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A Review On: Neurobiology of Addiction and Dopamine Role on Drug Addiction

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ABSTRACT

Drug addiction, also known as substance dependence, is a chronically relapsing disorder characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence) . Addiction and substance dependence (as currently defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition) will be used interchangeably throughout this paper to refer to a final stage of a usage process that moves from drug use to addiction. Clinically, the occasional but limited use of a drug with the potential for abuse or dependence is distinct from escalated drug use and the emergence of a chronic drug-dependent state. An important goal of current neurobiological research is to understand the neuropharmacological and neuroadaptive mechanisms within specific neurocircuits that mediate the transition from occasional, controlled drug use and the loss of behavioral control over drug-seeking and drug-taking that defines chronic addiction.

Addiction has been conceptualized as a chronic relapsing disorder with roots both in impulsivity and compulsivity and neurobiological mechanisms that change as an individual moves from one domain to the other. In addiction, drug-taking behavior progresses from impulsivity to compulsivity in a three-stage cycle: binge/intoxication, withdrawal/negative effect, and preoccupation/anticipation. As individuals move from an impulsive to a compulsive disorder, the drive for the drug-taking behaviour shifts from positive to negative reinforcement. Impulsivity and compulsivity can coexist in different stages of the addiction cycle.

Dopamine is one of the better-known brain chemicals, with lots of attention for its role as a "happy" chemical or relating to addiction. It has numerous important roles beyond that, though, and plays a big part in a host of medical conditions including addiction, schizophrenia, and Parkinson's disease. Dopamine's role in reward and motivation is a key aspect of addiction. Whether it's drugs, food, gambling, shopping, or sex, getting your "fix" gives your brain the good feeling dopamine creates. Your brain can crave that to an unhealthy degree, giving you the motivation to repeat the behavior that leads to the dopamine release.

KEYWORD: Dopamine, addiction, neuropharmacology, behavioural, neuroscience, deep brain stimulation, drug vaccine

I. INTRODUCTION

This article reviews scientific advances in the prevention and treatment of substance-use disorder and related developments in public policy. In the past two decades, research has increasingly supported the view that addiction is a disease of the brain. Although the brain disease model of addiction has yielded effective preventive measures, treatment interventions, and public health policies to address substance-use disorders, the underlying concept of substance abuse as a brain disease continues to be questioned, perhaps because the aberrant, impulsive, and compulsive behaviors that are characteristic of addiction have not been clearly tied to neurobiology. Here we review recent advances in the neurobiology of addiction to clarify the link between addiction and brain function and to broaden the understanding of addiction as a brain disease. We review findings on the desensitization of reward circuits, which dampens the ability to feel pleasure and the motivation to pursue everyday activities; the increasing strength of conditioned responses and stress reactivity, which results in increased cravings for alcohol and other drugs and negative emotions when these cravings are not sated; and the weakening of the brain regions involved in executive functions such as decision making, inhibitory control, and self-regulation that leads to

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repeated relapse. We also review the ways in which social environments, developmental stages, and genetics are intimately linked to and influence vulnerability and recovery. We conclude that neuroscience continues to support the brain disease model of addiction. Neuroscience research in this area not only offers new opportunities for the prevention and treatment of substance addictions and related behavioral addictions (e.g., to food, sex, and gambling) but may also improve our understanding of the fundamental biologic processes involved in voluntary behavioral control.

In the United States, 8 to 10% of people 12 years of age or older, or 20 to 22 million people, are addicted to alcohol or other drugs.[1] The abuse of tobacco, alcohol, and illicit drugs in the United States exacts more than $700 billion annually in costs related to crime, lost work productivity, and health care.[2-4] After centuries of efforts to reduce addiction and its related costs by punishing addictive behaviors failed to produce adequate results, recent basic and clinical research has provided clear evidence that addiction might be better considered and treated as an acquired disease of the brain (see Box 1 for definitions of substance-use disorder and addiction). Research guided by the brain disease model of addiction has led to the development of more effective methods of prevention and treatment and to more informed public health policies. Notable examples include the Mental Health Parity and Addiction Equity Act of 2008, which requires medical insurance plans to provide the same coverage for substance-use disorders and other mental illnesses that is provided for other illnesses,[5] and the proposed bipartisan Senate legislation that would reduce prison sentences for some nonviolent drug offenders,[6] which is a substantial shift in policy fueled in part by the growing realization among law-enforcement leaders that "reducing incarceration will improve public safety because people who need treatment for drug and alcohol problems or mental health issues will be more likely to improve and reintegrate into society if they receive consistent care."[7]

