

The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies

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Received 18 May 2004; received in revised form 12 July 2004; accepted 21 July 2004

Abstract

Imaging studies have provided evidence of how the human brain changes as an individual becomes addicted. Here, we integrate the findings from imaging studies to propose a model of drug addiction. The process of addiction is initiated in part by the fast and high increases in DA induced by drugs of abuse. We hypothesize that this supraphysiological effect of drugs trigger a series of adaptations in neuronal circuits involved in saliency/reward, motivation/drive, memory/conditioning, and control/disinhibition, resulting in an enhanced (and long lasting) saliency value for the drug and its associated cues at the expense of decreased sensitivity for salient events of everyday life (including natural reinforcers). Although acute drug intake increases DA neurotransmission, chronic drug consumption results in a marked decrease in DA activity, associated with, among others, dysregulation of the orbitofrontal cortex (region involved with salience attribution) and cingulate gyrus (region involved with inhibitory control). The ensuing increase in motivational drive for the drug, strengthened by conditioned responses and the decrease in inhibitory control favors emergence of compulsive drug taking. This view of how drugs of abuse affect the brain suggests strategies for intervention, which might include: (a) those that will decrease the reward value of the drug of choice; (b) interventions to increase the saliency value of non-drug reinforcers; (c) approaches to weaken conditioned drug behaviors; and (d) methods to strengthen frontal inhibitory and executive control. Though this model focuses mostly on findings from PET studies of the brain DA system it is evident that other neurotransmitters are involved and that a better understanding of their roles in addiction would expand the options for therapeutic targets.

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Keywords: PET; Striatum; Dopamine; Reward; Motivation; Predisposition; Salience; Nucleus accumbens (NAc); Orbitofrontal cortex (OFC); Cingulate gyrus

1. Introduction

Investigations of the molecular, cellular and brain circuits disrupted by chronic exposure to drugs of abuse have advanced the understanding of the neurobiology of addiction. Though the exact mechanisms underlying addiction are not sufficiently understood, it is likely that addiction results from a combination of

genetic and biological factors that interact with environmental events.

A central concept in drug abuse research is that increased dopamine (DA) in limbic brain regions is associated with the reinforcing effects of drugs (Di Chiara and Imperato, 1988; Koob and Bloom, 1988). The reinforcing effects of psychostimulant drugs such as cocaine have traditionally been associated with an initial blockade of dopamine transporters (DAT), leading to increases in extracellular DA (Egilmez et al., 1995). With some drugs such as nicotine, the increase in DA is secondary to direct stimulation of DA cell firing. With drugs such as opiates and alcohol, increased

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DA is due to disinhibition of DA cells. Though for many years drug addiction was predominantly associated with limbic brain regions involved in the acute reinforcing effects of drugs, recent brain imaging studies have implicated the frontal cortex, and more recently the temporal insula as well as the thalamus, which are involved in modulation of long-term drug effects (Goldstein and Volkow, 2002). While once regarded as a neurotransmitter involved only in reward, the modern view of DA has shifted to that of a neurotransmitter with involvement in signaling saliency of events (including rewarding, aversive, novel, and unexpected stimuli), in driving motivation, in predicting reward or failure to receive it, and in facilitating memory consolidation of salient events.

Advances in the understanding of brain DA mechanisms provide a new perspective on drugs of abuse and addiction. These drugs can induce addiction not only because they are experienced as pleasurable but because they are processed as salient events, inherently motivating procurement of more drugs, thus serving to consolidate the memory of the reinforcing event (Fenu and Di Chiara, 2003). With repeated drug exposure, the reinforcing effects of these drugs are due not only to pharmacological consequences but also to the learned conditioned responses and the enhanced saliency value that the individual acquires through experience. The neural circuits involved in these acquired (conditioned) effects suggest explanations for drug craving and compulsive drug consumption by addicted individuals, even when the drugs are no longer perceived as pleasurable.

Brain imaging studies have contributed substantially to advances in the understanding of drug addiction. Here, we will review some of the studies based on this area of investigation.

