

Brain Involvement

The Brain Reward System The brain reward system, also known as the *pleasure center* is a key structure involved in the subjective experience of pleasure from a number of stimuli such as food, sexual behavior, the experience of novelty, and --- the use of drugs and alcohol.

Recent Scientific Articles on this Topic:

Neurobiology of addiction. Toward the development of new therapies. Koob GF, Ann N Y Acad Sci 2000;909:170-85

Drug addiction is a chronic relapsing brain disorder characterized by neurobiological changes that lead to a compulsion to take a drug with loss of control over drug intake. The hypothesis outlined here is that knowledge of the neurochemical systems involved in the transition from drug use to the compulsive use of addiction will provide the rational basis for development of pharmacotherapies for drug addiction. Much evidence has been obtained in identifying the midbrain-basal forebrain neural elements involved in the positive reinforcing effects of drugs of abuse and more recently in the neural elements involved in the negative reinforcement associated with drug addiction. Key elements for the acute reinforcing effects of drugs of abuse include a macrostructure in the basal forebrain called the extended amygdala that contains parts of the nucleus accumbens and amygdala and involves key neurotransmitters such as dopamine, opioid peptides, serotonin, GABA, and glutamate. Withdrawal from drugs of abuse is associated with subjective symptoms of negative affect, such as dysphoria, depression, irritability and anxiety, and dysregulation of brain reward systems involving some of the same neurochemical systems implicated in the acute reinforcing effects of drugs of abuse. In addition, acute withdrawal is accompanied by recruitment of the brain stress neurotransmitter system, corticotropin-releasing factor. Animal models of craving involve not only conditioning models but also models of excessive drug intake during prolonged abstinence, post-acute withdrawal, that may reflect continued dysregulation of drug reinforcement that could lead to vulnerability to relapse and represent an important

focus for pharmacotherapy. Such changes have been hypothesized to involve a change in set point for drug reward that may represent an allostatic state contributing to vulnerability to relapse and re-entry into the addiction cycle. Elucidation of the specific neuropharmacological changes contributing to this prolonged functional dysregulation will be the challenge of future research on the neurobiology of drug addiction.

The dopamine hypothesis of reward: past and current status. Spanagel R, Weiss F, Trends Neurosci 1999 Nov;22(11):521-7

Mesolimbic dopaminergic neurons are thought to serve as a final common neural pathway for mediating reinforcement processes. However, several recent findings have challenged the view that mesolimbic dopamine has a crucial role in the maintenance of reinforcement processes, or the subjective rewarding actions of natural rewards and drugs of abuse. Instead, there is growing evidence that dopamine is involved in the formation of associations between salient contextual stimuli and internal rewarding or aversive events. This evidence suggests that dopaminergic-neuron activation aids the organism in learning to recognize stimuli associated with such events. Thus, mesolimbic dopaminergic neurons have an important function in the acquisition of behavior reinforced by natural reward and drug stimuli. Furthermore, long-lasting neuroadaptive changes in mesolimbic dopamine-mediated transmission that develop during chronic drug use might contribute to compulsive drug-seeking behavior and relapse.

Neurobiology of tobacco smoking and other addictive disorders. Gamberino WC, Gold MS, Psychiatr Clin North Am 1999 Jun;22(2):301-12

Advances in research of the neurobiology of addictive disorders have provided clinicians with an evolving perspective on addiction. All drugs of abuse seem to share a common neurobiologic substrate involving the mesocorticolimbic system. Considerable evidence shows that these dopaminergic projections are involved in the positive brain reward, which drives addictive disorders; however, recent studies also implicate the neurotransmitters glutamate and serotonin in learning and sensitization to drug use. A

review of the neurobiology of tobacco smoking provides further examples of the mechanisms for reinforcing tobacco use, including the enhancement of memory and treatment of depression with nicotine and MAO-inhibiting chemicals in tobacco smoke respectively. The relevance of these advances may be realized through the destigmatization of addictive disorders and the development of new and improved treatment strategies.

Drugs of abuse and the brain. Leshner AI, Koob GF, Proc Assoc Am Physicians 1999 Mar-Apr;111(2):99-108

New insights into our understanding of drug abuse and addiction have revealed that the desire to use drugs and the process of addiction depend on effects on brain function. Drugs of abuse have been hypothesized to produce their rewarding effects by neuropharmacological actions on a common brain reward circuit called the extended amygdala. The extended amygdala involves the mesolimbic dopamine system and specific subregions of the basal forebrain, such as the shell of the nucleus accumbens, the bed nucleus of the stria terminalis, and the central nucleus of the amygdala. The psychomotor stimulants cocaine and amphetamine activate the mesolimbic dopamine system; opiates activate opioid peptide receptors within and independent of the mesolimbic dopamine system. Sedative hypnotics alter multiple neurotransmitter systems in this circuitry, including: 1) gamma aminobutyric acid; 2) dopamine; 3) serotonin; 4) glutamate; and 5) opioid peptides. Nicotine and tetrahydrocannabinol both activate mesolimbic dopamine function and possibly opioid peptide systems in this circuitry. Repeated and prolonged drug abuse leads to compulsive use, and the mechanism for this transition involves, at the behavioral level, a progressive dysregulation of brain reward circuitry and a recruitment of brain stress systems such as corticotropin-releasing factor. The molecular mechanisms of signal transduction in these systems are a likely target for residual changes in that they convey allostatic changes in reward set point, which lead to vulnerability to relapse.