Nonetheless, despite the scientific evidence and the resulting advances in treatment and changes in policy, the concept of addiction as a disease of the brain is still being questioned. The concept of addiction as a disease of the brain challenges deeply ingrained values about self-determination and personal responsibility that frame drug use as a voluntary, hedonistic act. In this view, addiction results from the repetition of voluntary behaviors. How, then, can it be the result of a disease process? The concept of addiction as a brain disease has even more disconcerting implications for public attitudes and policies toward the addict. This concept of addiction appears to some to excuse personal irresponsibility and criminal acts instead of punishing harmful and often illegal behaviors. Additional criticisms of the concept of addiction as a brain disease include the failure of this model to identify genetic aberrations or brain abnormalities that consistently apply to persons with addiction and the failure to explain the many instances in which recovery occurs without treatment. (Arguments against the disease model of addiction and counterarguments in favor of it[8])

Advances in neurobiology have begun to clarify the mechanisms underlying the profound disruptions in decision-making ability and emotional balance displayed by persons with drug addiction. These advances also provide insight into the ways in which fundamental biologic processes, when disrupted, can alter voluntary behavioral control, not just in drug addiction but also in other, related disorders of self-regulation, such as obesity and pathologic gambling and video-gaming — the so-called behavioral addictions. Although these disorders also manifest as compulsive behaviors, with impaired self-regulation, the concept of behavioral addiction9 is still controversial, particularly as it relates to obesity. This research has also begun to show how and why early, voluntary drug use can interact with environmental and genetic factors to result in addiction in some persons but not in others.

STAGES OF ADDICTION:

Figure 1. Stages of the Addiction Cycle

For heuristic purposes, we have divided addiction into three recurring stages: binge and intoxication, withdrawal and negative effect, and preoccupation and anticipation (or craving).[10] Each stage is associated with the activation of specific neurobiologic circuits and the consequential clinical and behavioral characteristics (Figure 1).

A. Binge and intoxication

All known addictive drugs activate reward regions in the brain by causing sharp increases in the release of dopamine.[11-13] At the receptor level, these increases elicit a reward signal that triggers associative learning or conditioning. In this type of Pavlovian learning, repeated experiences of reward become associated with the environmental stimuli that precede them. With repeated exposure to the same reward, dopamine cells stop firing in response to the reward itself and instead fire in an nticipatory

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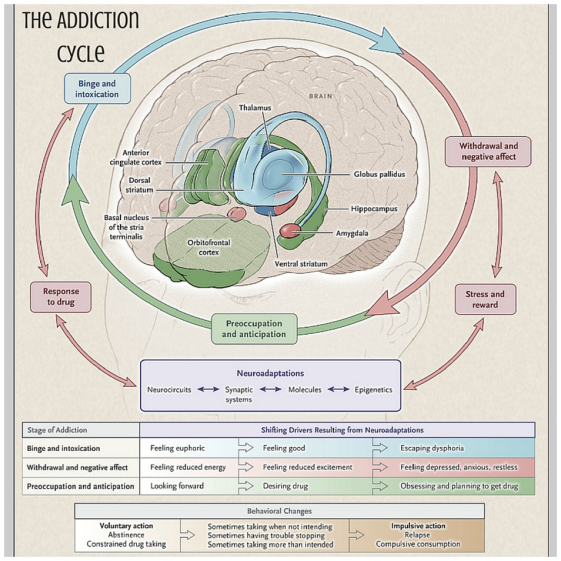

Figure 1. Stages of the Addiction Cycle.

response to the conditioned stimuli (referred to as "cues") that in a sense predict the delivery of the reward.[14] This process involves the same molecular mechanisms that strengthen synaptic connections during learning and memory formation. In this way, environmental stimuli that are repeatedly paired with drug use — including environments in which a drug has been taken, persons with whom it has been taken, and the mental state of a person before it was taken — may all come to elicit conditioned, fast surges of dopamine release that trigger craving for the drug[20] , motivate drug-seeking behaviors, and lead to heavy "binge" use of the drug.[21-23] These conditioned responses become deeply ingrained and can trigger strong cravings for a drug long after use has stopped (e.g., owing to incarceration or treatment) and even in the face of sanctions against its use.