2. Role of brain imaging in the investigation of drug addiction

Advances in imaging technologies such as positron emission tomography (PET) and magnetic resonance imaging (MRI) have made it possible to investigate the mechanisms of action of abused drugs directly in the human brain, as well as to document long-term consequences of addiction on the brain. PET can be used in the living human brain to measure radiotracers labeled with short-lived positron-emitting isotopes that selectively bind to specific receptors, transporters, and enzymes involved in synthesis and metabolism of neurotransmitters (Volkow et al., 1996, 1999b, 2002a, 2003a). Most PET studies of the neurochemistry of drug abuse have concentrated on investigating brain DA activity attributed to the acute effects of drugs as well as changes during addiction (Volkow et al., 1999b,

2002a, 2003a). More recently, PET has been used to examine the effects of drugs on other neurotransmitters such as the opiate and the GABA systems (Springer, 1999).

Brain function and neurochemistry in addicted subjects is also being explored using functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) (Daumann et al., 2003; Kimberg et al., 2001; Stein, 2001). fMRI is based on disruption of the magnetic properties in tissue when oxyhemoglobin changes to deoxyhemoglobin (Springer, 1999). Since this occurs when brain tissue is stimulated, fMRI can be used to measure changes in regional brain activity. Measures of brain activation with fMRI have higher spatial and temporal resolution than those achieved with PET methods that measure brain glucose metabolism or cerebral blood flow. MRS measures the chemical composition of brain tissue (Ross et al., 1992) based on the magnetic properties of hydrogen or of phosphorus, which change as a function of the chemical structural environment of the compound. Most studies using MRS in drug-addicted subjects have measured *N*-acetyl aspartate, a marker of neuronal viability, and myoinositol, a marker of glial proliferation (Chang et al., 1996). Some recent MRS studies of addiction have focused on GABA (Chang et al., 2003). Currently MRS is limited by its poor sensitivity and spatial resolution, restricting the measurements to relatively large areas of the brain.

PET and fMRI studies have identified brain areas and circuits involved in various states of the drug-addiction process (e.g., intoxication, withdrawal, craving, etc.) and have begun to link activity in these neural circuits to behavior (Breiter et al., 1997). Another innovation is the use of imaging to delineate the interactions between environmental variables and brain circuits as a means to understand mechanisms by which environmental factors affect the propensity to self-administer drugs (Morgan et al., 2002). A recent and very promising application of brain imaging has been to define endophenotypes for molecular genetic studies of psychiatric disorders. Applications of this strategy have included assessment of the functional consequences of polymorphisms in the COMT gene on the function of the prefrontal cortex (Mattay et al., 2003), and assessment of the effects that the serotonin transporter gene polymorphism has on the sensitivity of limbic brain regions to stress (Hariri et al., 2002).

The use of imaging technology to evaluate the effects of drugs on brain development is also very relevant as addiction often begins during the adolescent years. A better understanding of the changes in neurochemistry and function of the human brain during childhood and adolescence should allow insight into the increased vulnerability to abusing drugs during these periods of development.

3. Imaging the acute effects of drugs of abuse

Preclinical studies have consistently shown that drugs of abuse induce large increases in DA in the nucleus accumbens (NAc), an effect linked with their ability to act as reinforcers (Koob and Bloom, 1988). PET studies have corroborated the relevance of increases in DA levels in the reinforcing effects of drugs of abuse in human subjects as well as the importance of the dynamic characteristics of the DA increases. Fast and supraphysiological DA increases are linked with the reinforcing effects of stimulant drugs as assessed by the subjective reports of “high” and “euphoria” in addicted as well as non-addicted subjects. (Fig. 1) (reviewed in Volkow et al., 2004). This clear link between DA increases and reinforcement in human studies may seem inconsistent with recent animal studies that emphasize the role of DA primarily in prediction of reward rather than reinforcement itself (Schultz et al., 2000; Tremblay and Schultz, 1999). The apparent discrepancy may reflect qualitative differences between animal studies, which have scrutinized DA increases associated with natural reinforcers and human studies, which have examined DA increases associated with drugs of abuse. The magnitude and duration of DA increases induced by abused drugs are significantly greater and longer than for natural reinforcers, but the mechanisms responsible for these increases also differ. Multiple, indirect processes result in DA increases with natural reinforcers such as food (e.g., reinforcement for food being due to various factors such as palatability, decrease in hunger, and increases in brain glucose, which require food to be consumed, digested, and absorbed). Stimulant drugs such as cocaine, methylphenidate, and amphetamine

