The Dark Side of Drug Addiction

Drug addiction is a chronic relapsing disorder. Neurobiological changes are the basis for compulsive drug-taking, accompanied by loss of control over drug intake and the emergence of a negative emotional state when access to the drug is blocked. Clinically, a distinction is made between the escalated drug use of addiction and the occasional but limited taking of drugs with the potential for abuse and dependence.

As addiction develops, neuroplastic brain reward systems are transformed. This is the "dark side" of drug addiction: the decline in normal reward-related neural mechanisms and persistent recruitment of the brain's antireward systems that accompany drug use. Progressive worsening of the brain reward system perpetuates compulsive use of the drug.

George F. Koob, PhD, of the Scripps Research Institute in La Jolla, California, studies the behavior of rodents in an effort to understand the neuropharmacologic and neuroadaptive mechanisms that enable the crossover from occasional, controlled drug user to the behaviors of an addict. Knowledge of these neurochemical systems may elucidate vulnerability to addiction and suggest pharmacotherapies for drug addiction.

Cycle of Addiction

Drug addiction has elements of both an impulse control disorder and a compulsive disorder that are mediated by separate but overlapping neural circuits. The individual with an impulse control disorder experiences an increasing sense of tension or arousal before committing the impulsive act such as drug-taking; pleasure, gratification or relief during the act; and in some cases, regret, self-reproach or guilt following the act. The individual with a compulsive disorder feels anxiety and stress before the compulsive, repetitive act, and relief from stress by performing the act. In the progression from an impulsive disorder to a compulsive disorder, the motivation for the behavior shifts from positive reinforcement to negative reinforcement, when removal of the aversive state increases the probability of the behavior.Drug addiction follows this pattern in a collapsed cycle of addiction involving 3 stages:

- Binge/intoxication;
- Withdrawal/negative affect; and
- Preoccupation/anticipation (craving).

Addiction involves a long-term persistent plasticity of the neural circuits that control 2 different reward systems: declining function of brain reward systems driven by natural rewards and stimulation of antireward systems that bring on aversive states.

Brain Reward System

Studies of the acute reinforcing effects of drugs of abuse in the binge/intoxication stage have identified the neurobiological substrates involved in the reward response. Drugs with the potential for abuse and dependence, such as the opioid analgesics, initially produce positive reinforcing effects from actions at the ventral tegmental area in the midbrain and the nucleus accumbens and amygdala of the basal forebrain. Activation of the mesocorticolimbic dopamine pathway is the primary route of positive reinforcement in addiction for psychostimulant drugs, but the opioid peptides (endorphins), serotonin, and gamma-aminobutyric acid (GABA) have key roles for nonpsychostimulant drugs. These so-called "reward neurotransmitters" induce hedonic

effects of euphoria and a feeling of well-being.

Brain Antireward System

Withdrawal from a drug of abuse induces symptoms of negative affect such as dysphoria, depression, irritability, and anxiety. Dysregulation of brain reward systems involves some of the same neurochemical pathways implicated in the drug's acute reinforcing effects, but in this case, they represent an opponent process. During acute abstinence, increases in brain reward thresholds (a higher set point for drug reward) are a consequence of altered reward neurotransmitters. This in turn may contribute to the negative motivational state of withdrawal and vulnerability to relapse. Neurochemical changes during opioid withdrawal include decreases in dopaminergic and serotonergic transmission and increased sensitivity of opioid receptor transduction mechanisms. Escalating doses of opioids, like those seen in the human pattern of morphine or heroin use, are associated with profound alterations in the function of mu-opioid receptors. A decrease in baseline reward mechanisms leads to an increase in drug intake to compensate for the shift in reward baseline.

For the addict, the situation deteriorates. Stress response systems of the body contribute to the negative emotional state associated with abstinence and can exacerbate drug taking throughout the addiction cycle. In response to taking the drug, the neuroendocrine system kicks in to attempt to restore the brain to normal function. Chronic drug use adversely affects the hypothalamic-pituitary-adrenal axis, disrupting regulation of hypothalamic corticotropin releasing factor (CRF). Particularly important is activation of CRF in the extrahypothalamic brain stress system of the extended amygdala. The extended amygdala is a structure comprised of the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and a transition zone in the medial subregion of the nucleus accumbens and a major projection to the lateral hypothalamus.CRF controls hormonal, sympathetic, and behavioral responses to stress. During acute withdrawal of the drug, production of adrenocorticotropic hormone, corticosterone, amygdala CRF, norepinephrine, dynorphin, and inhibition of neuropeptide Y induce brain arousal, stress-like responses, and a dysphoric, aversive state. The activation and recruitment of brain and hormonal stress responses contribute to a deviation in brain reward set point. These are the sources of negative reinforcement that lead to compulsive drug-seeking behavior and addiction.