As is true with other types of motivational learning, the greater the motivational attribute associated with a reward (e.g., a drug), the greater the effort a person is willing to exert and the greater the negative consequences he or she will be willing to endure in order to obtain it.[24,25] However, whereas dopamine cells stop firing after repeated consumption of a "natural reward" (e.g., food or sex) satiating the drive to further pursue it, addictive drugs circumvent natural satiation and continue to directly increase dopamine levels,[11,26] a factor that helps to explain why compulsive behaviors are more likely to emerge when people use drugs than when they pursue a natural reward .

B. Withdrawal and negative affect

An important result of the conditioned physiologic processes involved in drug addiction is that ordinary, healthful rewards lose their former motivational power. In a person with addiction, the reward and motivational systems become reoriented through conditioning to focus on the more potent release of dopamine produced by the drug and its cues. The landscape of the person with addiction becomes restricted to one of cues and triggers for drug use. However, this is only one of the ways in which addiction changes motivation and behavior.

For many years it was believed that over time persons with addiction would become more sensitive to the rewarding effects of drugs and that this increased sensitivity would be reflected in higher levels of dopamine in the circuits of their brains that process reward (including the nucleus accumbens and the dorsal striatum) than the levels in persons who never had a drug addiction. Although this theory seemed to make sense, research has shown that it is incorrect. In fact, clinical and preclinical studies have shown that drug consumption triggers much smaller increases in dopamine levels in the presence of addiction (in both animals and humans) than in its absence (i.e., in persons who have never used drugs).[22,23,27,28] This attenuated release of dopamine renders the brain's reward system much less sensitive to stimulation by both drug-related and non–drug-related rewards.[29-31] As a result, persons with addiction no longer experience the same degree of euphoria from a drug as they did when they first started using it. It is for this same reason that persons with addiction often become less motivated by everyday stimuli (e.g., relationships and activities) that they had previously found to be motivating and rewarding. Again, it is important to note that these changes become deeply ingrained and cannot be immediately reversed through the simple termination of drug use (e.g., detoxification).

In addition to resetting the brain's reward system, repeated exposure to the dopamine-enhancing effects of most drugs leads to adaptations in the circuitry of the extended amygdala in the basal forebrain; these adaptations result in increases in a person's reactivity to stress and lead to the emergence of negative emotions.[32,33] This "antireward" system is fueled by the neurotransmitters involved in the stress response, such as corticotropin-releasing factor and dynorphin, which ordinarily help to maintain homeostasis. However, in the addicted brain, the antireward system becomes overactive, giving rise to the highly dysphoric phase of drug addiction that

ensues when the direct effects of the drug wear off or the drug is withdrawn[34] and to the decreased reactivity of dopamine cells in the brain's reward circuitry.[35] Thus, in addition to the direct and conditioned pull toward the "rewards" of drug use, there is a correspondingly intense motivational push to escape the discomfort associated with the aftereffects of use. As a result of these changes, the person with addiction transitions from taking drugs simply to feel pleasure, or to "get high," to taking them to obtain transient relief from dysphoria (**Figure 1**).

Persons with addiction frequently cannot understand why they continue to take the drug when it no longer seems pleasurable. Many state that they continue to take the drug to escape the distress they feel when they are not intoxicated. Unfortunately, although the short-acting effects of increased dopamine levels triggered by drug administration temporarily relieve this distress, the result of repeated bingeing is to deepen the dysphoria during withdrawal, thus producing a vicious cycle.

C. Preoccupation and anticipation

The changes that occur in the reward and emotional circuits of the brain are accompanied by changes in the function of the prefrontal cortical regions, which are involved in executive processes. Specifically, the down-regulation of dopamine signaling that dulls the reward circuits' sensitivity to pleasure also occurs in prefrontal brain regions and their associated circuits, seriously impairing executive processes, among which are the capacities for self-regulation, decision making, flexibility in the selection and initiation of action, attribution of salience (the assignment of relative value), and the monitoring of error.[36] The modulation of the reward and emotional circuits of prefrontal regions is further disrupted by neuroplastic changes in glutamatergic signaling.[37] In persons with addiction, the impaired signaling of dopamine and glutamate in the prefrontal regions of the brain weakens their ability to resist strong urges or to follow through on decisions to stop taking the drug. These effects explain why persons with addiction can be sincere in their desire and intention to stop using a drug and yet simultaneously impulsive and unable to follow through on their resolve. Thus, altered signaling in prefrontal regulatory circuits, paired with changes in the circuitry involved in reward and emotional response, creates an imbalance that is crucial to both the gradual development of compulsive behavior in the addicted disease state and the associated inability to voluntarily reduce drug-taking behavior, despite the potentially catastrophic consequences.

