The Neurobiology of Addiction-like Behaviors

Elisabeth J. Van Bockstaele

Addiction remains one of society’s major public health problems, posing a significant threat to the health as well as the social and economic fabric of individuals, families, communities, and nations. Over the past two decades, preclinical and clinical studies have yielded significant new information that has contributed to improving understanding of the neural substrates underlying the biological basis of addiction-like behaviors. However, even as scientists learn more about the neurobiological underpinnings of addiction, a great deal remains unknown, and new categories of addictions (e.g., prescription medications, food, Internet, gambling, sex, and shopping) are being defined.

The articles in this issue focus on the neurobiology of addiction-like behaviors and show that addiction is varied and complex, and often comorbid with other psychiatric disorders. Convergent evidence from the fields of neuroscience, genetics, and psychiatry has provided significant insight into the neurobiological adaptations that underlie addiction-like behaviors.

Wu and Schulz (2012) discuss the importance of the development of appropriate animal models to study addiction-like behaviors. As reviewed by Quinones-Jenab and Jenab (2012), the contribution of gender has taken on new importance in the management of addiction-related behaviors. Studies examining the influence of sex in substance abuse have shown differences in all aspects of drug abuse history—from age of first use to progression to dependence and propensity to relapse after drug abstinence.

More recently, an emphasis has been placed on the study of addiction-like behaviors as they relate to non-drug-related “reinforcers” such as food. Corwin and Babbs (2012) introduce the notion of binge eating in the context of addiction-like behaviors. Barson and colleagues (2012) consider the neurobiological mechanisms that control food intake, particularly excessive intake, and how these systems may be coopted to control consumption of the commonly used drug alcohol. Finally, Michaelides and colleagues (2012) discuss the striking similarities between drug addiction and obesity in functional impairment in discrete brain regions and neurotransmitter circuits.

To understand addiction-like behaviors, it is necessary to elucidate the fundamental neural (e.g., synaptic) adaptations that occur after a single exposure to a “natural” reward or addictive drug and, subsequently, how repetitive exposure may lead to neural circuit dysfunction that defines the phenotype of addiction. As basic knowledge of the association between adaptive experience and dependent plasticity continues to progress, it will lead to a better understanding of the substrates underlying neural circuit dysfunction and circuit remodeling in addiction-like behaviors, which will in turn enable the identification of novel targets for intervention and treatment (Luscher and Malenka 2011).

Neural Substrates of Addiction

Understanding the classification of behaviors in the context of addiction is a subject of extensive debate. Historically, the term addiction became largely synonymous with compulsive alcohol and drug use. However, the observation that compulsive behaviors related to non-drug-related activities (e.g., gambling, eating, and shopping) had similar clinical, phenomenological, and other biological profiles of drug dependency prompted reconsideration of the core features of addiction. Addiction has therefore been defined as a condition of dysfunctional motivated behavior (Volkow and Li 2004).

In general terms, addiction is defined as compulsive behavioral engagement with diminished control over the behavior, and an appetitive urge or craving state. It is considered a chronic relapsing disorder that is characterized by compulsive behaviors despite adverse consequences to self or others (Koob and Le Moal 2006).

For substance abuse, addiction-like behaviors are characterized by several phases, including acquisition, maintenance, escalation, and dependence. Although family history represents one of the greatest risk factors for drug addiction, genetic factors likely explain only about 50% of the risk. Genetic linkage studies have provided significant advances regarding the genetic variations underlying drug addiction (Maze and Nestler 2011), but much remains to be understood.

Research has also focused on environmental influences, although it is widely accepted that a combination of environmental stimuli and an individual’s genetic constitution determines initial responses to drugs of abuse, as well as maladaptations to repeated drug exposure that underlie the transition to an addicted state (Maze and Nestler 2011).
“Natural” rewards (e.g., food and sex) and drugs of abuse mediate their reinforcing properties by targeting the mesocorticolimbic dopamine system, a brain circuit that is defined by projections from the ventral tegmental area to its major targets: the nucleus accumbens, a brain region involved in motor and limbic functions, and the prefrontal cortex, a brain region involved in decision making and executive functions (Koob 1992). Investigators increasingly recognize that most drugs of abuse share a common mechanism involving increases in extracellular concentrations of dopamine in the nucleus accumbens via activation of dopaminergic neurons in the ventral tegmental area (Willuhn et al. 2011). This working model predicts that dopamine release in response to drug-related stimuli will be enhanced over stimuli associated with natural reinforcers, which may result in aberrant goal-directed behaviors that contribute to drug addiction. Although dopamine is integral to the initial euphoric effects of several drugs of abuse (Di Chiara and Imperato 1988), several lines of evidence indicate that neural circuits outside the reward pathway become engaged and contribute to the initiation of drug-seeking activities (Goto and Grace 2005; Hyman et al. 2006).

