after intracerebroventricular injection. Comparison with the effects of oxytocin and nerve growth factor on c-fos stimulation and maintenance of tolerance suggested that the AVP-induced increase in the synthesis of c-fos in the septum is important for the effect of the peptide on tolerance. Our work also showed that endogenous AVP plays a role in maintenance of ethanol tolerance, leading us to investigate AVP synthesis during chronic ethanol treatment. In mice, hypothalamic AVP mRNA levels were greatly decreased following chronic ethanol ingestion. Although plasma osmolarity was increased in these mice, suggestive of dehydration, plasma vasopressin levels were not increased. Similar results were obtained with vasopressin mRNA in rats, although the effects on plasma AVP levels were somewhat different. The results suggest that ethanol exposure may decrease AVP synthesis and interfere with the regulation of AVP secretion. Understanding the mechanism by which AVP influences tolerance to ethanol may lead to benign means for the manipulation of tolerance and, possibly, of ethanol intake.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA00705-03 LPPS

PERIOD COVERED

October 1, 1988 - September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

In Vitro Models for Ethanol Effects on Receptor-Mediated Processes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.L. Hoffman	Section Chief	LPPS, NIAAA
	B. Tabakoff	Scientific Director	NIAAA
Other:	F. Moses	Guest Researcher	USP, NIAAA

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Physiologic and Pharmacologic Studies

SECTION

Section on Receptor Mechanisms

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A major focus of our work involves an evaluation of the acute and chronic effects of ethanol in the CNS. However, the brain represents a heterogeneous collection of cell types, and distinction of direct and indirect effects of ethanol can be difficult. In vitro cell culture systems can be used to monitor specific, direct effects of ethanol, for comparison and contrast with results obtained in brain tissue and in vivo. Using a primary culture of cerebellar granule cells, we found that ethanol, at low concentrations, inhibited glutamate-stimulated cyclic GMP production. Cyclic GMP production stimulated by atrial natriuretic peptide (ANP) was much less sensitive to inhibition by ethanol. The results suggested that glutamate receptor-effector coupling is altered by ethanol. In these cells, glutamate-stimulated cyclic GMP production, which is calcium-dependent, is mediated by kainate and N-methyl-D-aspartate (NMDA) receptors. Ethanol was a more potent inhibitor of the response to NMDA than the response to kainate, and produced substantial inhibition at pharmacologically-relevant concentrations. The effect of ethanol on the cyclic GMP response did not appear to involve an action at the GABA receptor-coupled chloride channel, and, although both ethanol and phencyclidine inhibited the response, these two agents did not interact in inhibiting NMDA-stimulated cyclic GMP production. However, glycine enhancement of the cyclic GMP response to NMDA was reduced in the presence of ethanol. The results suggest a specific site of action for ethanol within the NMDA receptor-gated channel, i.e., ethanol may interfere with the ability of the co-agonists, glycine and NMDA, to modify the permeability of the receptor-operated ion channel. NMDA receptors are involved in neuronal plasticity and development, as well as epileptiform seizures, and these results therefore suggest possible mechanisms for ethanol's effects on memory and fetal development, as well as for withdrawal symptoms that occur following chronic ethanol ingestion.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 AA 00405-02 LPPS

PERIOD COVERED
October 1, 1988 to September 30,1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Detection and regulation of specific cellular phosphoproteins

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.M. Martensen	Research Chemist	LPPS, NIAAA
Others:	R.L. Kincaid	Section Chief	LPPS, NIAAA

COOPERATING UNITS *(if any)*
Johns Hopkins Univ. (M.D. Lane); Lab. of Molec Immunoregulation, NCI, NIH (W. Farrar); Univ. of Madrid (M. Mazon) Lab. of Molecular Neurogenetics, NIMH, ADAMHA (B. Martin)

LAB/BRANCH
Laboratory of Physiologic and Pharmacologic Studies

SECTION
Immunology

INSTITUTE AND LOCATION
NIAAA, 12501 Washington Ave., Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Immunoadsorption of phosphotyrosine-containing proteins from cells was utilized to detect proteins that were targets for protein tyrosine kinase (ptk) activity involved in signal transduction. Interleukin-3 which induces the proliferation of an immune cell line, FDC-P1, activated a ptk activity. Some of the substrates of the ptk contained phosphorylated serine/threonine residues indicating these proteins were targets of two different protein kinase activities. A proliferative response to phorbol ester of this cell line involves the activation of protein kinase C. Phorbol ester administered to the cells also activated ptk activity that targeted many of the same proteins seen above. Growth control here results in cooperative activities of two seperate kinase activities. Synthetic peptides comprising domains common to several phosphoprotein phosphatases were utilized to produce antibodies to detect cross-reacting proteins in various cells and tissues. Antibodies that were purified from peptide-Sepharose columns bound to calcineurin (CN) or recombinant proteins containing the peptide-immunogenic domains on Western blots. The Ca2+/CaM-dependent protein phosphatase CN was phosphorylated by Ca2+/CaM-dependent protein kinase II. Cleavage of radiolabeled CN by CNBr and separation of peptides by HPLC demonstrated a single labeled peptide containing phosphoserine (Ser-P). Sequencing the peptide and knowledge of the structure of methionyl peptides deduced from the cDNA of CN enabled the position the Ser-P modification site to be identified; it was juxtaposed with the CaM binding site. The residue was resistant to autocatalytic hydrolysis unless stimulated by effectors of CN phosphatase activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA 00404-02 LPPS

