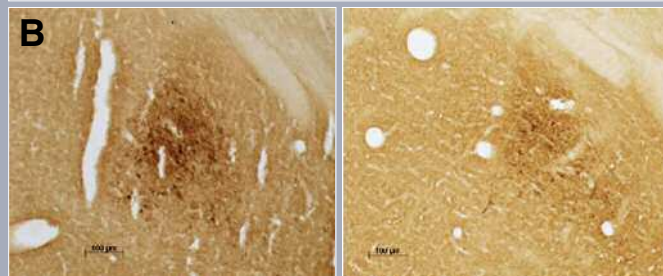
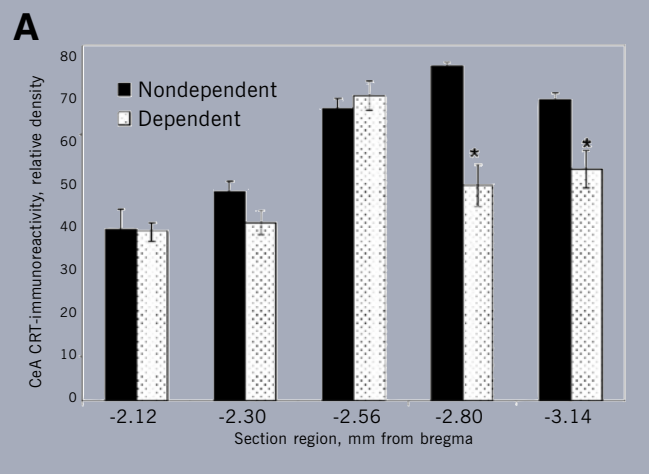


## Committee on the Neurobiology of Addictive Disorders

Corticotropin-releasing factor (CRF) immunoreactivity in the central nucleus of the amygdala (CeA). Ethanol dependence was induced by intermittent exposure to ethanol vapors for 4 weeks, and animals were sacrificed after 2 hours of withdrawal. Brains were removed, and CRF expression was measured in the CeA by using immunohistochemical techniques. The data are expressed as the relative density of CRF immunoreactivity (n = 3 animals).

A, CRF immunoreactivity was measured from 5 serial sections throughout the CeA. From bregma, these sections were -2.12 mm, -2.30 mm, -2.56 mm, -2.80 mm, and -3.14 mm. CRF immunoreactivity was significantly decreased in the CeA at bregma -2.80 and -3.14 in withdrawn, dependent animals relative to control animals. B, Representative micrographs (20x) from the CeA (bregma -2.80 mm) show CRF staining within this brain region. \* P < .01 compared with nondependent animals. Bar graph by Cindy Funk, Ph.D., research associate; immunohistochemical brain photo, by Elena Crawford, scientific associate. Work done in the laboratory of G.F. Koob, Ph.D., professor. Reprinted with permission from Funk, C.K., O'Dell L.E., Crawford, E.F., Koob, G.F. Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. *J. Neurosci.* 26:11324, 2006. Copyright 2006 by the Society for Neuroscience.





*Lily Alvarez, Ph.D., Research Associate, and  
Loren Parson, Ph.D., Associate Professor*

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*George Koob, Ph.D.*

## Chairman's Overview

The faculty of the Committee on the Neurobiology of Addictive Disorders consists of 6 faculty members with a common goal of understanding the function of the brain emotional systems and how these systems malfunction in disease. We focus on the neurobiological mechanisms involved in motivated and emotional behavior and how these mechanisms are altered with the development of addiction, stress, and eating disorders. We integrate and translate basic research findings across multiple domains, from molecular cell biology to neurocircuitry to clinical studies. The committee also forms the foundation for the Pearson Center for Alcoholism and Addiction Research, with the goal of developing novel medications for the treatment of addictive disorders. Here, I summarize what we are doing and the background that led to this work.

Barbara Mason has been a leader in developing treatment of psychiatric disorders, including depression and addiction. Currently, she is involved in the clinical evaluation of medications for the treatment of substance dependence. The goal of ongoing studies in her laboratory is to develop medications that reduce the risk of relapse and the signs and symptoms of protracted absti-

nence. The approach involves short-term laboratory studies in humans and long-term, double-blind, placebo-controlled clinical trials. The topic of her current research funded by the National Institutes of Health is the development of new pharmacologic treatments for alcohol and cannabis dependence. Dr. Mason and I are codirectors of the Pearson Center for Alcoholism and Addiction Research. She is a current recipient of a Merit Award from the National Institute on Alcohol Abuse and Alcoholism.

