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A Behavioral/Systems Approach to the Neuroscience of Drug Addiction

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Drug addiction is likely to affect all of our lives, with any luck not through our own actions but probably because of one or more of our family and friends. Now firmly entrenched as a brain disease (Leshner, 1999; Wise, 2000), drug addiction is among the most costly such diseases in modern society. Drug addiction is most often defined as a chronically relapsing disorder in which the addict experiences uncontrollable compulsion to take drugs, while simultaneously the repertoire of behaviors not related to drug seeking, taking, and recovery, declines dramatically. What transpires to lead the drug user into this cyclical, self-destructive pattern of behavior? Through a rapid escalation of basic neuroscience research, we have begun to answer this critical question at both the cellular/molecular and behavioral/systems levels of analysis. There have been many excellent recent reviews regarding the molecular mechanism of drug addiction (see references below). Such has not been the case from a systems neuroscience perspective. The present set of mini-reviews has been solicited to address issues concerning the brain systems responsible for specific immediate behavioral consequences of drug intake, how such systems are altered during the process of repeated drug administration, and whether additional systems become engaged during the process of drug dependence, withdrawal, and relapse to drug-taking. The aim of these reviews is to provide the nonspecialist neuroscientist with a contemporary yet comprehensible overview of exciting recent developments in our understanding of brain circuits related to specific aspects of drug addiction.

Drug addiction is presently viewed as a complex neuroadaptive process through which drugs of abuse alter cellular and molecular aspects of neural function in such a way as to render the brain circuits mediating various behavioral effects of these drugs more, or less, responsive to those effects. This process guides behavior in maladaptive directions during which severe physical and social consequences engulf and disable the addict. Cellular and molecular mechanisms of tolerance, sensitization (reverse tolerance), and dependence are rapidly being identified for almost all classes of abused drugs, and both established and new molecules are being investigated intensively using the most modern and advanced technologies available to neuroscience (Nestler, 2001b,d). As the neurobiology of drug addiction has advanced, the discovery of precise cellular and molecular adaptations related to the addictive process has been substantial. Alterations in many molecules have been newly implicated. From long-suspected involvement of the cAMP pathway in tolerance to and dependence on opiates (Sharma et al., 1975), we have identified a dedicated role of cAMP-related molecules in the actions of several drugs of abuse. The cAMP-dependent protein kinase and the cAMP response element-binding protein are but two examples. Molecules that interact both upstream and downstream of these effectors are also implicated and include various neurotransmitter receptors, inhibitory and stimulatory G-proteins, protein kinases and phosphatases, ion channels, immediate early genes, and gene transcription factors (for review, see Berke and Hyman, 2000; Nestler, 2001a,b). At the cellular level, alterations in synaptic and whole-cell plasticity accompany sensitization and withdrawal (Bonci and Williams, 1996; Zhang et al., 1998; Thomas et al., 2001; Ungless et al., 2001), as do structural changes in dendrites (Robinson and Kolb, 1997, 1999).

Clearly, dopamine (DA) is the molecule most directly implicated in the positive reinforcing (rewarding, pleasurable) effects of all drugs of abuse. The ability of addictive drugs to enhance DA neurotransmission, particularly within the mesocorticolimbic DA system, is a well documented commonality among the various classes of abused drugs (for review, see Wise and Bozarth, 1987; Koob, 1992; White, 1996; Spanagel and Weiss, 1999). This DA reward system, which originates in the midbrain ventral tegmental area (VTA; A10 DA neurons) and projects to the nucleus accumbens (NAc), prefrontal cortex (PFC), and other limbic areas, has long been the major focus of our attempts to identify cellular and molecular mechanisms underlying addiction. However, the past decade has witnessed an emerging willingness to place the DA system within a broader context of neuronal circuitry engaged by specific drugs and particular behavioral sequences involved in the acts of drug seeking, drug taking, and recovery from drug actions (withdrawal, relapse, etc.).

One critical component of this broader conceptualization of drug reward circuitry is the glutamate neuronal system innervating and directly influencing the mesocorticolimbic DA system. Glutamatergic inputs to the VTA and NAc, arising from the PFC, hippocampus, and basolateral amygdala, have all been implicated in addiction. Indeed, a recurring theme in modern addiction research is the extent to which neuroadaptations responsible for various aspects of the addiction process are similar to those responsible for other forms of neural plasticity studied in cellular models of learning, such as long-term potentiation and long-term depression (Wolf, 1998; Berke and Hyman, 2000; Nestler, 2001c); however, glutamate is not the only other system under intense scrutiny. We have long been baffled by the role of other monoamine transmitters in the actions of drugs of abuse. In recent years, a new emphasis on both serotonin and norepinephrine has reemerged, along with clear implications for various neuropeptide systems, including the opioid peptides and the stress-related

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peptides of the hypothalamus–pituitary–adrenal axis (Kreek and Koob, 1998). Moreover, as will be seen in several of the mini-reviews, brain GABAergic and cholinergic systems are fruitful avenues for continued research. Finally, conceptualization of the role of DA pathways has been enlarged to include the nigrostriatal system as it becomes engaged in stereotypic responses that define the process of addiction (Everitt and Wolf, 2002).

