Chapter 11
The Motivational Impact of Nicotine and Its Role in Tobacco Use: Final Comments and Priorities

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Minimizing the incidence of tobacco use requires a broad spectrum approach across the lifespan. For adolescents who are at risk for initiation, changes in public policy in the United States have reduced access to cigarettes, and school-based prevention programs have been implemented with some success (Nabors, Iobst, & McGrady, 2007). Mass media campaigns targeting youth at risk have also shown some efficacy (Emery et al., 2005), although this may not generalize to televised campaigns that are sponsored specifically by tobacco companies (Wakefield et al., 2006). When prevention efforts fail and tobacco use ensues, intervention strategies tend to shift from universal campaigns that reach the general population to more intense behavioral and pharmacological interventions that target selected groups or individuals. Although there has been an increasing emphasis on tobacco cessation programs that target youths in school (Curry et al., 2007), the quit rate among youths is low. As a result, tobacco use often escalates into a pattern that may be characterized as dependent use, coupled with a high rate of relapse upon each quit attempt. Understanding the neurobehavioral motivational systems involved in tobacco use and dependence, which is the subject of this book, is important for improving treatment strategies. In this last chapter, we present a few final comments for emphasis and provide a perspective from the National Institutes of Health (NIH) for future research.

Some Final Comments

As a whole, the combination of chapters in this book highlights the multi-faceted nature of the work being conducted on the motivational aspects of tobacco use. The concepts and mechanisms covered range from molar to molecular, from "craving" to cyclic AMP responsive element binding protein (CREB). While there is little doubt that a multi-pronged approach to the problem of tobacco use will advance the field at a brisk pace, the ultimate answers from a health perspective rest at the level of human trials. Three chapters from this book concentrated on some of

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the most relevant issues regarding tobacco smoking behavior in humans (Perkins, 2007; Rose, 2007; Tiffany, Warthen, & Goedeker, 2007). In the Perkins chapter, a strong case is made for sex differences in smoking cessation, with females being generally less responsive than males to nicotine replacement, which has obvious implications in treatment. However, since studies with laboratory animals indicate that female hormones tend to enhance, rather than blunt, the psychoactive effects of nicotine (Chaudhri et al., 2005; Faraday, Blakeman, & Grunberg, 2005; Harrod et al., 2004), it is possible that sex differences observed in humans may be associated more with socio-psychological factors than with neurohormonal status. The work of Perkins suggests that conditioning cues may be especially important, and the chapter by Tiffany and colleagues provides ample support for this notion. Given the role of environment cues, which are both discrete (e.g., image of a lit cigarette) and contextual (e.g., familiar tavern), the efficacy of various treatment strategies in blunting the impact of these cues needs direct experimental investigation. In the chapter by Rose, a comprehensive coverage of currently available pharmaco- and immunotherapies shows that multiple strategies can be effective in reducing the reinforcing effect of nicotine and tobacco use. However, since environmental cues may be critical triggers for relapse among smokers attempting to quit, a major challenge will be to determine to what extent these therapies, as well as future therapies, blunt the impact of smoking-related cues independent of nicotine. Indeed, since some conditioned responses to nicotine may involve neurobehavioral mechanisms independent from the unconditioned effects of nicotine (Forget, Hamon, & Thiébot, 2005; Papp, Gruca, & Willner, 2002), it might be useful to develop alternate therapies that specifically target the conditioning processes underlying tobacco use and relapse.

The importance of factors other than the direct primary and secondary reinforcing effects of nicotine in controlling the motivation to use tobacco is further highlighted in the chapters by Caggiula et al., (2007), Markou and Paterson (2007), and Bevins (2007). Caggiula's work points to a reward-enhancing effect of nicotine that is independent of its conditioned reinforcing effect. In essence, the notion is that nicotine is able to enhance the positive incentive value of environmental reinforcers. This is an important point that requires further investigation to determine to what extent it is specific to nicotine or generalized to other drugs of abuse within the stimulant class (e.g., cocaine, amphetamine), as well as outside the stimulant class (e.g., morphine, diazepam). The chapter by Markou and Paterson also stresses the importance of factors beyond the primary and secondary reinforcing effects of nicotine, specifically providing evidence that the cognitive enhancing effect of nicotine and the avoidance of negative withdrawal symptoms contribute to the motivational aspects of tobacco use. In the chapter by Bevins, the role of nicotine as a conditioned stimulus and occasion setter in a Pavlovian preparation is also outlined, adding further to the complex interplay of the various roles that nicotine may serve in controlling motivated behavior. However, since much of this work has been limited to the preclinical level, it will be important to determine to what extent these various conditioning factors are applicable to human smokers.