In my own laboratory, we focus on neurobiological changes associated with prolonged access to drugs of abuse. Previously, we found that extended access to intravenous self-administration of cocaine produced not only a progressive increase in drug intake (escalation) but also significant reward deficits in animals with such escalation. We have now observed similar escalation in drug intake with prolonged access to methamphetamine, opioids, and nicotine. These animal models of excessive drug intake have been extended to alcohol. Animals are made dependent on alcohol and then are allowed access to alcohol during acute withdrawal. We found that drinking in alcohol-dependent rodents was 3–4 times that of nondependent animals. Dependence-induced drinking is selectively blocked by systemic administration of corticotropin-releasing factor 1 receptor antagonists, and the neurobiological area involved in corticotropin-releasing factor antagonism appears to be the central nucleus of the amygdala. These results suggest that a common component of extended access to drugs is the development of compulsive use concomitant with the development of dependence.

Michael Taffe has a major interest in the physiologic, motivational, and cognitive sequelae of use and abuse of drugs of abuse. Dr. Taffe directs the primate neurobehavioral laboratory and currently is engaged in bridging our cellular neurobiological studies in the research in rodents to the human clinical situation. Using rhesus macaques, he has discovered that 3,4-methylenedioxy-methamphetamine (MDMA; also known as "Ecstasy") and associated amphetamine drugs produce profound hyperthermia that is not a direct result of increases in activity produced by these drugs.

Loren (Larry) Parsons has a long-term interest in the neurochemical and neuropharmacologic changes that occur in critical brain motivational circuits associated with reward dysregulation in addiction. Currently, he is examining how self-administration of drugs of abuse affect endogenous endocannabinoids in the brain. Dr. Parsons and his team have identified specific endo-

cannabinoid effects in specific brain areas linked to specific components of the drug-dependence cycle: drug reward, withdrawal, and reinstatement of drug seeking. Alcohol withdrawal is associated with decreases in endocannabinoid activities in the central nucleus of the amygdala, providing a potential key component of neuroadaptation associated with alcohol dependence.

Eric Zorrilla is investigating how the brain reward and stress systems control food intake, an area of great current relevance because of the high incidence of obesity in the United States and the resulting health consequences. In collaboration with K.D. Janda, Department of Chemistry, Dr. Zorrilla and his team have identified ghrelin, a key player in the control of appetite. Ghrelin is produced by the stomach and signals to the brain a requirement for energy. Passive immunization with transfer of antibodies to ghrelin slowed the accumulation of body weight in rats. In addition, Dr. Zorrilla and his team have begun to characterize a pattern of bingelike intake of preferred food that produces a physiologic profile similar to some aspects of addictive-like behavior. The neurobiological basis of this phenomenon is being explored.

Marisa Roberto is exploring the effects of drugs of abuse on the cellular physiology of the central nucleus of the amygdala, a key structure in the brain involved in emotional processing. Using cellular recording of neuronal activity in slices of the amygdala, Dr. Roberto and members of her laboratory have identified key changes in the activity of both GABAergic and glutamatergic neurons associated with acute and chronic exposure to alcohol. Even more exciting, the effects of alcohol on the activity of these neurons appear to be mediated by actions on neuropeptides such as corticotropin-releasing factor and nociceptin, which have a key role in mediating neuroadaptation to the actions of alcohol. These studies provide a key translation of the neurocircuitry and neuropharmacologic studies of the Committee on the Neurobiology of Addictive Disorders to the level of cellular interactions.

Chitra Mandyam has been recruited as an assistant professor. She is a cell biologist/neuroscientist who will investigate how stress and drugs of abuse alter the neuroplasticity of the brain in adults. She and members of her group examine changes in the birth, survival, and dynamics of neurons in adults. Dr. Mandyam uses techniques including immunohistochemistry, immunoblotting, and in situ hybridization to answer specific questions about neuroadaptations produced by stress and drugs of abuse that can lead to psychiatric disorders and pathologic changes in the brain.