In addition to the involvement of select neural circuits, glutamate signaling has been recognized recently as an important response to numerous drugs of abuse including amphetamines, benzodiazepines, cocaine, ethanol, nicotine, and opiates (for review, see Cunha-Oliveira et al. 2008; Kalivas et al. 2009; Koob 2003). Disruption of normal glutamate transmission has been implicated in drug-dependent excitotoxicity, drug seeking, and reinstatement as well as reward and reinforcement (Kalivas et al. 2006, 2009; Knackstedt and Kalivas 2009). For many drugs of abuse, glutamate-opioid interactions are important determinants of addictive processes in the brain, and both stress and exposure to drugs of abuse engage the glutamatergic system at common neural sites (Fitzgerald et al. 1996). As with many addictive compounds, opiate abuse can lead to disturbances in excitatory amino acid signaling, particularly through homeostatic disruption of glutamate, a ubiquitous excitatory neurotransmitter in the nervous system (Cunha-Oliveira et al. 2008). As a result, numerous investigators have explored the nature of glutamate-opioid interactions in drug abuse in the hopes of better identifying potential therapeutic targets for the treatment of addiction.

Animal Models for the Study of Addiction-like Behaviors

Animal studies have been crucial in elucidating the neurobiological basis of addiction-like behaviors. Such models have provided a means to directly manipulate variables of interest and have been critical for elucidating the neuropharmacological mechanisms involved in different phases of the addiction process. Animal models often focus on the ability of the drug itself to directly regulate the animal’s behavior, thereby allowing comparisons with human studies.

The initial demonstration in laboratory animals that drugs could serve as reinforcers resulted in the development of self-administration paradigms that have been useful as models of human drug abuse. However, with the recognition of the existence of distinct phases in the addiction process, investigators have become increasingly interested in developing more comprehensive models that can inform the differential vulnerability to drug abuse, the transition from controlled to compulsive drug use, and relapse to drug use after a period of abstinence.

Understanding the progression to addiction-like behaviors and the biological basis for vulnerability to relapse in animal models will enable closer comparison with the human condition. To this end, an emphasis is placed on the design of preclinical research experiments that will best inform translational and clinical studies.

In the first article of this issue, Wu and Schulz (2012) discuss animal models used to study drug reward and addiction with particular emphasis on the development of models for alcohol addiction research.

Quinones-Jenab and Jenab (2012) review the role of gonadal hormones as a factor contributing to the sexually dimorphic pattern of behavioral responses to cocaine. Interestingly, for example, in females, estradiol has facilitatory effects, but progesterone inhibits most cocaine responses. Furthermore, the authors discuss chromosomal mechanisms that contribute to drug abuse vulnerability.

Corwin and Babbs review current rodent models of bingeing, their contributions to scientific understanding of bingeing, their validity in the face of DSM criteria (APA 2000), and their overlap with knowledge of addiction. These models indicate that certain foods, in very specific contexts, can provoke behavioral changes and hijack neuronal systems involved in the normal regulation of food intake in a manner similar to that of drugs of abuse.

The article by Barson, Morganstern, and Leibowitz (2012) provides a detailed review of animal models used by researchers to study excessive food intake as well as the brain regions involved in mediating food consumption. This review is followed by an analysis of the neurochemicals involved in food intake regulation, with a particular focus on the orexigenic neuropeptides. Finally, the authors consider how the involvement of selected neurochemicals may generalize to other abused substances such as alcohol.

Using preclinical and clinical noninvasive neuroimaging, Michaelides and colleagues (2012) explain that drug addiction and obesity are strikingly similar in functional impairment in discrete brain regions and neurotransmitter circuits. Similar abnormalities in brain glucose metabolism are observed in the prefrontal cortex (a region critical for inhibitory control) and the hippocampus (a region critical for memory) as well as impairments in dopamine signaling in the striatum (a region involved in food and drug reward, which are goal-oriented behaviors). This article provides compelling evidence for the use of noninvasive brain imaging strategies for modeling motivational diseases such as drug addiction and obesity in humans.

The issue concludes with important recommendations for members of institutional animal care and use committees.
(IACUCs) by Hughes-Moore (2012) as these committees consider the multiple facets involved in investigations into the neurobiology of addiction-like behaviors.

References