THE ROLE OF DOPAMINE IN ADDICTION:

Addictive drugs are inherently rewarding. They highjack the brain's dopamine system to increase dopamine levels in the nucleus accumbens, a key focal point for reward neurocircuitry in the brain.[38] While dopamine is critical for the rewarding effects of drugs, its role in substance use disorders is still evolving. Nearly 20 years ago, Nora Volkow (National Institute on Drug Abuse, National Institutes of Health) showed via positron emission tomography imaging that higher dopamine levels correspond with a more intense high in healthy volunteers given intravenous methylphenidate (MPH), a central nervous stimulant also known as Ritalin. There was considerable variability in dopamine levels across subjects; some individuals experienced neither increased dopamine levels nor "high." Administration of oral MPH, which takes longer to enter the brain, resulted in no high with slower increases in dopamine levels.[39]

Since the rate of dopamine increase plays a factor in whether a drug will produce a rewarding effect, the different properties and effects of dopamine receptors in the brain are likely to play significant roles. The prefrontal cortex contains both dopamine D1 and D2 receptors. D2 receptors have an approximately 10- to 100-fold greater affinity for dopamine than D1 receptors and are therefore activated at lower dopamine concentrations. Under normal circumstances, the prefrontal cortex receives a low level, stable flow of dopamine owing to relatively slow, tonic firing of dopamine neurons in the ventral tegmental area (VTA) that project to the cortex. However, in response to an unexpected event, such as an extraordinary reward or very aversive event, dopamine neurons fire much more quickly. This phasic firing results in an abrupt, yet transient, increase in dopamine. The high levels of dopamine achieved during phasic firing are able to activate D1 receptors and are thought to be required for dopamine's full rewarding effects.[40,41] Drugs of abuse, particularly psychostimulants, mimic the high dopamine concentrations produced by phasic firing and thus activate both D1 and D2 receptors.[42]

D1 receptors stimulate both reward, via pathways modulating the striatum and cortex, and conditioning and memory mechanisms that involve the amygdala, medial orbitofrontal cortex (OFC), and hippocampus. The conditioning/memory

processes critical to addiction allows individuals to automatically associate a stimulus with a reward or punishment. Perhaps paradoxically, several studies have shown that addictive drugs fail to increase dopamine release in addicted individuals compared with non addicted controls. MPH did not significantly increase dopamine levels among active[43] or detoxified cocaine addicts.[44] Cocaine users also reported less of a high from MPH than controls.[44] However, among active addicts shown a video to produce craving, increased dopamine was observed in the dorsal striatum. The magnitude of this dopamine increase was associated with the extent of drug craving.[43] These data suggest that in addiction there is thus a switch from the drug itself initiating dopamine release to drug cues and stimuli initiating dopamine release. This shift from reward to conditioning involves dopamine phasic firing leading to drug cravings and compulsive drug use in response to drug and other conditioned cues.[38]

Normally, D2 receptors modulate the effects of D1 receptors via the striatal indirect pathway;[42] however, several studies have shown that addicted subjects have lower expression of dopamine D2 receptors.[45] Reductions in D2 receptors among addicted subjects are associated with decreased activity in the OFC, anterior cingulate gyrus, and dorsolateral prefrontal cortex areas of the brain involved in emotion regulation and decision making. Because impairments in the orbitofrontal and anterior cingulate cortices are associated with compulsive behaviors, impaired dopamine signaling in these areas in addicted subjects may be partially responsible for their compulsive behavior and impulsivity.[38] In animal studies, increased dopamine D2 receptor expression in the nucleus accumbens reduced drug consumption in models of both alcohol and cocaine dependence.[46,47] In humans, a recent study in methamphetamine users demonstrated that regular aerobic exercise can upregulate striatal dopamine D2 and D3 receptors; whether this results in reduced cravings and drug use remains to be seen.[48]