## INVESTIGATORS' REPORTS

### Neurobiology of Addiction

G.F. Koob, B.J. Mason, L.H. Parsons, M.A. Taffe, E.P. Zorrilla, M. Roberto, C. Mandyam, H.N. Richardson, R.H. Purdy,\* K.R. Buffkins, M. Le Moal,\*\* S.H. Ahmed, L. Stinus,\*\* L. Pulvirenti,\*\*\* K. Inoue,\*\*\*\* A. Tabarin,\*\*\*\*\* Y. Zhao, V. Sabino, C.K. Funk, R. Crean, B.M. Walker, T.N. Greenwell, S. Wee, N. Gilpin, O. George, L. Alvarez, P. Cottone, L. Orio, K. Misra, M. Cruz, R. Lintz, I. Polis, E. Crawford, R. Schroeder, T. Kimber, M. Cole, M.A. Arends, M. Brennan, S. Davis, D. Stouffer, Y. Grant, S. Quello, K. Morikawa

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In the Laboratory of Psychopharmacology, we continue to focus on the neuropharmacologic mechanisms involved in motivated and emotional behavior and how these mechanisms are altered in addiction, stress, and genetic variability.

In studies on the neurobiology of addiction, we continue to explore the role of neurochemical systems in the extended amygdala in the neuroadaptations associated with the transition from drug taking to drug dependence that is an integral part of the development of addiction. We are developing animal models for excessive drug intake and charting the changes in neurocircuitry associated with such intake.

#### ANIMAL MODELS OF ESCALATED DRUG INTAKE WITH PROLONGED ACCESS

Previous research established that prolonged access to cocaine and alcohol can produce progressive increases in drug intake that are paralleled by decreases in reward function. This escalation in drug intake is paralleled also by decreased reward, as indicated by elevations in thresholds for intracranial self-stimulation. More recent studies suggest that a similar escalation in drug intake with prolonged access also can occur with intake of methamphetamine, opioids, and nicotine.

Animals with prolonged 6-hour access to methamphetamine intake showed pronounced escalation, whereas animals with 1-hour access to the drug showed no escalation. Chronic exposure to methamphetamine produced a withdrawal syndrome, as indicated by

decreases in appetitive responding for a sweetened solution. Similarly, 23 hours of access to heroin produced strong escalation in heroin intake and resulted in dependence, as indicated by both motivational and physical signs of withdrawal. More importantly, in rats with 23 hours of access to heroin, sensitive measures of diurnal activity and meal patterns revealed early signs of the onset of dependence. Access to nicotine for 23 hours also produced motivational and physical dependence, as indicated by physical signs, anxiety-like behavior, measures of meal patterns, and measures of diurnal activity. A marked increase in nicotine intake occurred during 23 hours of access after deprivation from access to the drug. This nicotine deprivation effect is long-lasting and increases with repeated deprivations.

These results suggest that a common component of extended access to drugs is the development of compulsive use concomitant with the development of dependence. This compulsive use not only has face validity for the human condition but also heuristic value for exploring the neurobiological mechanisms associated with the development of dependence.

#### DEPENDENCE-INDUCED INTAKE OF ALCOHOL

The animal models of excessive drug intake have been extended to alcohol; animals are made dependent on alcohol and then allowed access to it during acute withdrawal. Withdrawal-induced drinking in these animals is 3–4 times greater than drinking in nondependent animals. Dependence-induced drinking is selectively blocked by systemic administration of antagonists selective for receptor 1 of corticotropin-releasing factor (CRF<sub>1</sub>).

The neurobiological substrate for CRF antagonism appears to be the central nucleus of the amygdala. Administration of a combined CRF<sub>1</sub>/CRF<sub>2</sub> peptide antagonist into the central nucleus of the amygdala dose dependently reversed the excessive drinking associated with alcohol dependence. No effect was observed in nondependent animals. Microinjections of the antagonist into the bed nucleus of the stria terminalis and shell of the nucleus accumbens had no effect. The alcohol-dependent animals also had decreases in CRF immunoreactivity in the central nucleus of the amygdala at the same time point during withdrawal, suggesting increased release of CRF. Taken together, these results suggest a powerful contribution of increased CRF activity in the central nucleus of the amygdala to the motivation for excessive drinking in alcohol dependence.