have direct actions on DA cells, and administration results in rapid uptake into the brain, leading to much faster increases in synaptic DA levels than those from natural reinforcers. Cocaine and amphetamine block DAT, the main mechanism for removal of DA from the synapse, and continue to increase DA with repeated administration. This is in contrast to natural reinforcers, which tend to lose their ability to increase DA with repeated exposure. Indeed, it has been shown that natural reinforcers like food rapidly induce tolerance in the responses of the NAc shell, whereas drugs of abuse do not (Di Chiara, 2002).

Although imaging studies have mostly focused on DA, the interaction of DA with other neurotransmitters such as glutamate (involved in molecular changes including long-term potentiation, associated with learning) and GABA (the main neurotransmitter in DA projections) plays an important role in modulating the magnitude of the DA responses to drugs (Bell et al., 2000; Cornish and Kalivas, 2001). It is also likely that with repeated drug administration neural adaptations in glutamatergic and GABAergic circuits will increase their influence on the brain’s responses to the drug of abuse.

Because the neural and behavioral effects of acute drug administration tend to be of short duration, fMRI is better suited than PET to identify brain circuits activated during drug intoxication and their association with the drug’s behavioral effects. Since PET measures reflect averages over time (e.g., 30 min for metabolism and 60 s for blood flow, depending on the radiotracer), important temporal patterns with short durations may be masked. Such changes can be detected by fMRI measures that reflect averages over a much shorter interval (e.g., <5 s). fMRI studies have revealed a complex pattern of dynamic brain changes with differing temporal patterns during drug intoxication, with some areas activated and others deactivated. In some regions, the temporal sequence of these dynamic patterns of change is similar to patterns of behavioral effects of abused drugs, such as the perception of self-reported “high” and “drug craving” (Breiter et al., 1997; Stein, 2001).

It is well recognized that drug effects are also modulated by non-pharmacological variables including context and conditioned responses (Ciccocioppo et al., 2004; Robinson and Berridge, 1993; Rolls, 2000; White, 1996). These variables shape a subject’s expectation of the effects of a drug, which in turn modify responses to that drug (Mitchell et al., 1996). Indeed, PET studies have shown that expectation markedly modifies the regional brain metabolic response to intravenous administration of the stimulant drug methylphenidate (MP) in cocaine abusers (Volkow et al., 2003b). In a study using a double-blind, balanced placebo design, brain metabolism as well as self-reports of

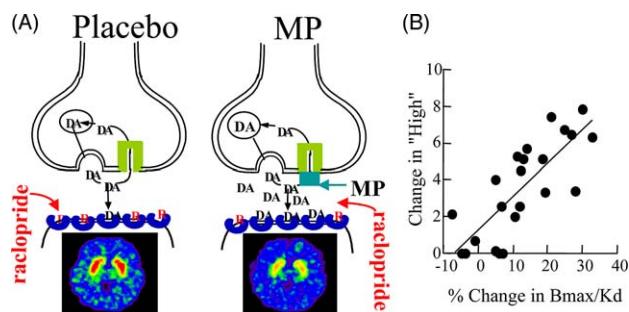


Fig. 1. (A) Diagram illustrating the PET-raclopride method to measure changes in DA induced by administration of MP. Subject is tested on two occasions; one after placebo and one after MP. MP blocks DA transporters, allowing DA to accumulate in the synapse. Since [11C]raclopride can only bind to those DA D2 receptors that are not occupied by DA, the difference in its binding between placebo and MP reflects MP-induced increases in synaptic DA. (B) Correlation between MP-induced increases in DA (assessed as percent change in B_{max}/K_d (measure of DA D2 receptor availability obtained with [11C]raclopride)) and self-reports of “high” induced by MP. The larger the DA increases the more intense the “high” induced by MP.

