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The neural rejuvenation hypothesis of cocaine addiction

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A leading hypothesis guiding current molecular and cellular research into drug addiction conceptualizes key aspects of addiction as a form of memory in which common neuroplasticity mechanisms that mediate normal learning and memory processes are 'hijacked' by exposure to drugs of abuse to produce pathologic addiction-related memories. Such addiction-related memories are particularly robust and long-lasting and once formed are less amenable to updating. Here we propose a neural rejuvenation hypothesis of cocaine addiction. According to this hypothesis, repeated exposure to drugs of abuse induces some plasticity mechanisms normally associated with brain development within the reward circuitry that mediate the highly efficient and unusually stable memory abnormalities that characterize addiction.

Addiction and memory: the neural rejuvenation hypothesis

Despite its complex nature, drug addiction is essentially an acquired behavioral state formed in vulnerable individuals after they repeatedly experience cascades of emotional and motivational extremes during bouts of drug exposure and withdrawal. A major focus of the field has therefore been on identifying and characterizing drug-induced neuroadaptations in brain regions relevant to addiction [1,2]. An interesting observation over the years is the implication of many widely reported mechanisms of neuroplasticity that mediate diverse aspects of normal learning and memory in the development of drug addiction [3]. Another interesting consensus that is equally applicable to the fields of drug addiction and learning and memory is that although it has been possible to identify numerous molecular and cellular adaptations involved in both phenomena, it has not yet been possible to understand the biological basis underlying the uniquely strong memories and habits such as those that characterize a drug-addicted state or other forms of powerful emotional memory.

In 1931, Edwin Holt suggested that some embryonic or developmental mechanisms might be used during learning [4]. It is generally true that younger brains are better in forming memories and, by analogy, are more vulnerable to the plastic changes that underlie addiction [5,6]. These considerations raise the possibility that addiction, and other forms of extremely durable emotional memory, are mediated in part by mechanisms normally involved in development. In other words, drugs of abuse awaken and then utilize in key brain regions highly efficient plasticity mechanisms, which normally occur during development, to produce abnormally robust and stable forms of memories related to addiction.

The goal of this article is to review an increasing body of experimental evidence to support this rejuvenation hypothesis of drug addiction, according to which, exposure to drugs of abuse reopens juvenile forms of plasticity at the molecular, cellular, and circuitry levels within the reward pathways in the brain (Box 1), and that through drug-induced neural rejuvenation and subsequent re-maturation, strong and durable maladaptive plastic changes are formed as drug-associated memories [7–9]. We focus on cocaine-induced plasticity in the nucleus accumbens (NAc) to illustrate the general theme of the rejuvenation hypothesis. Related mechanisms induced by other drugs of abuse and in other brain regions will be discussed more briefly to demonstrate the widespread role of juvenile-like plasticity in addiction.

Insights from molecular results

At the transcriptional level

The NAc (Box 1) is a critical component of the reward pathways in the brain that mediate addiction-related behavioral abnormalities [10,11]. Two prominent and extensively studied transcriptional responses in the NAc after exposure to cocaine or other drugs of abuse are activation of CREB and accumulation of ΔFosB, two transcription factors that regulate synaptogenesis and circuitry development [12,13].

CREB is rapidly but transiently activated in the NAc by initial exposure to cocaine or other drugs of abuse, and can be activated repeatedly by chronic drug exposure [13,14]. During brain development, CREB and its downstream targets are among the central signaling pathways that regulate the survival, maturation, and integration of newly generated neurons into established neural networks [15]. Particularly during synaptogenesis, activation of CREB is essential for the growth of new axons, formation of new postsynaptic dendritic spines, prevention of nonspecific

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Box 1. Brain reward pathways, the nucleus accumbens, and addiction

In 1954, James Olds and Peter Milner found that electrical stimulation of certain brain regions appeared to give pleasure to experimental animals [122]. It was later found that the same brain regions function similarly in humans. These brain regions form several relatively separate neural circuits that are thought to mediate reward-associated behavioral responses, and thus are called the brain reward pathways. Among these pathways, the mesolimbic dopamine pathway, comprising the reciprocal projection between the forebrain nucleus accumbens (NAc) and the midbrain ventral tegmental area (VTA), has been most extensively examined because of its clear role in responding to, predicting, and pursuing rewards. In the 1970s, Gordon Mogenson and colleagues proposed that the NAc is an interface between emotion and behavior; it functions to prioritize emotional and motivational arousals for behavioral output [123]. This notion has since been supported by extensive experimental evidence. Drug addiction can be viewed as an emotional and motivational disorder that develops after repeated exposure to drugs of abuse, and is expressed as compulsive and persistent drug-seeking and -taking. The NAc has been implicated in both the development and expression of addictive behaviors. An overly simplified scenario is that exposure to drugs of abuse induces persistent changes in the NAc, with some of these changes causing the NAc to preferentially prioritize drug-related emotional and motivational arousals into behaviors.

synaptogenesis, and refinement of synaptic connections [16–19]. Within the NAc, activation of CREB upregulates several functional clusters of genes, in particular genes associated with synaptic development, neuronal growth, and cell adhesion [20]. These genes, once repetitively transcribed and translated following repeated exposure to cocaine or other drugs of abuse, may provide essential construction blocks for the reshaping of NAc circuits.