**NEUROCIRCUITS IN ADDICTION**

The conceptual framework for the neurobiological changes that drive addiction continue to evolve. Three major neurocircuits have been identified in the brain that drive different components of the addiction process: the reward circuit in the nucleus accumbens involving dopamine and opioid peptides as prominent neurochemical components, the antireward circuit in the extended amygdala involving CRF and other neuromodulatory agents as prominent neurochemical components, and the craving circuit in the prefrontal cortex involving glutamatergic connections. Studies in humans and animals have revealed at least 3 common components of addiction: decreases in reward, increases in brain stress systems, and hypofunctioning of the prefrontal cortex associated with impulsivity and impaired decision making. The identification of explicit neurocircuitry and neurochemical elements in the different stages of the addiction cycle provides a conceptual framework for identifying molecular targets for individual differences that underlie vulnerability to pathologic changes that affect the emotional systems of the brain.

**MEDICATIONS FOR TREATMENT OF ADDICTION**

An additional thrust of the Laboratory of Psychopharmacology and the Pearson Center for Alcoholism and Addiction Research has been to develop novel medications for the treatment of addiction. The combination of information from animal models and data from studies in humans has provided a conceptual framework not only for developing new medications for the clinic but also for validating the animal models. Animal models that have indicated targets for medications that may be selective for treatment of addiction include extended-access intravenous self-administration, dependence-induced drinking, and binge drinking. Drugs such as naltrexone and acamprosate (which are on the market for treatment of alcoholism) have shown efficacy in these models. Novel targets such as nalmefene and a GABAergic modulator have also been explored.

Additional studies in the development of medication include collaborations with K.D. Janda, Department of Chemistry, in which novel immunologic and chemical-immunologic approaches are used in the pharmacologic characterization of novel approaches to drug elimination. Immunoconjugates that induce an effective immune response to  $\Delta^9$ -tetrahydrocannabinol, the active ingredient in marijuana, and catalytic antibodies capable of degrading  $\Delta^9$ -tetrahydrocannabinol developed by Dr. Janda and coworkers may be useful

for future immunopharmacologic approaches to treatment of addiction.

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## Laboratory of Clinical Psychopharmacology

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The focus of research in the Laboratory of Clinical Psychopharmacology, the clinical component of the Pearson Center for Alcoholism and Addiction Research, is the clinical evaluation of medications for treatment of substance dependence. Our primary aim is to reduce the risk of relapse and the signs and symptoms of protracted abstinence, such as disturbances of mood and sleep, associated with an increased risk for relapse. Projects range from proof-of-concept early-phase laboratory studies in humans to long-term, double-blind placebo-controlled studies of clinical efficacy.

A critical aspect of our conceptual framework is dynamic feedback from the scientists involved in preclinical and clinical studies, which are designed to streamline information and provide converging evidence for ultimate clinical use of medications. We also anticipate that the results of the clinical laboratory studies will in turn be useful in the preclinical animal studies to further refine basic research involving animal models and the neuropharmacologic approach. Using this approach, we have identified areas of research that are being translated into long-term studies of the clinical efficacy of various medications for treatment of alcohol, nicotine, and cannabis dependence.

### DEVELOPMENT OF A HUMAN LABORATORY MODEL

We developed a human experimental model of various components of the alcoholism cycle. We use cue reactivity and mood induction techniques in the laboratory and assessment of substance use, mood, and sleep under natural conditions. The parameters of the model are used to evaluate potential treatments for various components of the alcoholism cycle.

In an important validation study of the model, we found that acamprosate, a medication approved by the Food and Drug Administration to reduce relapse in early abstinence from alcohol, is highly involved in mediating responsivity to affective as well as alcohol cues in recently abstinent patients with alcoholism. A 5-year renewal of this project by the National Institute on Alcohol Abuse and Alcoholism enables us to use the model to rapidly screen medications that may prevent relapse to drinking.