Craving and Relapse

The preoccupation/anticipation stage of the addiction cycle is mediated via afferent projections to the extended amygdala and nucleus accumbens. There are different stimuli for craving a drug of abuse, leading to relapse. It can be drug-induced, cue-induced, or stress-induced.

Chronic relapse is a significant problem in drug addiction, with about half of all addicts relapsing into drug taking. Addicts can return to compulsive drug taking long after acute withdrawal exhibiting behavior that corresponds to the preoccupation/anticipation stage of addiction. Drug-related cues and stressors are a powerful inducement to return to drug use. Areas of the brain associated with drug and cue-induced reinstatement are the prefrontal cortex (orbitofrontal, medical prefrontal, prelimbic/cingulate), and the basolateral amygdala. The neurotransmitters involved in relapse are dopamine, opioid peptides, glutamate, and GABA. Relapse can also be precipitated by stress and the release of CRF, glucocorticoids and norepinephrine. Many different stressors can provoke drug craving and drug-seeking behavior.

Animal Studies

It has been possible to study the effects of both short- and long-term exposure to drugs of abuse in a rodent extended-access model. This animal model has been used to study the transition from drug use to addiction, including such behaviors as escalating drug intake driven by dependence, self-administering drug despite adverse consequences, and a narrowing of the behavioral repertoire for drug seeking. Extended access to drugs of abuse produces dramatic

increases in drug intake and dependence over time that mirror human behavior. Extended access also produces anxiety-like responses mediated by an increase in extracellular CRF secreted by the central nucleus of the amygdala during withdrawal, effects that are reversed by CRF receptor antagonists. Giving a CRF receptor antagonist blocks excessive drug taking, providing promise for a possible treatment for addiction.

Evidence from animal research also supports the similarities between stress and drugs of abuse in their effects on neurochemistry, electrophysiology, and morphology of neurons in the reward pathway. Exposing a rodent to an acute stressor increases the release of CRF and corticosterone in the hypothalamic pituitary adrenal axis, which in turn activates CRF in the amygdala. Molecular studies support the concept that stress and addictive drugs act through common molecular mechanisms within similar brain circuits to perpetuate the addiction cycle The long-lasting nature of addiction suggests that changes in gene expression might be required for the development and persistence of this disease.

Summary

Rewards are pleasurable, but addictions hurt. The neurobiological underpinnings of reward and addiction involve different but overlapping neuroanatomic circuits.

Addiction is not a single incident, but rather occurs by a series of events initiated by the acute rewarding effects of drugs followed by a transition into chronic drug use. Drug addiction is associated with a long-term persistent decrease in the function of normal motivational systems driven by 2 sources: (1) decreased function of brain reward systems (mediating natural rewards) and (2) increased antireward systems recruited in an opponent process to excessive activation of the brain reward system.

The deficit state for normal reward that is produced by excessive drug taking, rather than a hyperactive or sensitized reward state for drugs per se, is the motivation to seek drugs. Excessive drug taking results in not only the short-term amelioration of the reward deficit but also in suppression of the antireward system.

Acute withdrawal of all major drugs of abuse increases brain reward thresholds, anxiety-like responses, and CRF in the amygdala that are of motivational significance. The amygdala has powerful emotional machinery, and brain stress responses recruit its dark side. Worsening of the underlying neurochemical dysregulations (decreased dopamine and opioid peptide function, increased CRF activity) lead to a chronic deviation of reward set point that is fueled not only by dysregulation of reward circuits but also by recruitment of brain and hormonal stress responses. Brain arousal stress systems in the extended amygdala may be important not only for the negative emotional states that drive dependence on drugs of abuse but also may overlap with the negative emotional components of chronic pain syndromes.