COMPUTATIONAL MODELING OF DOPAMINE CELLS

According to a computational model of dopamine release in response to rewards and expectations, dopamine neurons encode reward prediction errors in their firing rates—they increase their firing rates if results are better than expected and decrease their firing rates if results are worse than expected.[49] To test this model and its relationship to behavior, P. Read Montague (Virginia Polytechnic Institute and State University; University College London) has used functional magnetic resonance imaging (fMRI) to monitor the effects of reward prediction error on both brain activity and future behavior in subjects participating in a betting task in a fictitious market. The study found neural signatures associated with reward prediction error and fictive error (how much a person gains versus how much they could have gained if they had bet more). Fictive error was associated with activation in the ventral caudate, ventral putamen, and posterior parietal cortex as well as with behavioral changes. The higher the fictive error, the more likely a person was to change their next bet.[50] Fictive error signatures were present in the brains of both smokers and nonsmokers; the magnitude of these signatures did not correlate with a change in behavior in smokers.[51]

Using electrochemistry to monitor dopamine release in real time while subjects completed such tasks showed that dopamine release roughly correlates with market activity at long timescales. However, at short, millisecond timescales, a different pattern emerged. With high bets, increases in dopamine fluctuations correlated with reward prediction errors; however, as the bet size decreased, the correlation reversed. At low bet sizes, increased dopamine fluctuations were seen with negative errors and vice versa. This behavior suggests two sources of dopamine fluctuation—one that communicates a prediction error and one that communicates a fictive error.[52]

New insights into our understanding of drug abuse and addiction have revealed that the desire to use drugs and the process of addiction depend on effects on brain function. Drugs of abuse have been hypothesized to produce their rewarding effects by neuropharmacological actions on a common brain reward circuit called the extended amygdala. The extended amygdala involves the mesolimbic dopamine system and specific subregions of the basal forebrain, such as the shell of the nucleus accumbens, the bed nucleus of the stria terminalis, and the central nucleus of the amygdala. The psychomotor stimulants cocaine and amphetamine activate the mesolimbic dopamine system. Repeated and prolonged drug abuse leads to compulsive use, and the mechanism for this transition involves, at the behavioral level, a progressive dysregulation of brain reward circuitry and a recruitment of brain stress systems such as corticotropin-releasing factor. The molecular

mechanisms of signal transduction in these systems are a likely target for residual changes in that they convey allostatic changes in reward set point, which lead to vulnerability to relapse.[53]

VARIOUS STUDIES INVOLVE DOPAMINE ROLE IN DRUG ADDICTION

Volkow, N.D et.al. study: The involvement of dopamine (DA) in drug reinforcement is well established, but much less is known about its contribution to addiction. Volkow, N.D et.al. have used positron emission tomography to investigate in humans the role of DA in drug reinforcement, addiction and drug vulnerability. We have shown that during drug intoxication increases in striatal DA are associated with the drug's reinforcing effects only if the DA changes occur rapidly. These results corroborate the relevance of drug-induced DA increases and of pharmacokinetics in the rewarding effects of drugs in humans. During withdrawal, we have shown significant reductions in DA D_2 receptors and in DA release in drug abusers, which is likely to result in decreased sensitivity to non-drug-related reinforcing stimuli. The DA D_2 reductions were associated with decreased activity in the orbitofrontal cortex, which we postulate is one of the mechanisms underlying compulsive drug administration in the addict. In fact, during craving the orbitofrontal cortex becomes hyperactive in proportion to the desire for the drug. In non-drug-abusing subjects striatal DA D_2 receptors levels predicted the reinforcing responses to stimulant drugs, providing evidence that striatal DA D_2 receptors modulate reinforcing responses to stimulants in humans and may contribute to the predisposition for drug self-administration.[54]