### CLINICAL RESEARCH

We obtained positive results in our proof-of-concept human laboratory study of a nonaddicting GABAergic modulator in non-treatment-seeking individuals with alcohol dependence. For example, compared with a placebo, the modulator significantly reduced measures of craving in response to alcohol cues. We are currently conducting a 12-week, double-blind, placebo-controlled, dose-ranging study to evaluate this drug as a treatment for drinking relapse and for the signs and symptoms of protracted abstinence, such as craving, anxiety, and insomnia, that may occur after acute alcohol withdrawal and that can precipitate a relapse to drinking. The study sample will consist of 150 recently abstinent outpatient volunteers who are alcohol dependent. This project is funded by the National Institute on Alcohol Abuse and Alcoholism.

We also have received funding from the National Institute on Drug Abuse to conduct a 12-week, double-blind, placebo-controlled study of a GABAergic modulating drug as a potential treatment for cannabis dependence. We hypothesize that this drug will improve signs and symptoms of cannabis withdrawal and, as a result, facilitate setting a quit date, promote longer-term abstinence, and decrease the risk and severity of relapse to cannabis use.

We recently received funding from the National Institute on Drug Abuse to develop a translational research center for neurobiological studies on the development of cannabis dependence. As designed, the center will draw together a critical mass of investigators to explore the neurobiological basis for the development of cannabis dependence, identify the mechanisms for vulnerability to this dependence, and characterize the potential cognitive pathologic changes associated with cannabis abuse and dependence.

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## Neurochemistry of Addiction

L.H. Parsons, L. Alvarez-Jaimes, I. Polis, D. Stouffer

**W**e have continued to investigate the involvement of endogenous cannabinoid signaling in the mediation of drug reward and the development of drug dependence. We found that extracellular endocannabinoid levels are increased in the nucleus accumbens by voluntary ethanol and heroin self-administration but not by cocaine self-administration. We have extended these observations by evaluating the influence of these drug-induced changes in endocannabinoid levels on the motivation for drug consumption.

Administration of SR 141716A, an antagonist of the cannabinoid-1 (CB<sub>1</sub>) receptor, into the nucleus accumbens in rats significantly reduced both ethanol and heroin intake without altering cocaine self-administration. Endocannabinoids and their receptors also are present in several other brain regions that participate in drug reward. We found that ethanol self-administration in rats was dose dependently reduced by infusions of CB<sub>1</sub> antagonists into the medial prefrontal cortex and basolateral amygdala; infusions into the ventral tegmental area produced weaker changes, and infusions into the central nucleus of the amygdala resulted in no changes. In ongoing studies, we are characterizing the effect of drug self-administration on endocannabinoid levels in these regions and the influence of these endocannabinoid changes on amino acid and monoamine mechanisms implicated in the mediation of drug reward.

Growing evidence indicates an endocannabinoid influence in the vulnerability to drug relapse. For example, systemic administration of the CB<sub>1</sub> receptor antagonist SR 141716A attenuated drug-seeking behavior induced by drug-associated conditioned cues or drug-priming injections. Remarkably, this effect occurred across a range of drug classes, including opiates, psychostimulants, nicotine, and ethanol, pointing to the endocannabinoid system as a practical target for pharmacotherapies to prolong drug abstinence. We found that direct administration of SR 141716A into the medial prefrontal cortex and core subregion of the nucleus accumbens in rats dose dependently reduced cue-induced reinstatement of heroin-seeking behavior,

whereas infusions into the basolateral amygdala had no effect. We hypothesize that CB<sub>1</sub> receptors modulate cue-induced activation of cortical glutamatergic projections to the nucleus accumbens; we will test this hypothesis in the coming year.

In humans with alcoholism, withdrawal is associated with increased anxiety and depression that can be relieved by the resumption of drinking. It has been theorized that this form of negative reinforcement contributes to relapse drinking and excessive alcohol intake. Preclinical studies in rodents implicate dysregulated neuronal signaling in the central nucleus of the amygdala in these withdrawal-associated behaviors. In this context, we observed significant decreases in extracellular endocannabinoid levels in the central nucleus of the amygdala during the course of a 12-hour withdrawal period in alcohol-dependent rats. A strong increase in extracellular glutamate levels also occurred, with a temporal profile that mirrored the decline in endocannabinoid content. Subsequent resumption of ethanol drinking restored dialysate endocannabinoid and glutamate concentrations to prewithdrawal baseline levels.