Unlike CREB, whose activation is transient, ΔFosB, because of its unusual stability, accumulates gradually in response to repeated exposure to cocaine or other drugs of abuse [12,21]. It has been proposed that ΔFosB makes an important contribution to certain long-lasting cellular and behavioral alterations following drug exposure. On upregulation of ΔFosB, NAc neurons express a large number of genes related to synaptic and circuitry development, in particular glutamate NMDA receptors (NMDARs) and several other components of excitatory synapses [20]. NMDARs play a critical role in synaptogenesis [22]. Thus, ΔFosB-induced NMDAR regulation may participate in the formation of new excitatory synapses and new circuits following exposure to cocaine or other drugs of abuse (see below).

Several other transcription factors, including c-Fos [23] and NFκB [24], and numerous forms of epigenetic regulation [21] induced by exposure to cocaine are also potentially important, but are not discussed in this article. Rather, activation of CREB and ΔFosB signaling is used here as a prototype of how diverse types of transcriptional mechanisms contribute to the re-emergence of developmental forms of plasticity in the NAc after exposure to cocaine or other drugs of abuse.

At the neurotrophic level

Chip-based gene screening has shown that expression levels of neurotrophins and their receptors are increased in the NAc of human cocaine abusers [25]. In the neonatal brain, neurotrophins are expressed at high levels in brain sites where new synapses are formed and new circuits are defined [26]. In the developed brain, expression of neurotrophins can be reinduced during reparative processes after brain injury [26]. Following exposure to cocaine or certain other drugs of abuse, one neurotrophin, brain-derived neurotrophic factor (BDNF), is upregulated in the NAc shell, ventral tegmental area (VTA), and related reward regions [27–29] and is directly implicated in cocaine self-administration, conditioned place preference, and locomotor sensitization [27–30].

During brain development, BDNF promotes synapse formation both pre- and postsynaptically. Presynaptically, BDNF promotes axonal branching and organization [31]. Postsynaptically, BDNF promotes dendritic arborization [32], increases the number, size, and motility of dendritic spines [33–35], and enhances the synthesis of synaptic proteins [36]. In animal models in which BDNF is overexpressed, increased numbers of synapses and docked neurotransmitter vesicles are observed [37].

The pro-synaptogenesis effects of BDNF are probably mediated by activation of the BDNF receptor TrkB [38,39], a type of tyrosine receptor kinase. After binding to BDNF, TrkB activates several intracellular and nuclear signaling pathways, among which is the ERK signaling cascade that directly phosphorylates CREB Ser 133 to induce CREB activation. Given the demonstrated role of CREB in dendritic spine formation, synaptic connectivity, synaptic protein expression, and synaptic plasticity, the pro-synaptogenesis effects of BDNF are probably mediated in part by BDNF activation of CREB [40–42]. Likewise, one of the promoter regions of the *Bdnf* gene is activated by CREB [43], creating a feed-forward loop that controls the synaptic effects of BDNF and CREB. Other signaling pathways downstream of BDNF, such as AKT-mTOR, are also probably involved in the regulation of synaptic structure and function, and warrant further study.

In animal studies, increased levels of *Bdnf* transcripts are observed in the NAc and related brain regions immediately after acute or repeated intraperitoneal injections of cocaine [28,44]. However, increased BDNF protein levels in the NAc build gradually during withdrawal from cocaine self-administration, and reach a maximum level only after 30 days of withdrawal [27]. This 'incubation' pattern (see below) suggests that BDNF upregulation might be a delayed downstream consequence of CREB activation after exposure to cocaine or, alternatively, might be partly independent of CREB activation and mediated by different mechanisms either locally within NAc or in several afferent brain regions.

Taken together, the results indicate that exposure to cocaine or other drugs of abuse induces alterations in transcription factors and neurotrophins, which have been intrinsically implicated in synaptogenesis and circuitry development in the developing brain. Because of these and other processes, dormant developmental mechanisms in the adult brain may be reawakened in response to drugs of abuse to restructure existing synapses or even form new synapses in the NAc and other addiction-associated brain regions. As discussed below, excitatory synapses in the NAc and other reward regions exhibit several characteristic developmental features after cocaine exposure.