How Drugs Act on the Brain

All drugs of abuse, including alcohol, are known to stimulate the brain reward system in both animals and humans.

Genetics

Alcoholism

Genetic research has focused on alterations of the gene that codes for receptors for the neurotransmitter dopamine. Dopamine is recognized as playing a key role in the feeling of euphoria associated with the use of alcohol and other substances.

Recent Scientific Articles on this Topic:

The microstructure of ethanol drinking: genetic and behavioral factors in the control of drinking patterns. Samson HH, *Addiction* 2000 Aug;95 Suppl 2:S61-72

The concept of craving can be examined in many different ways, depending upon the individual definition of the term. Using the concepts and procedures of regulatory behavior analysis, this review explores behavioral studies in rats that have some relationships to some of the possible processes that underlie the concept of craving in humans. Data are reviewed from studies employing both limited and continuous access to ethanol, examining the role of access availability, ethanol initiation, response cost, time since last access, composition of the ethanol containing solution and genetic selection. From this review, it is clear that rat models can implicate important variables involved in the control of human alcohol consumption.

Genetics of alcohol withdrawal. Schmidt LG, Sander T, *Eur Psychiatry* 2000 Mar;15(2):135-9

Alcohol withdrawal is a clinically and etiologically heterogeneous syndrome caused by a complex interaction of environmental (e.g., amount of ethanol) and genetic factors. Multiple genes are considered to be involved in various components of the syndrome, each of them contributing only modestly to withdrawal vulnerability. Association studies

using candidate genes of the dopamine, serotonin, gabaergic and opioidergic systems are reviewed and methodological limitations are discussed.

Clinical perspectives for the study of craving and relapse in animal models. Li TK,
Addiction 2000 Aug;95 Suppl 2:S55-60

Several major clinical models of alcoholism in which craving plays a role are summarized and key questions are raised regarding the course of craving in the emergence of alcoholism, how it varies in different stages of the disorder (e.g. active alcoholic, withdrawal, protracted abstinence) and what craving may contribute to major signs and symptoms of alcoholism. Turning to animal models, a plea is made for development of a standardized definition of human craving that can be represented and operationalized in animal models. Until there is scientific consensus on such a definition, four ways are elucidated in which animal model research can contribute to advances in our knowledge of human craving and the role it plays in addictive behavior: (1) engaging both basic and clinical researchers to identify parallel constructs of craving and predictors of craving for adoption in comparative human and animal model studies; (2) conducting exploratory research on craving in animal models using relapse to drinking as the dependent measure; (3) identifying mechanisms that underlie clinical signs and symptoms of alcoholism in animal models; and (4) identifying genetic models in basic research that account for variations in response to alcohol that may also occur in humans. This latter point is made in a discussion of the genetic contribution to voluntary alcohol consumption, the alcohol deprivation effect, tolerance and dependence, as illustrated by differences between alcohol-preferring (P) rats and -nonpreferring (NP) rats. The review concludes with four questions and issues that need to be among those that guide future research on craving.

Other drug use

Tobacco

Some research has examined the genetically determined differences among individuals with respect to how rapidly they metabolize nicotine.

Opiates

Research has also been done on differences in the metabolism of certain opiates such as codeine.

Recent Scientific Articles on this Topic:

Genetic vulnerability to drug abuse. Duaux E, Krebs MO, Loo H, Poirier MF, Eur Psychiatry 2000 Mar;15(2):109-14

Addiction to various substances, including drugs and alcohol, probably arises from a combination of environmental and genetic factors. The genetic vulnerability to drug addiction is supported by several familial, adoption and twin studies. However, as in other mental disorders, the genetic vulnerability to drug addiction appears complex: these disorders do not follow the rules of Mendelian inheritance. Instead, they are probably influenced by multiple susceptibility genes, each of which contributes to the disorder. The more genes necessary for a disorder, the harder it is to detect any of them. This difficulty is magnified by the role of environmental factors. Association studies using the candidate gene approach can identify susceptibility genes for drug abuse supported by the pathophysiological hypothesis of the illness. This review will focus on the clinical and molecular genetic studies in drug abuse.