On the basis of evidence that CB<sub>1</sub> receptors provide inhibitory control of glutamate release, these observations suggest that withdrawal-associated increases in excitatory neurotransmission in the amygdala are due in part to decreases in interstitial endocannabinoid levels. Accordingly, therapies that normalize deficient amygdalar endocannabinoid levels may be beneficial for alleviating withdrawal-associated affective dysfunction.

We also have continued to characterize serotonergic mechanisms that modulate drug consumption. We have found that activation of serotonin-1B receptors enhances the reinforcing effects of alcohol in rats, as indicated by a leftward shift of the ethanol self-administration concentration-effect function after administration of a serotonin-1B agonist. The results of localized drug infusions suggest an involvement of serotonin-1B receptors in the nucleus accumbens, ventral pallidum, and ventral tegmental area, but not the basolateral amygdala in this effect. A similar profile has been observed for serotonin-1B-mediated alterations in cocaine self-administration. We are evaluating the functional consequence of altered serotonin-1B receptor function in ethanol-dependent rats.

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## Primate Neurobehavioral Laboratory

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Currently, we are examining the effects of 3,4-methylenedioxyamphetamine (MDMA; also known as "Ecstasy") and drugs coabused with MDMA on thermoregulation and cognition. Persons who use MDMA recreationally report cognitive, mood, and sleep disturbances even after prolonged abstinence from the drug. Unregulated and severe hyperthermia is a common sign in MDMA overdoses that require emergency medical intervention and may play a unique role in MDMA-related fatality. Most users of MDMA also consume a variety of structurally related (amphetamine type) and unrelated (alcohol, cannabis, nicotine, caffeine) recreational drugs. Therefore, we use nonhuman models to determine the relative contributions of specific drugs of abuse to the acute and lasting health problems that occur in people who use MDMA.

In the past year, we focused on the effects of the structurally related amphetamine drugs 3,4-methylenedioxyamphetamine (MDA) and methamphetamine on body temperature and activity in rhesus monkeys. Among humans, methamphetamine and MDA are used intentionally or otherwise as a substitute for, or to com-

bine with, MDMA, and thus determining how these compounds may contribute to unregulated hyperthermia is critical. We also have explored the role of the route of drug administration, because these drugs are consumed orally by most people who use MDMA.

Our data indicate that MDA and methamphetamine elevate body temperature to a similar extent in monkeys as does MDMA, although the effects of MDA and methamphetamine can last much longer. Furthermore, we found that compared with intramuscular administration, oral administration of MDMA and methamphetamine modifies the rate and magnitude of temperature change only slightly. These studies also indicate that locomotor activity in monkeys can be either decreased (MDMA, MDA) or increased (methamphetamine); all 3 compounds increase body temperature. Together with our previous finding that ambient temperature has a minimal role in MDMA-induced hyperthermia, our results show clearly that exposure to MDMA itself raises body temperature. Medical emergencies in people who use MDMA are thus not uniquely caused by substitution of other drugs, high levels of activity, high ambient temperature, or atypical routes of administration. Rather, the emergencies likely are directly related to oral consumption of MDMA.

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## Neurobiology of Feeding, Motivation, and Stress

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**W**e study motivated behavior, with emphasis on brain reward and stress neurocircuits that control food intake. In the past year, in our research on ghrelin, a 28-residue stomach hormone that signals “energy insufficiency” to the brain, we made progress toward a vaccine to control body weight. Ghrelin hinders consolidation of weight loss. In collaborative studies with K.D. Janda, Department of Chemistry, we found that n-octanoylation and the N-terminal third residue of ghrelin are critical for the hormone’s biological activity. Therefore, we used active immunization to generate antibodies against the N terminus of ghrelin. The vaccine slowed the accrual of body weight and fat in rats in proportion to the amount of ghrelin-binding antibodies produced. We now are using passive immunization with transfer of antibodies (whole immunoglobulin G or single-chain variable fragments) targeting the acylated ghrelin N terminus. We also studied the roles of urocortin 2, urocortin 3, the benzodiazepine receptor, and, with T. Bartfai and X. Liu, Molecular and Integrative Neurosciences Department, galanin in the control of food intake and stress-related behavior.