Gaetano Di et.al. study: The effects of drugs and substances of abuse on central dopamine (DA) transmission studied by in vivo monitoring techniques have been examined and compared with those of conventional reinforcers and in particular with food. The similarities and differences in the action of drugs and conventional reinforcers on DA transmission can provide the basis for an hypothesis of the mechanism of drug addiction and compulsive drug use. This hypothesis states that drug addiction is due to excessive control over behaviour exerted by drug- related stimuli as a result of abnormal motivational learning induced by repeated drug exposure. Such abnormal motivational learning would derive from the repetitive non-habituating property of drugs of abuse to activate DA transmission phasically in the nucleus accumbens (NAc) 'shell'. Thus, activation of DA transmission by conventional reinforcers is under strong inhibitory control by previous exposure to the reinforcer (habituation); this, however, is not the case with drug reinforcers. Repetitive, non-adaptive release of DA in the NAc 'shell' by drugs of abuse would result in abnormal strengthening of stimulus-reward (incentive learning) and stimulus-response associations (habit learning) that constitute the basis for craving and compulsive drug use.[55]

Nora D. Volkow v et.al. study: Dopamine (DA) is considered crucial for the rewarding effects of drugs of abuse, but its role in addiction is much less clear. This review focuses on studies that used PET to characterize the brain DA system in addicted subjects. These studies have corroborated in humans the relevance of drug-induced fast DA increases in striatum [including nucleus accumbens (NAc)] in their rewarding effects but have unexpectedly shown that in addicted subjects, drug-induced DA increases (as well as their subjective reinforcing effects) are markedly blunted compared with controls. In contrast, addicted subjects show significant DA increases in striatum in response to drug-conditioned cues that are associated with self-reports of drug craving and appear to be of a greater magnitude than the DA responses to the drug. We postulate that the discrepancy between the expectation for the drug effects (conditioned responses) and the blunted pharmacological effects maintains drug taking in an attempt to achieve the expected reward. Also, whether tested during early or protracted withdrawal, addicted subjects show lower levels of D2 receptors in striatum (including NAc), which are associated with decreases in baseline activity in frontal brain regions implicated in salience attribution (orbitofrontal cortex) and inhibitory control (anterior cingulate gyrus), whose disruption results in compulsivity and impulsivity. These

results point to an imbalance between dopaminergic circuits that underlie reward and conditioning and those that underlie executive function (emotional control and decision making), which we postulate contributes to the compulsive drug use and loss of control in addiction.[56]

DrGeorge et.al. study: Drug addiction represents a dramatic dysregulation of motivational circuits that is caused by a combination of exaggerated incentive salience and habit formation, reward deficits and stress surfeits, and compromised executive function in three stages. The rewarding effects of drugs of abuse, development of incentive salience, and development of drug-seeking habits in the binge/intoxication stage involve changes in dopamine and opioid peptides in the basal ganglia. The increases in negative emotional states and dysphoric and stress-like responses in the withdrawal/negative affect stage involve decreases in the function of the dopamine component of the reward system and recruitment of brain stress neurotransmitters, such as corticotropin-releasing factor and dynorphin, in the neurocircuitry of the extended amygdala. The craving and deficits in executive function in the so-called preoccupation/anticipation stage involve the dysregulation of key afferent projections from the prefrontal cortex and insula, including glutamate, to the basal ganglia and extended amygdala. Molecular genetic studies have identified transduction and transcription factors that act in neurocircuitry associated with the development and maintenance of addiction that might mediate initial vulnerability, maintenance, and relapse associated with addiction.[57]

Nora DVolkow et.al. study:Drug addiction is characterized by a set of recurring processes (intoxication, withdrawal, craving) that lead to the relapsing nature of the disorder. We have used positron emission tomography to investigate in humans the role of dopamine (DA) and the brain circuits it regulates in these processes. We have shown that increases in DA are associated with the subjective reports of drug reinforcement corroborating the relevance of drug-induced DA increases in the rewarding effects of drugs in humans. During withdrawal we have shown in drug abusers significant reductions in DA D2 receptors and in DA release. We postulate that this hypodopaminergic state would result in a decreased sensitivity to natural reinforcers perpetuating the use of the drug as a means to compensate for this deficit and contributing to the anhedonia and dysphoria seen during withdrawal. Because the D2 reductions are associated with decreased activity in the anterior cingulate gyrus and in the orbitofrontal cortex we postulate that this is one of the mechanisms by which DA disruption leads to compulsive drug administration and the lack of control over drug intake in the drug-addicted individual. This is supported by studies showing that during craving these frontal regions become hyperactive in proportion to the intensity of the craving. Craving is also associated with activation of memory circuits including the amygdala (implicated in conditioned learning), hippocampus (implicated in declarative learning), and dorsal striatum (implicated in habit learning) all of which receive DA innervation. We therefore postulate that dopamine contributes to addiction by disrupting the frontal cortical circuits that regulate motivation, drive, and self-control and by memory circuits that increase the motivational salience of the drug and drug-associated stimuli.[58]