“high” were almost 50% higher when this drug (which acts like cocaine by blocking DAT) was expected than when it was not. The expectancy-induced increases in thalamic metabolism were most clearly related to the enhanced perception of “high”, suggesting that this brain region may play an important role in the regulation of drug responses by expectation. The thalamus (mediodorsal and paraventricular nuclei) receives direct projections from DA cells and is thus a direct target for drug effects. The thalamus also receives indirect projections from the NAc, a brain region linked to the reinforcing effects of drugs, and direct projections from the orbitofrontal cortex (OFC), implicated in salience attribution. The thalamus also sends projections back to these regions, forming cortico-striatal-thalamic loops (Glick et al., 1992; Herve et al., 1981; Packard et al., 1997) through which the thalamus could modulate the reinforcing responses to drugs of abuse (Deutch et al., 1998).

4. Brain circuits implicated in addiction by imaging studies

Drugs of abuse increase DA in both addicted and non-addicted subjects, so this is not a sufficient condition for addiction. However, a compulsive drive to continue drug taking despite subsequent consequences is triggered only in addicted subjects. Loss of control and compulsive drug seeking and drug taking uniquely characterize the behavioral manifestations of drug addiction. What are corresponding abnormalities in underlying brain circuits? Imaging studies of addicts have provided evidence of disruption in multiple brain circuits, including those involved with reward/saliency, motivation/drive, inhibitory control/disinhibition, and memory/conditioning (Volkow et al., 2003a). These DA circuits are connected to one another through direct or indirect innervations that are both glutamatergic (excitatory) and GABAergic (inhibitory). Although specific brain regions are associated with each circuit (Herve et al., 1981; Packard et al., 1997), it is becoming evident that a given region participates in more than one circuit and that additional circuits (e.g., executive control) are affected in some drug-addicted subjects (see Goldstein and Volkow, 2002).

Studies of reward circuit(s) include assessment of limbic regions (e.g., amygdala, ventral striatum, ventral cingulate) and neurotransmitters (e.g., dopamine, opioids) that are traditionally linked to reinforcing stimuli. PET and single photon emission computed tomography (SPECT) studies have revealed lower DA D2 receptor availability in striatum (including ventral striatum) in a wide variety of drug addictions (cocaine, heroin, alcohol, and methamphetamine) when compared with controls (reviewed in Volkow, 2004). The

reduction of striatal D2 receptors appears to be long lasting and to persist after protracted detoxification. Since DA D2 receptors are involved in the response to reinforcing properties of natural as well as drug stimuli, we have hypothesized that reduced expression levels in drug-addicted subjects would make them less sensitive to natural reinforcers. This lowered sensitivity is further exacerbated by the decrease in DA cell activity (release) in addicted subjects, which has been documented by PET studies comparing the magnitude of DA increases induced by DAT blockade with MP (Volkow et al., 1997). In these studies, MP-induced striatal DA increases in cocaine abusers (including ventral striatum) were significantly blunted when compared with those of controls. Since DA increases induced by MP are dependent on DA release, a function of DA cell firing, we speculated this difference likely reflected decreased DA cell activity in the cocaine abusers.

These brain imaging studies suggest two abnormalities in drug-addicted subjects that would result in decreased output of DA circuits related to reward: decreases in DA D2 receptors and decreases in DA release. Each would contribute to decreased sensitivity to natural reinforcers. However, we postulate that the large and long lasting increases in DA induced by drugs are likely to still be able to activate reward circuits. Because of this, the relative salience of drug over natural reinforcers may be amplified in the drug-addicted subject, even though the DA circuit is dampened by drug exposure. In addition, since reinforcement from natural reinforcers would not be able to compete with that from drug, the motivational choices of the individual may become fixed, as depicted in Fig. 2. Indeed, fMRI studies comparing brain responses to natural reinforcers between addicted and non-addicted subjects have shown decreased activation in limbic regions in addicted individuals (Martin-Soelch et al., 2001). In contrast to non-addicted subjects, addicted patients did show marked limbic activation by drug-related stimuli. As well, studies measuring mu opioid receptors in cocaine abusers have shown significant increases in receptor availability that are likely to reflect decreased endogenous opioid release, likely contributing further to drug craving and abuse (Zubieta et al., 1996).