In addition, we developed models of the hedonic (rather than homeostatic) control of food intake. Rats with intermittent, limited access to highly preferred food ate increasing quantities of these foods even when fed to satiation before given access to the preferred foods. Conversely, with increasing experience with preferred foods, rats ate less than normal amounts of their otherwise acceptable chow, despite weight loss. Thus, food intake became controlled less by nutritional need and more by taste in both positive (“binge”) and negative (“finickiness”) directions. Rats had increased anxiety-like behavior when access to preferred food was withdrawn and, despite consuming fewer calories overall

than rats maintained on chow, ultimately became heavier and fatter, with elevated levels of adipokines associated with metabolic syndrome.

Treatment with opioid receptor antagonists, which reduce pleasurable aspects of addictive substances such as ethanol, heroin, and morphine, reduced both binge-like eating and finickiness. Thus, intermittent access to preferred food had effects that resemble those of addictive substances, and opioid receptor antagonists reduced the influence of food preference on food intake.

In studies on addiction to classic substances of abuse, we found that opioid receptor antagonists reduced binge-like alcohol drinking in rats genetically selected to prefer alcohol and that antagonists of corticotropin-releasing factor type 1 receptors reduced the heightened intake associated with ethanol withdrawal. In collaboration with G.F. Koob, Committee on the Neurobiology of Addictive Disorders, we developed models of heroin and nicotine dependence. We found that the pattern of drug intake and consumption of alternative, natural rewards (e.g., food or water) similarly changed during the development of dependence to either drug, suggesting a commonality in the nature and neurobiology of addiction.

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## Neurophysiology of Peptides and Drugs of Abuse in the Extended Amygdala

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The central nucleus of the amygdala is a key element in extended amygdalar circuitry and is considered crucial in mediating the behavioral effects of acute and chronic drug consumption. Our research centers on the effects of acute and chronic ethanol on neurons in the central nucleus of the amygdala, particularly neurons of the  $\gamma$ -aminobutyric acid (GABA) and glutamatergic systems. Our aims are to uncover (1) the physiologic mechanisms that underlie the acute action of ethanol and the involvement of neuropeptides such as corticotrophin-releasing factor and nociceptin and (2) the neuroadaptations associated with ethanol-dependence.

Our electrophysiologic data strongly suggest that corticotrophin-releasing factor and GABA systems in the central amygdala are intimately related and balanced at the synaptic level and that they are likely involved in stress or anxiolytic mechanisms leading to drug addiction. Ethanol can disrupt their balance, leading to increased GABA release and inhibition of amygdalar discharge. However, nociceptin decreases GABA release and opposes the effects of both ethanol and

corticotrophin-releasing factor. We are collaborating with L.H. Parsons, Committee on the Neurobiology of Addictive Disorders, to confirm these in vitro findings in freely moving rats to better translate the findings to the human condition.

We have characterized several neuroadaptations in the GABAergic system associated with alcohol dependence and have investigated the effects of a structural analog of GABA that has anticonvulsant properties. Our data indicate that this compound reverses both cellular and behavioral measures of ethanol dependence and suggest that this GABAergic drug is a potential medication for treatment of alcoholism.

We also found that acute exposure to ethanol inhibits responses in neurons in the central amygdala mediated by receptors for *N*-methyl-D-aspartate (NMDA), principally at postsynaptic sites. Prolonged exposure to ethanol increased the sensitivity of NMDA receptors and increased glutamate release. Importantly, these changes were reversed with ethanol withdrawal. These physiologic data correlated with molecular studies showing that chronic exposure to ethanol increased mRNA and protein levels of selective NMDA receptor subunits in neurons in the central amygdala. In collaboration with P.J. Kenny, Department of Biochemistry, we found that nicotine increased NMDA receptor-mediated transmission by facilitating glutamate release and that chronically self-administered nicotine increased expression of NMDA receptor subunits in the central amygdala.

Understanding the cellular adaptations induced by chronic exposure to alcohol and other drugs of abuse will provide insight into how the transition to addiction occurs and, possibly, potential treatments.