A concerted interplay between cellular/molecular and behavioral/systems neuroscience with respect to the process of addiction has never been so crucial. Identifying the systems involved in specific behaviors directs cellular/molecular studies of both acute and chronic drug actions. Similarly, identification of new molecules selectively altered by repeated drug administration, perhaps in brain areas not "routinely" considered with addiction circuits, can expand our concepts of brain circuitry modulating the addiction process. We are fortunate that the neuroscientists who have agreed to provide the six mini-reviews in this series work at both levels of analysis, thereby providing a comprehensive multidisciplinary perspective on the neurobiology of addiction. In putting together the teams of scientists to provide these reviews, I have specifically paired two investigators who do not necessarily collaborate directly, so that they mold perhaps different perspectives to provide a consensus as to the most important new developments in drug addiction research. As these reviews emphasize, our efforts to tie specific brain circuits to precise aspects of behavioral changes has broadened considerably the number of affected brain regions and highlighted the need to expand cellular and molecular studies to these areas. This has been made possible by the refinement of sophisticated behavioral approaches coupled to systems neuroscience.

When surveying the advances made with respect to the neuroscience of drug addiction, it is easy for the nonspecialist to get the incorrect impression that brain circuits have evolved to allow maladaptive patters of behavior. Actually, brain reward circuits subserve a much more critical evolutionary function: reward induced by natural reinforcers such as food and sexual interactions. Accordingly, we begin our series of reviews with a look at how the neuroscience of natural rewards is related to addictive drugs. Kelley and Berridge (2002) review current thinking of how the DA reward system encodes specific aspects of the reward process and how such encoding is impacted by natural rewards. They also provide compelling arguments for commonalities in the actions of natural rewards and drugs of abuse within both traditional reward areas and brain regions not normally considered within such circuitry.

After considering natural rewards, the next three reviews focus on the major classes of illicit drugs of abuse: psychomotor stimulants (amphetamine, cocaine), opiates (morphine, heroin), and cannabinoids (marijuana). In a somewhat expanded mini-review, Everitt and Wolf (2002) summarize the rapidly expanding field of psychostimulant addiction from a systems perspective. We have allowed this more detailed treatment not only because more work has focused on this class of drugs but also because these authors provide excellent descriptions of most of the sophisticated behavioral procedures that are also touched on in the other mini-reviews. The interested reader would be well served by first reading this mini-review to become familiar with the animal models used to study drug-seeking, conditioned reinforcement, and behavioral sensitization.

As pointed out by De Vries and Shippenberg (2002), in contrast to psychostimulants, considerably less is known regarding the mechanisms of opiate addiction and relapse to opiates after withdrawal. Their commentary in this regard is well informed given that these authors could just as easily have reviewed the psychostimulants. This is another feature of the scientists whom I have chosen to participate in this series; many of them work across different drug classes, giving unique perspectives on the similarities and differences between various drugs of abuse. In this case, De Vries and Shippenberg emphasize that recent findings challenge previous notions regarding the role of one neurotransmitter or brain region in opiate addiction and point to activity of several neurotransmitter and neuropeptide systems in brain circuits mediating mood and affect underlying the addiction process.

Maldonado and Rodriguez de Fonseca (2002) tackle the job of integrating an explosive recent literature regarding the perhaps controversial concept of cannabinoid addiction. As social issues swirl with respect to the medical use and possible decriminalization of marijuana, neuroscientists have taken advantage of the relatively recent cloning of cannabinoid receptors, the identification of endogenous cannabinoids, and the development of specific and potent cannabinoid compounds to begin the identification of circuits involved in cannabinoid reward, dependence, and withdrawal. Maldonado and Rodriguez de Fonseca (2002) beautifully integrate discoveries at the behavioral/systems level with those at the cellular/molecular level to argue persuasively that addiction to cannabinoids shares common features with other drugs of abuse. The remarkable interactions between cannabinoid and opioid systems are particularly emphasized.

The last two mini-reviews turn to the two major licit drugs of abuse: alcohol and nicotine. Weiss and Porrino (2002) describe the unique challenges in alcohol addiction research that emerge from the multiple molecular targets of ethanol in several brain circuits. We have come far from the days of considering ethanol as a "modifier of membrane fluidity." Specific binding sites for ethanol within GABA-A and NMDA receptors provide particular challenges given the almost ubiquitous expression of these receptors throughout the nervous system. Weiss and Porrino (2002) clearly and concisely review the involvement of DA, opioid, and other systems in ethanol motivation and reward, adaptations relevant for the transition to dependence and relapse, and issues relevant to the treatment of alcoholism.

Finally, Picciotto and Corrigall (2002) team up to review the neuronal system involved in behaviors related to nicotine addiction and the molecular genetics that have identified which subtypes of nicotinic acetylcholine receptors are implicated in distinct brain regions. Nicotine presents its own challenges given that one does not typically identify this drug as exerting the profound euphoria associated with other drugs of abuse. Yet the DA reward system is again clearly implicated in the addictive properties of nicotine, but so are several other neurochemical systems and brain circuits. One primary example is the involvement of the pedunculopontine tegmental nucleus, a brain region not traditionally linked to the actions of other drugs of abuse, in the acquisition of nicotine self-administration [however, see Bechara et al. (1998)].