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Control of calcium and phosphorylation-regulated signalling pathways

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R.L. Kincaid	Section Chief	LPPS, NIAAA
Others:	T.M. Martensen	Research Chemist	LPPS, NIAAA
	J. Tamura	Visiting Fellow	LPPS, NIAAA
	S. Higuchi	Guest Worker	LPPS, NIAAA
	S.C. Dixon	Microbiologist	LPPS, NIAAA
	C.A. Marietta	Research Physiologist	LPPS, NIAAA
	P.R. Giri	Visiting Associate	LPPS, NIAAA

COOPERATING UNITS *(if any)* Penn State Univ. (M.L. Billingsley, C.D. Balaban); Lab. of Immunology, NIAID, NIH (M. Sitkovsky); Univ. of Rome (R. Geremia) Molec. Neurogenetics Branch, NIMH, ADAMHA, (B.M. Martin); Albert Einstein College of Medicine (G.A. Orr)

LAB/BRANCH
Laboratory of Physiologic and Pharmacologic Studies

SECTION
Immunology

INSTITUTE AND LOCATION
NIAAA, 12501 Washington Ave., Rockville, MD 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.4	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Molecular characterizations of the calmodulin(CaM)-dependent protein phosphatase, calcineurin (CN) and phosphodiesterase (PDE) are being carried out. Analysis of cDNA and genomic clones from yeast, mouse and human libraries indicate multiple forms of the catalytic subunit of CN. These all contain a highly conserved region (35-45% identity with other mammalian phosphatases) fused to a CaM-binding regulatory domain; a 24 residue peptide based on the latter inhibits activity by blocking CaM interaction with the phosphatase. Tissue-specific mRNAs were observed in brain, muscle and testis, suggesting alternative splicing of the gene for this enzyme. Phosphorylation of CN by CaM-dependent protein kinase was demonstrated on a serine near the CaM-binding domain, causing a slight increase in phosphatase activity toward P-Inhibitor I. The existence of molecular isoforms and their ability to be modified covalently may provide for complex, substrate-specific modes of regulation by this protein phosphatase. In brain, the CaM-dependent isoform of PDE is selectively expressed in the dendrites and soma of cerebellar Purkinje cells and pharmacologic denervation of excitatory climbing fiber input to these neurons causes an immediate, marked loss of PDE immunoreactivity; such findings suggest that PDE gene expression in some differentiated neurons may be regulated in a trans-synaptic manner. Recent developmental studies show that the appearence of rat brain PDE does coincide with periods of extensive synaptogenesis. However, some regions (e.g., midbrain) showed expression in early stages that diminished as development progressed, implying that PDE may be required for establishing neuronal patterns in specific areas.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA00707-01 USP

PERIOD COVERED

October 1, 1988 - September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Discriminative Stimulus Effects of Ethanol

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

PI:	K.A. Grant	Staff Fellow	USP, NIAAA
	B. Tabakoff	Scientific Director	NIAAA

COOPERATING UNITS *(if any)*

Uniformed Services University of Health Sciences, Bethesda (J. Barrett)

LAB/BRANCH

Unit for Special Projects

SECTION

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The discriminative stimulus properties of ethanol were investigated using pigeons and orally administered ethanol. This procedure can be used to determine if specific neurotransmitter systems are involved in acute behavioral action of centrally active drugs. Since both biochemical and electrophysiological data indicate that ethanol antagonizes N-methyl-D-aspartate (NMDA) neurotransmission, a drug discrimination procedure was implemented to investigate if acute behavioral effects of ethanol were mediated through NMDA antagonism.

