

Neurobiology of addiction. Toward the development of new therapies

by

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ABSTRACT

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.

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