Regarding the molecular level of analysis, the remaining chapters by Brunzell and Picciotto (2007), Placzek and Dani (2007) and Dwoskin et al., (2007) represent some novel approaches for understanding the critical cellular targets that may inform novel medication development. The fact that three chapters are dedicated to molecular/neurochemical levels of analysis probably represents an accurate reflection of the general enthusiasm for this type of analysis for enhancing biomedical treatments for tobacco dependence. The chapter by Placzek and Dani characterizes the complex interplay of various neurotransmitter systems, including both monoamines and excitatory amino acids, in controlling reward-relevant midbrain dopamine systems. The chapters by Brunzell and Picciotto and by Dwoskin and colleagues present the most updated nomenclature for the nicotinic cholinergic receptor subtypes, implicating an important role for high affinity β2-containing receptors and their associated intracellular signaling cascades in the addiction process. Inhibition of the reward-relevant binding sites, as well as inhibition of the ion channel and/or the intracellular signaling cascades involved in synaptic plasticity, may all represent therapeutic targets for future research.

Future Priorities: The NIH Perspective

The NIH, and the National Institute on Drug Abuse (NIDA) in particular, has a long-standing commitment to research aimed at understanding nicotine addiction and in developing a variety of behavioral and pharmacological approaches to its amelioration. Indeed, NIDA has been at the forefront of efforts to recognize and publicize the addictive nature of nicotine. Research support has been provided for investigations of the direct effects of voluntary nicotine exposure (i.e., self-administration), as well as for studies of the consequences of involuntary exposure (gestational/prenatal).

NIDA supports a wide range of basic and clinical research; for example, the mechanisms of nicotine reward, the effects of nicotine on brain structure and function, the genetic, social and environmental antecedents of vulnerability to addiction, and the consequences of direct and indirect exposure to nicotine. Across all of these areas, NIDA supports research investigating the effects of sex or gender, and age or developmental stage. NIDA encourages research at multiple levels of analysis (from cells to social groups) and recognizes the value in a diversity of research paradigms and techniques. The extent of NIDA's interest in nicotine research is too broad to cover here, but some of NIDA's continuing and future research priorities for nicotine addiction are outlined below.

Long-Term Surveys of Tobacco Use

NIDA tracks patterns of drug use, including tobacco use, among adolescents and other populations through support of long-term epidemiological studies, such as the Monitoring the Future (MTF) survey (http://www.monitoringthefuture.org/). The

MTF has conducted drug use surveys among 12th grade students since the mid-1970s and began including 8th and 10th graders in 1990. In addition to monitoring drug use patterns, data from the MTF allow the identification of emerging trends that can guide the development of responsive prevention efforts.

Genetics/Epigenetics

Genetics clearly contribute to an individual's vulnerability to nicotine addiction (e.g., Mineur & Picciotto, 2007). Moreover, epigenetic research is beginning to identify environmental influences on gene expression that contribute to addiction vulnerability. Two efforts that demonstrate NIDA's commitment to understanding the genetic and epigenetic underpinnings of nicotine addiction are the Perlegen polymorphism contract and the NIDA Center for Genetics Studies. The Perlegen polymorphism contract supports a high throughput genome-wide search for single nucleotide polymorphisms (SNPs) that differentiate between individuals who are nicotine-dependent and those who smoked but never became dependent. The NIDA Center for Genetic Studies (http://zork.wustl.edu/nida/) is a resource that stores clinical data, diagnostic data, pedigree information, and biomaterials (including DNA, plasma, cryopreserved lymphocytes, and/or cell lines) from human subjects participating in studies from NIDA-supported Principal Investigators that form the NIDA Genetics Consortium (NGC). NGC data and resources can be made available to qualified investigators.