N.D.Volkow et.al. study : Dopamine is involved in drug reinforcement but its role in addiction is less clear. Here we describe PET imaging studies that investigate dopamine's involvement in drug abuse in the human brain. In humans the reinforcing effects of drugs are associated with large and fast increases in extracellular dopamine, which mimic those induced by physiological dopamine cell firing but are more intense and protracted. Since dopamine cells fire in response to salient stimuli, supraphysiological activation by drugs is experienced as highly salient (driving attention, arousal, conditioned learning and motivation) and with repeated drug use may raise the thresholds required for dopamine cell activation and signaling. Indeed, imaging studies show that drug abusers have marked decreases in dopamine D2 receptors and in dopamine release. This decrease in dopamine function is associated with reduced regional activity in orbitofrontal cortex (involved in salience attribution; its disruption results in compulsive behaviors), cingulate gyrus (involved in inhibitory control; its disruption results in impulsivity) and dorsolateral prefrontal

cortex (involved in executive function; its disruption results in impaired regulation of intentional actions). In parallel, conditioning triggered by drugs leads to enhanced dopamine signaling when exposed to conditioned cues, which then drives the motivation to procure the drug in part by activation of prefrontal and striatal regions. These findings implicate deficits in dopamine activity linked with prefrontal and striatal deregulation—in the loss of control and compulsive drug intake that results when the addicted person takes the drugs or is exposed to conditioned cues. The decreased dopamine function in addicted individuals also reduces their sensitivity to natural reinforces. Therapeutic interventions aimed at restoring brain dopaminergic tone and activity of cortical projection regions could improve prefrontal function, enhance inhibitory control and interfere with impulsivity and compulsive drug administration while helping to motivate the addicted person to engage in non-drug related behaviors.[59]

NEWER APPROACHES TO STUDYING ADDICTION: DEEP BRAIN STIMULATION

While optogenetics has proven to be a useful tool in the laboratory, it is currently less feasible as a treatment in humans. Deep brain stimulation (DBS) involves sending electrical impulses to specific areas of the brain via implanted electrodes. DBS is currently used in the treatment of a number of neurological conditions, especially Parkinson's disease, but also epilepsy and OCD.

Meaghan Creed (University of Geneva) uses DBS to depotentiate synapses in the nucleus accumbens. DBS has been shown to be effective in abolishing some of the neurological and behavioral effects of cocaine in mice. The background for this work comes from findings that addictive drugs alter both the quality and the quantity of synaptic transmission in the D1 receptor expressing spiny neurons of the nucleus accumbens. These changes persist long after the drug is out of the system. One of the consequences of the strong dopaminergic response stimulated by cocaine and other drugs of abuse is a switch in the D1 medium spiny neurons in the nucleus accumbens from $GluA2^+$ AMPA receptors to $GluA2^-$ AMPA receptors. This enhances the strength of the excitatory transmission onto D1 MSNs and over-potentiates the synapse.[60-62] Depressing or desensitizing the synapse may be able to reverse the effects of addictive drugs. Optogenetic stimulation has been shown to reverse cocaine-induced synaptic plasticity in mice both with reference to synaptic strength and the composition of AMPA receptors. In addition, optogenetic stimulation abolished cocaine-induced hyperactivity.[63]

Creed's laboratory, using DBS at a frequency similar to that used in Parkinson's disease, reduced synaptic strength and hyperactivity in mice in response to cocaine; however, the effects were transient. The stimulation was ineffective if the cocaine was administered as little as 4 h after DBS. Lower frequencies, similar to those used in optogenetics experiments, showed no effects on synaptic strength or behavior. DBS thus may be nonspecifically stimulating several inputs in the brain. Stimulating dopamine signaling may cancel the intended dopamine-lowering effect. Adding a dopamine antagonist to low-frequency DBS, optogenetically inspired DBS (oiDBS), significantly suppressed cocaine-induced hyperactivity and reversed cocaine-induced synaptic plasticity. Importantly, the effects of a single 10-min oiDBS session persisted for at least 1 week. Subsequent work revealed that the effects of oiDBS are dependent on mGluR, since pretreatment with an mGluR blocker abolished the oiDBS effects.[63]

NEWER APPROACHES TO TREATING ADDICTION: DRUG VACCINES

Ron Crystal (Weill Cornell Medical College) described work in developing vaccines against addictive drugs that would prevent them from entering and thus affecting the brain. Addictive drugs are small molecules that are not highly immunogenic, however. Though the immune system does not readily produce good antibodies directed against addictive drugs, this hurdle is being addressed via two approaches.

