Drug Addiction: To the Cortex...and Beyond!

A logical beginning to understanding drug addiction was to identify the molecular binding site of the drug and determine its pharmacological mechanism. For the better part of the 20th century, this strategy was employed to understand why certain drugs were addictive. This research tack has provided us with in-depth knowledge of molecular sites of drug action as well as the immediate sequence of cellular changes produced by drug binding. A general understanding that has arisen from these studies is that increased dopamine transmission in the basal ganglia, particularly the nucleus accumbens, is responsible for the sense of reward and perhaps the addictive properties of the drugs (1). However, even as this synthesis of information regarding the acute effects of drugs was pointing researchers toward the importance of dopamine in reward and reinforcement, it was becoming ever more apparent that addiction produced by chronic drug use was associated with long-term changes in brain circuitry distal to dopamine transmission. Moreover, it appeared possible that these nondopaminergic neuroadaptations were encoding the behavioral changes that define addiction (2).

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The idea of encoding drug-induced behavioral changes in a memory-like fashion permits the incorporation of a commonly observed clinical characteristic of addiction, namely that drug-associated environmental stimuli have inordinate power to direct behavior (3). Indeed, drug-seeking by addicts is often described as an almost unconscious behavior that is seemingly immune from conscious control. As such, these behaviors can be viewed as a form of procedural memory that is triggered by environmental stimuli indicative of the drug experience. Procedural memories are encoded in a distributed circuit that integrates the association cortex with the basal ganglia, thalamus, and limbic nuclei. Recent imaging studies with cocaine addicts have revealed functional activation of components of this circuit following exposure to drug-associated cues (3, 4).

Three articles published in this issue of the *Journal* are a perfect illustration of our growing understanding that although the acute pharmacological impact of psychostimulants is on dopamine transmission, many of the long-term neurological changes mediating addictive behaviors are distributed into cortical and allocortical circuitry. The first article by Volkow et al. used positron emission tomography (PET) to examine a population of methamphetamine abusers for changes in dopamine transporter levels in the caudate and putamen. The methamphetamine abusers had significant dopamine transporter reduction in the basal ganglia. Given the well-established capacity for repeated administration of high doses of methamphetamine to destroy dopamine terminals in experimental animals, this probably constitutes a direct pharmacological consequence of the drug on dopamine transmission (5). The methamphetamine abusers also demonstrated deficiencies in motor and memory tasks that, while correlated with the apparent level of dopamine transporters in the caudate, may also be related to the cortical changes observed in Volkow et al.'s second study. In this companion article, the same methamphetamine abusers underwent PET to measure glucose metabolism. It is interesting to note that a general increase in brain metabolism relative to the comparison subjects was observed, as well as increased metabolism in the parietal cortex, accompanied by reductions in the thalamus and caudate. Thus, enduring changes in brain metabolism were produced in cortical circuitry distal to dopamine synapses (i.e., the parietal cortex) as well as in the dopamine axon terminal fields. Moreover, Volkow et al. noted that the pattern of regional

brain metabolic abnormalities produced in the methamphetamine abusers differed from the changes elicited by acute methamphetamine administration. This study clearly supports the concept of a transfer of neural plasticity from the site of acute pharmacological action at dopamine synapses into cortical circuitry.

In contrast to the experiments by Volkow et al. that examined the basal state of activity in patients with psychostimulant dependence, Adinoff et al. evaluated the response of the addicts to a pharmacological challenge. Procaine injection is known to elicit metabolic activation of cortical and subcortical brain regions that are part of the limbic system (6), and Adinoff et al. used single photon emission computed tomography to demonstrate that the pattern of limbic activation elicited by procaine differed between cocaine-addicted and comparison subjects. The most marked distinctions were procaine-induced blood flow increases in the orbitofrontal cortex of cocaine abusers and in the bilateral anterior cingulate, insular, and right amygdalar regions of the comparison subjects. Again, these findings point to important alterations in cortical and allocortical regions that may be distal to the acute pharmacological actions of cocaine on dopamine transmission.

The articles in this issue of the *Journal* present data that are generally aligned with an emerging portrait of psychostimulant addictions being mediated by long-term neuroadaptations in the cortex that are secondary to the pharmacological changes elicited by acute drug administration. However, this is a hypothesis that requires further empirical substantiation. For example, all changes in gene expression produced in animal models of psychostimulant addiction to date can be regulated by dopamine transmission (7). Also, with the exception of the parietal cortex as reported by Volkow et al., other regions showing addiction-related metabolic differences receive dopamine innervation (albeit sparse in some regions). Thus, it is possible that long-term alterations in dopamine transmission may be directly mediating some changes in cortical activity. In the final analysis, it is probable that aspects of addiction will be found to arise directly from long-term changes in dopamine transmission (e.g., the loss of dopamine innervation produced in methamphetamine addicts reported in this issue). However, an expanding database indicates that long-term neuroadaptations that are distributed in cortical and allocortical circuitry may be more critical mediators of addiction.

Even as data from imaging studies such as those in this issue of the *Journal* are a call to determine the cellular underpinnings of the functional changes in cortical regions, so do they also prompt us to go beyond individual cortical regions. The functional circuit revealed by the procaine challenge in the article by Adinoff et al. points us toward the need to understand how drug-induced changes in cortical nuclei may pathologically regulate the functional circuits that ultimately mediate addictive behaviors.

References

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