Although not addressed in this set of reviews, it is important to point out that brain imaging studies have clearly indicated that many of the brain structures related to drug reward systems are also engaged by other rewards such as money (Knutson et al., 2001), romantic love (Bartels and Zeki, 2000), and maternal attachment (Lorberbaum et al., 1999). As one progresses through this series of mini-reviews, it will become apparent that there are many commonalities between different drugs with respect to the

systems involved in similar aspects of behaviors associated with the addiction process. Yet there are also many important differences. I am hopeful that the reader will sense the excitement that exists in the neurobiology of addiction and the need for continued research to identify what some refer to as the molecular "switch" (Leshner, 1998) and the various components of the "spiraling distress–addiction cycle" (Kreek and Koob, 1998) that underlies the transition from drug taking to drug addiction.

REFERENCES

Bartels A, Zeki S (2000) The neural basis of romantic love. NeuroReport 11:3829–3834.

Bechara A, Nader K, Van der Kooy D (1998) A two-separate-motivational-systems hypothesis of opioid addiction. Pharmacol Biochem Behav 59:1–17.

Berke JD, Hyman SE (2000) Addiction, dopamine, and the molecular mechanisms of memory. Neuron 25:515–532.

Bonci A, Williams JT (1996) A common mechanism mediates long-term changes in synaptic transmission after chronic cocaine and morphine. Neuron 16:631–639.

De Vries TJ, Shippenberg TS (2002) Neural systems underlying opiate addiction. J Neurosci 22:3321–3325.

Everitt BJ, Wolf ME (2002) Psychomotor stimulant addiction: a neural systems perspective. J Neurosci 22:3312–3320.

Kelley AE, Berridge KC (2002) The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci 22:3306–3311.

Knutson B, Adams CM, Fong GW, Hommer D (2001) Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 21:RC159(1–5).

Koob GF (1992) Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 13:177–184.

Kreek MJ, Koob GF (1998) Drug dependence: stress and dysregulation of brain reward pathways. Drug Alcohol Depend 51:23–47.

Leshner AI (1998) Drug addiction research: moving toward the 21st century. Drug Alcohol Depend 51:5–7.

Leshner AI (1999) Science-based views of drug addiction and its treatment. JAMA 282:1314–1316.

Lorberbaum JP, Newman JD, Dubno JR, Horwitz AR, Nahas Z, Teneback CC, Bloomer CW, Bohning DE, Vincent D, Johnson MR, Emmanuel N, Brawman-Mintzer O, Book SW, Lydiard RB, Ballenger JC, George MS (1999) Feasibility of using fMRI to study mothers responding to infant cries. Depress Anxiety 10:99–104.

Maldonado R, Rodriguez de Fonseca F (2002) Cannabinoid addiction: behavioral models and neural correlates. J Neurosci 22:3326–3331.

Nestler EJ (2001a) Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci 2:119–128.

Nestler EJ (2001b) Molecular neurobiology of addiction. Am J Addict 10:201–217.

Nestler EJ (2001c) Neurobiology. Total recall–the memory of addiction. Science 292:2266–2267.

Nestler EJ (2001d) Psychogenomics: opportunities for understanding addiction. J Neurosci 21:8324–8327.

Picciotto MR, Corrigall WA (zens) Neuronal systems underlying behaviors related to nicotine addiction: neural circuits and molecular genetics. J Neurosci 22:3338–3341.

Robinson TE, Kolb B (1997) Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. J Neurosci 17:8491–8497.

Robinson TE, Kolb B (1999) Morphine alters the structure of neurons in the nucleus accumbens and neocortex of rats. Synapse 33:160–162.

Sharma SK, Klee WA, Nirenberg MJ (1975) Dual regulation of adenylate cyclase accounts for narcotic dependence and tolerance. Proc Natl Acad Sci USA 72:3092–3096.

Spanagel R, Weiss F (1999) The dopamine hypothesis of reward: past and current status. Trends Neurosci 22:521–527.

Thomas MJ, Beurrier C, Bonci A, Malenka RC (2001) Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. Nat Neurosci 4:1217–1223.

Ungless MA, Whistler JL, Malenka RC, Bonci A (2001) Single cocaine exposure *in vivo* induces long-term potentiation in dopamine neurons. Nature 411:583–587.

Weiss F, Porrino LJ (2002) Behavioral neurobiology of alcohol addiction: recent advances and challenges. J Neurosci 22:3332–3337.

White FJ (1996) Synaptic regulation of mesocorticolimbic dopamine neurons. Annu Rev Neurosci 19:405–436.

Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. Psychol Rev 94:469–492.

Wise RA (2000) Addiction becomes a brain disease. Neuron 26:27–33.

Wolf ME (1998) The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. Prog Neurobiol 54:1–42.

Zhang X-F, Hu X-T, White FJ (1998) Whole-cell plasticity in cocaine withdrawal: reduced sodium current in nucleus accumbens neurons. J Neurosci 18:488–498.