Active vaccination strategies conjugate the addictive drug to adenovirus capsid proteins, which are highly immunogenic. Crystal has developed a cocaine vaccine by conjugating the cocaine analogue GNE to adenovirus that has been denatured so that it cannot replicate.[64] The vaccine, dAd5GNE, can engender high anticocaine antibody titers in both rodent and nonhuman primate models.[65] The vaccine prevents cocaine distribution in the brain in rodent models, even with frequent administration and at very high doses.[66] It also reduces cocaine self-administration in nonhuman primates.[67]

A phase 1 clinical trial is underway in human cocaine users. Participants receive 6 monthly injections of either conjugate vaccine or placebo. The study will investigate the ability of three

different vaccine doses to produce anticocaine antibodies and will assess safety.[68]

In passive immunization approaches, expression of a gene that encodes an anticocaine antibody is delivered to the liver using an adeno-associated virus vector. Transfection with the AAvrh.10 vector containing this anticocaine antibody gene can produce high, persistent anticocaine antibody titers following a single administration to animals. In mice, AAvrh.10 reduced cocaine levels in the brain and reduced cocaine-induced hyperactivity for periods of months after the transfection.[69]

II. SUMMARY AND CONCLUSIONS

Much progress in neurobiology has provided a useful neurocircuitry framework with which to identify the neurobiological and neuroadaptive mechanisms involved in the development of drug addiction. The brain reward system implicated in the development of addiction is composed of key elements of the basal forebrain with a focus on the nucleus accumbens and central nucleus of the amygdala. Neuropharmacological studies in animal models of addiction have provided evidence for the activation of specific neurochemical mechanisms in specific brain reward neurochemical systems in the basal forebrain (dopamine, opioid peptides, GABA, and endocannabinoids) during the binge/ intoxication stage. During the withdrawal/ negative affect stage, dysregulation of the same brain reward neurochemical systems occurs in the basal forebrain (dopamine, opioid peptides, GABA, and endocannabinoids). There is also recruitment of brain stress/aversion systems (CRF and dynorphin) and dysregulation of brain antistress systems (neuropeptide Y) that contribute to the negative motivational state associated with drug abstinence. During the preoccupation/ anticipation stage, neurobiological circuits that engage the frontal cortex glutamatergic projections to the nucleus accumbens are critical for drug-induced reinstatement, whereas basolateral amygdala and ventral subiculum glutamatergic projections to the nucleus accumbens are involved in cue-induced reinstatement. Stress-induced reinstatement appears to be mediated by changes in the antireward systems of the extended amygdala. The changes in craving and antireward (stress) systems are hypothesized to remain outside of a homeostatic state, and as such convey the vulnerability for the development of dependence and relapse in addiction. Genetic studies to date in animals suggest roles for the genes encoding the neurochemical elements involved in the brain reward (dopamine, opioid peptide) and stress (neuropeptide Y) systems in the vulnerability to addiction. Molecular studies have identified transduction and transcription factors that may mediate the dependence-induced reward dysregulation (CREB) and chronic-vulnerability changes (ΔFosB) in neurocircuitry associated with the development and maintenance of addiction. Human imaging studies reveal similar neurocircuits involved in acute intoxication, chronic drug dependence, and vulnerability to relapse.

Although no exact imaging results necessarily predict addiction, two salient changes in established and unrecovered substance-dependent individuals that cut across different drugs are decreases in orbitofrontal/prefrontal cortex function and decreases in brain dopamine D_2 receptors. No molecular markers are sufficiently specific to predict the vulnerability to addiction, but changes in certain intermediate early genes with chronic drug exposure in animal models show promise of long-term changes in specific brain regions that may be common to all drugs of abuse. The continually evolving knowledge base of the biological and neurobiological aspects of substance use disorders provides a heuristic framework to better develop diagnoses, prevention, and treatment of substance abuse disorders.

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