Motivational/drive circuits are intricately connected to the reward circuit, since pleasure serves to motivate behavior. Primate studies have shown a prominent role for DA in motivation that appears to be mediated in part via the regulation of higher cortical centers in the brain (e.g., OFC, ventral CG) (Hollerman and Schultz, 1998; Koob, 1996). Decreased activity of the OFC and the anterior cingulate gyrus (CG) has consistently been documented in imaging studies of drug-addicted subjects. Moreover, activity levels in OFC and CG have

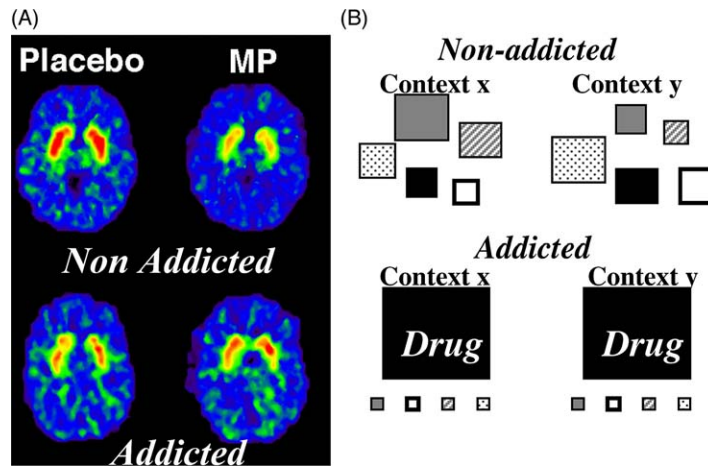


Fig. 2. (A) Images of DA D2 receptors measured with [11C]raclopride at baseline (placebo) and after intravenous MP in non-addicted subject and in addicted cocaine abusers. Note the reduced binding of [11C]raclopride in addicted subjects during placebo and their blunted response to MP. (B) Diagram illustrating our hypothesis that the decreases in D2 receptors and the blunted activity of DA cells will result in a decreased sensitivity to natural reinforcers while still having strong responses to drugs of abuse. Since the difference in the rewarding value of natural versus drug reinforcers in the addicted subject is so large (natural reinforcers cannot compete with the drug reinforcers), the motivational choices of the individual become fixed. We illustrate this by the different sizes of boxes, which reflect the relative saliency value of different natural reinforcers (identified by different shading tones); the drug reinforcer is represented as the back box. In non-addicted subjects, the value of the reinforcer differs and this value changes as a function of the context (e.g., food is very reinforcing when the subject has not eaten but decreases in value once this need has been satisfied), allowing for other reinforcers (e.g., social interaction) to become preeminent. In the addicted subject, the difference between the drug and the natural reinforcers is so large that drug seeking and taking becomes fixed.

been shown to be associated with the availability of DA D2 receptors (Fig. 3) (Volkow et al., 1993; Volkow et al., 2001). DA-mediated disruption of the OFC would be expected to affect the motivational process of assignment of saliency value to a stimulus as a function of its context, and the DA-mediated disruption of the anterior CG would be expected to affect the process of

inhibitory control. We have postulated that these disruptions in OFC and CG underlie the compulsive drug intake and the loss of control by drug-addicted subjects when exposed to the drug or to drug-related stimuli. Despite this pattern of decreased activity when drug-free, addicted subjects show increased (not decreased) OFC activation when presented with drug-related