Nicotine Vaccine

As mentioned in the chapter by Rose (2007), the possibility of immunizing an individual against a specific drug, such as nicotine, relies on employing the body's own immune system to sequester nicotine molecules in the bloodstream, so as to prevent them from ever entering or affecting the brain. In 2000, NIDA embraced this concept and decided to support and guide a major nicotine vaccine effort in collaboration with Nabi, a Florida-based pharmaceutical company. Studies on NicVAX®, the nicotine conjugate vaccine that resulted from this joint research endeavor, show it to be safe and capable of generating antibodies that block nicotine's entry into the brain (Hatsukami et al. 2005). An effective nicotine vaccine would be an important addition to currently available treatment options, particularly as a treatment option to prevent relapse following abstinence, and would improve the likelihood of reducing adult tobacco use.

Drug Exposure and Development

The relationship between drug exposure and development is complex and wide-ranging. Of particular interest are the neurobiological and behavioral consequences

of drug exposure during the in utero, perinatal, and adolescent periods. As a result of NIDA supported research, we are beginning to understand how genetic variability, learning, social influence, environmental cues, and neurobiological changes/adaptations, affect vulnerability and co-morbidity throughout development. We are using this knowledge to shape prevention and treatment strategies.

Co-morbidity

It is widely recognized that nicotine addiction is often found in association with addiction to alcohol and other drugs. Addiction to nicotine is also highly associated with several mental disorders, including schizophrenia and depression (e.g., Williams & Ziedonis, 2004). Since co-occurrence of smoking and mental disorders is an area that overlaps the missions of multiple NIH Institutes, NIDA works with the National Institute on Mental Health (NIMH) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to promote research that investigates common neural substrates, genetic variability, and other factors that will allow a more complete understanding of these co-morbid disorders. By understanding the interaction among the host of important social, environmental, genetic, and biological factors, it is hoped that effective, tailored interventions may be developed for this complex population of smokers.

Neurobiological Substrates of Behavior

An area of continuing high priority for NIDA is to understand the neurobiological mechanisms of nicotine addiction. NIDA's support of basic research into the neurobiological substrates of behavior includes: (1) studies relating drugs of abuse to neural systems; (2) behavioral consequences of receptor subtype activation/inactivation; (3) function of endogenous systems (e.g., endorphins, anandamide, excitatory amino acids, etc., in health and disease); (4) neural mechanisms of drug-induced modification of cognitive processes (e.g., learning, memory, attention, associations, decision making); (5) models of addiction, including neural circuits underlying natural and drug reward, biobehavioral models of craving, relapse, compulsive behavior, and extinction; and (6) behavioral, physiological, or biochemical consequences of acute or chronic exposure to addictive drugs.

National Cooperative Drug Discovery Group (NCDDG)

Over the past decade or so, there have been major advances in our understanding of the protein targets, neural circuitry, and behavioral phenomena associated with addiction, and in the effects of drugs of abuse on CNS processes associated with addictive behavior; some of these advances have been covered in the chapters by Brunzell and Picciotto (2007), Placzek and Dani (2007) and Dwoskin et al., (2007).

The NCDDG is a ligand discovery and translational initiative in which the objective is the development of molecules with a particular profile of action as prototypes for medications to treat addiction or serve as tools to advance research in the treatment development domain. Components of NIDA-relevant NCDDG research projects can include, but are not limited to: (1) assessment of the behavioral profile of novel ligands in tests of reinforcement, relapse, and withdrawal; (2) tests of the ability of novel ligands to modulate cellular processes of plasticity in reward-relevant regions of the brain; (3) assessment of ligand efficacy on G-protein coupled receptors and ligand-gated ion channel activation; and (4) receptor activation effects on down-stream intracellular systems or in modulating the release of addiction-relevant neurotransmitters.

Finally, it should be mentioned that the highlights of NIDA's efforts and emerging priorities are regularly updated on www.smoking.drugabuse.gov. Information on Funding Opportunity Announcements (FOAs) in which NIDA participates can be found at: http://www.nida.nih.gov/funding/. Importantly, however, NIDA also depends upon extramural scientists to help shape the research agenda through regular communication at scientific meetings and symposia, as exemplified by the Nebraska Symposium on Motivation.

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