Subjects were trained to discriminate between the effects of 1.5 g/kg ethanol (i.g.) and water under a fixed-ratio 30 schedule of food reinforcement. After the pigeons reach the criteria set for demonstrating discrimination, test sessions were conducted in which ethanol and a series of NMDA antagonists were administered. The dissociative anesthetic phencyclidine (PCP) and the related arylcyclohexylamine ketamine completed substituted for ethanol at doses that were void of nonspecific decrements in behavior. The specific noncompetitive antagonist of NMDA-associated calcium channels, MK-801, resulted in complete generalization from the ethanol cue, however, only at a dose that also disrupted rates of responding. The results indicate that PCP, ketamine and MK-801 have discriminative stimulus effects similar to those of ethanol. Since all these compounds are known to antagonize NMDA neurotransmission, the results suggest that some of the discriminative stimulus effects of ethanol are mediated by antagonism of NMDA. Thus, the antagonism of the NMDA/calcium channel complex found in in vitro biochemical and electrophysiological studies can also be demonstrated in acute behavioral preparations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 AA00706-01 USP

PERIOD COVERED: October 1, 1988 - September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effects of Ethanol on NMDA-mediated Neuronal Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	C.S. Rabe	Special Volunteer	USP, NIAAA
	B. Tabakoff	Scientific Director	NIAAA
Other:	J. Contrera	Special Volunteer	USP, NIAAA

COOPERATING UNITS (if any)

NONE

LAB/BRANCH: Unit for Special Projects

SECTION:

INSTITUTE AND LOCATION: NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.75	1.25	.50

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

One of the potential mechanisms by which ethanol might produce its characteristic central nervous system (CNS) depression is through direct inhibition of excitatory transmission. Glutamate is the most abundant excitatory neurotransmitter present in the CNS. Therefore, we have begun examining the effect of ethanol on glutamate-mediated transmission in cultures of cerebellar neurons.

Glutamate acts through at least three independent receptors subtypes to produce stimulation of neurons: the NMDA, kainate and quisqualate receptors. Of these receptors, the NMDA receptor was found to be most sensitive to inhibition by ethanol. At physiologically relevant concentrations, NMDA-stimulated calcium uptake was inhibited by ethanol to a much greater extent than was kainate-stimulated calcium uptake.

NMDA receptor activity is regulated by a number of factors. In addition to NMDA binding to its receptor and opening the associated ionophore, channel function may be regulated by additional agents which act at sites other than the NMDA binding site. For example, Mg^{2+} binds within the ion channel to block ion flux through the ionophore. PCP-like drugs also bind within the channel (but at a site different than the Mg^{2+} binding site) to block ion flux. Zn^{2+} binds to the receptor ionophore complex to reduce channel opening frequency. Finally, glycine binds to the complex to potentiate channel opening. Preliminary results indicate that the mechanism whereby ethanol produces depression of ion flux may involve the glycine receptor, since at high concentrations, glycine is able to reverse ethanol induced depression of ion flux through the channel. In contrast, the efficacy of Mg^{2+}- and PCP-induced depression of calcium flux through the ionophore is unchanged by ethanol.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AA00400-04 USP

PERIOD COVERED

October 1, 1988 - September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Selective Breeding for Ethanol Tolerance

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K.A. Grant	Staff Fellow	USP, NIAAA
	B. Tabakoff	Scientific Director	NIAAA
Other:	P.L. Hoffman	Section Chief	LPPS, NIAAA

COOPERATING UNITS *(if any)*

VRB, SAS, NIH (N. Watson, W. Jackson, C. Hansen); BIOCON, Rockville (B. Till)

LAB/BRANCH

Unit for Special Projects

SECTION

INSTITUTE AND LOCATION

NIAAA, 12501 Washington Avenue, Rockville, Maryland 20852

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	0.8	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This experiment examines if tolerance to ethanol following chronic exposure is influenced by genetic factors. Selective breeding pressure will be placed on the degree of tolerance attained by rats from a genetically heterogeneous stock. Based on the results of previous studies showing the development of chronic tolerance in the N:NIH outbred rat stock was widely distributed, unimodal, and without sex differences a selective breeding program was initiated. Sixty pairs of rats (one male and one female) from the original gene pool were obtained and ranked according to the degree of tolerance obtained. From these original 60 pairs, 40 control rats (20 male and 20 female) were randomly selected and paired, 40 high tolerant rats were selected on the basis of their tolerance development and 40 low tolerant rats were selected. Two replicate lines of the control, high tolerant and low tolerant rats, each composed of 10 breeding pairs were then assigned with the restriction that the breeding pairs had no common parents or grandparents. The offspring of these breeders (the S(0) generation) were than tested for the development of chronic tolerance to ethanol and assigned mates according to a rotational breeding scheme. Their offspring will be the first selected generation for the project. When the selection is complete, the animals of each selected line will theoretically contain all alleles associated with the selected trait, while alleles not associated with the trait will be randomly distributed. Thus, these animals will be a resource for investigators interested in neurobiological and behavioral correlates of chronic functional tolerance to ethanol.

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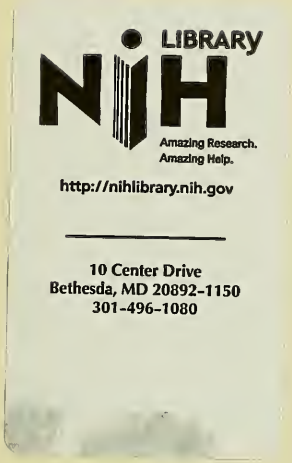

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