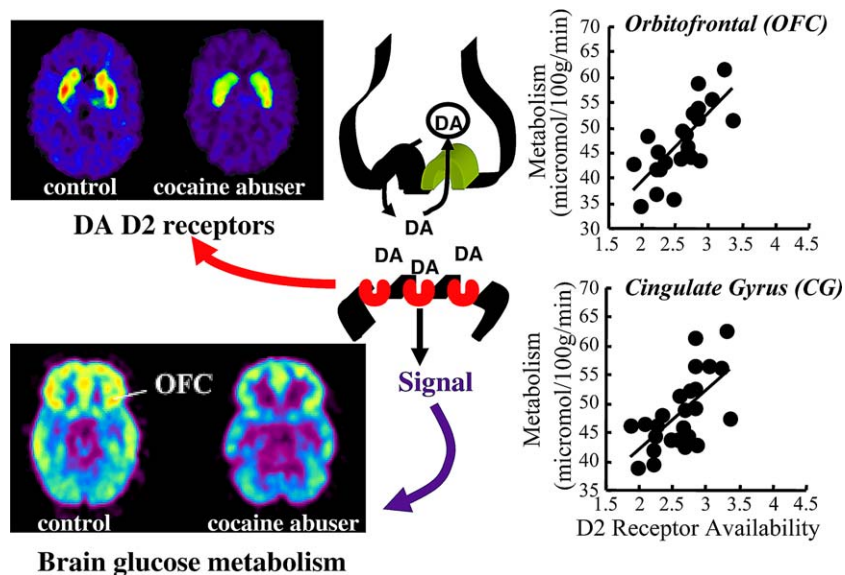


Fig. 3. (A) Images of DA D2 receptors and of brain glucose metabolism, which is used as an indicator of brain function in controls and in cocaine abusers. Drug-addicted subjects have decreases in DA D2 receptors in striatum and decreases in metabolism in the orbital frontal cortex (OFC). (B) Correlations between DA D2 receptors and OFC metabolism in detoxified cocaine and in detoxified methamphetamine abusers. Note that the subjects with the lowest measures of D2 receptor availability have the lowest metabolism in OFC.

stimuli or memories, or if given drug. Moreover, this enhanced activation is associated with the intensity of desire for the drug. This has led us to speculate that OFC and CG hypermetabolism could trigger compulsive drug intake just as hypermetabolism of OFC and CG contributes to compulsive behaviors in patients with obsessive compulsive disorders (Volkow and Fowler, 2000). Decreased activity of the OFC during withdrawal with increased activity of the OFC during exposure to the abused drug suggests that this region is selectively activated by the drug in the addicted subject and may contribute to an enhanced motivation to take the drug. Disruption of this circuit is consistent with the behavior of the drug addict, whose compulsion to take the drug overrides competing cognitive-based tendencies not to take the drug (Fig. 4). Drug taking may continue even when the drug is no longer perceived as pleasurable and at the risk of facing almost certain and adverse consequences, including incarceration.

Inhibitory control is regulated by several brain regions, including anterior CG as well as lateral OFC, which (as outlined above) are disrupted in addicted subjects (Goldstein and Volkow, 2002). Frontal abnormalities in drug-addicted subjects also are manifested in the dorsolateral prefrontal cortex, which is expected to affect processes involved in executive control (Royall et al., 2002). Converging information from preclinical studies documents drug-induced changes in prefrontal cortex: significant dendritic branching and spine density resulting from repeated drug administration (Robinson et al., 2001). Disruption of prefrontal activity in drug-addicted subjects could lead to impairments in self-monitoring and behavior control, playing

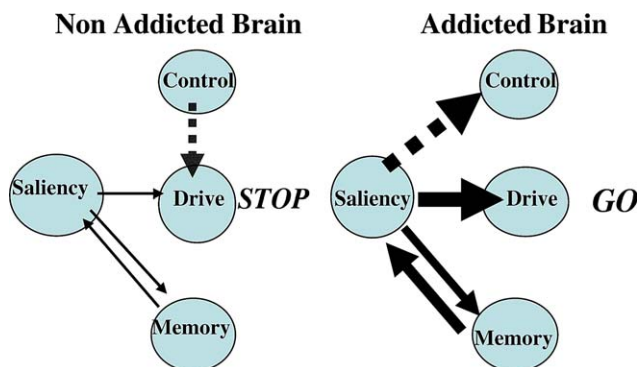


Fig. 4. Addiction model proposed based on imaging findings documenting abnormalities in brain circuits involving saliency/reward, motivation/drive, memory/conditioning, and control/disinhibition. These circuits interact with one another and change as a function of experience and context. During addiction, the enhanced saliency value of the drug in the reward, motivation, and memory circuits overcomes the inhibitory control exerted by the prefrontal cortex. A positive feedback loop initiated by consumption of the drug and perpetuated by the enhanced activation of the motivation/drive and memory circuits results in compulsive drug seeking and taking. (Modified from Fig. 6 in Volkow et al., 2003a).

an important role in the cognitive changes that perpetuate drug self-administration (Kaufman et al., 2003).

Multiple memory systems have been proposed to be involved in drug addiction, including conditioned-incentive learning (mediated in part by NAc and amygdala), habit learning (mediated in part by the caudate and the putamen), and declarative memory (mediated in part by the hippocampus) (see the review by White, 1996). These effects of abused drugs on memory systems of the brain suggest ways that neutral stimuli can acquire reinforcing properties and motivational salience through conditioned-incentive learning. Habit learning, manifested when common stimuli automatically elicit well-learned and appropriate sequences of behavior, is also affected by and may contribute to addiction. In the extreme, this may be associated with perseveration and contribute to ritualistic behaviors that are linked with drug intake (Powell, 1995). Declarative memory is involved in learning and associating affective conditions or circumstances with drug taking experiences. Studies with PET and fMRI have shown that cue-elicited craving as well as intoxication activate brain regions involved in memory, including hippocampus and amygdala (Childress et al., 1999; Grant et al., 1996; Kilts et al., 2001; Wang et al., 1999).

5. Imaging differences between subjects in their responses to drugs: implications for vulnerability

A challenging question in the neurobiology of drug abuse is why some individuals are more vulnerable to becoming addicted to drugs than others. Based on the brain circuits known to be involved in addiction (as reviewed earlier), multiple hypotheses can be formulated. Advances in our understanding of drug addiction from brain imaging studies allow the postulation that vulnerability may result from decreased sensitivity of reward circuits to natural reinforcers, disrupted activity of control circuits, increased sensitivity to conditioned drug stimuli, increased responses of motivation/drive circuits to drugs, and neurobiological factors involved in modulation of these circuits. However, in studies of drug addicts, it is difficult to determine if the brain abnormalities are pre-existing conditions that lead to drug abuse or, instead, are consequences of a history of drug abuse. Preclinical studies can provide relevant information bearing on this important distinction. Several neurotransmitters, including DA, glutamate, opioids, and serotonin, have been identified in studies using knockout mice as neurotransmitters that could modulate the predisposition to drug self-administration (Laakso et al., 2002).

Human imaging studies suggest that differences in DA circuits may be one mechanism underlying the

variability in responsiveness to drugs of abuse, which in turn could influence vulnerability. Specifically, baseline measures of striatal DA D2 receptors in non-addicted subjects have been shown to predict subjective responses to the reinforcing effects of intravenous MP; individuals describing the experience as pleasant had significantly lower levels of receptors compared with those describing MP as unpleasant (Volkow et al., 1999a). This finding was replicated in a separate study that showed an inverse relationship between the levels of DA D2 receptors and the subjective report of drug liking in response to intravenous MP (Volkow et al., 2002b). Subjects with low receptor levels reported the highest scores on drug liking, while those with the highest receptor levels had the lowest scores on drug liking. This suggests that the relationship between DA levels and reinforcing responses follows an inverted u-shaped curve: too little is not sufficient for reinforcement but too much is aversive, with the optimal level of stimulation in the middle (Fig. 5). Thus, in subjects with high D2 receptors, intravenous MP leads to aversive responses because the level of stimulation of the DA circuit is too high, whereas in subjects with low receptors the large increases in DA are required (due to low receptor levels) to bring the activity of the DA circuit into the optimal (mid) range.

The association of D2 receptor levels with drug liking has implications for understanding individual differences in vulnerability to drug abuse. High D2 receptor levels may protect against drug self-administration. Support for this was provided by preclinical

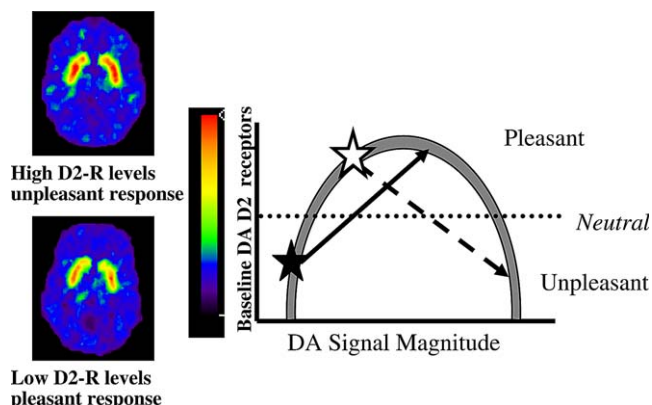


Fig. 5. We postulate an inverted u-shaped curve to describe the relationship between the intensity of the DA signal elicited by intravenous MP and the reinforcing effects of the drug. There is an optimal level of stimulation for the DA signal to be perceived as pleasurable; too little stimulation or excessive stimulation would result in unpleasant responses. In subjects with low DA D2 receptors (closed star), the large MP-induced increases in DA result in optimal stimulation and perception of the effects of the drug as pleasant, but in subjects with high D2 receptors (open star), the large MP-induced DA increases moves them to the far right on the curve, resulting in over-stimulation and perception of drug effects as unpleasant.

studies, which showed that upregulation of DA D2 receptors in NAc dramatically reduced alcohol intake in animals previously trained to self-administer alcohol (Thanos et al., 2001). A protective role for high numbers of DA D2 receptors against substance abuse is suggested. Since baseline levels of DA D2 brain receptors can be affected by stress (Papp et al., 1994) and social hierarchy (Morgan et al., 2002), variations in DA D2 receptor levels may be one of the neurobiological mechanisms that underlies the effect of environment on predisposition to abusing drugs.

6. Implications for treatment

Drug addiction leads to profound disturbances in an individual's behavior that affect his/her immediate environment, usually resulting in isolation, marginalization, or incarceration. The stress of social isolation is likely to result in changes in stress circuits, further increasing vulnerability to drug use and relapse. Treatments for addiction must consider not only the neurobiological changes but also the social infrastructure of the addicted person. Because of its chronic nature, long-term treatment for addiction is usually necessary.

As outlined in this paper, evidence has accumulated about how the brain changes as an individual becomes addicted. This view of how drugs of abuse affect the brain suggest strategies for intervention, which might include: (a) those that will decrease the reward value of the drug of choice; (b) interventions to increase the reward value of non-drug reinforcers; (c) approaches to weaken conditioned drug behaviors; and (d) methods to strengthen frontal inhibitory and executive control.

Medications to decrease a drug's reward value can interfere with its reinforcing effects or can make the effects unpleasant. Medications that affect the same neurotransmitter system as the drug of abuse but with slower pharmacokinetic properties clearly can interfere with rewarding effects. This has been remarkably successful, for example, in the management of heroin addiction with methadone or with buprenorphine, and to a certain extent, smoking, with nicotine patches and gum (see review Kreek et al., 2002). However, this approach, so far, has not been successful in developing medications for treating addictions to stimulant drugs like cocaine or methamphetamine. Attempts to use drugs to produce DAT blockade with long duration to interfere with the rapid, euphoria-producing effects of cocaine have been made. Replacement of cocaine with oral MP or oral amphetamine did not decrease cocaine consumption when compared with placebo in most drug-addicted individuals. However, in addicts who also suffered from attention deficit hyperactivity disorder (ADHD), this strategy appeared to be successful, and treatment with oral MP decreased drug consumption

(Grabowski et al., 1997; Shearer et al., 2003). This suggests the intriguing hypothesis that cocaine use by some subjects with comorbid ADHD and cocaine addiction may reflect attempts to self-medicate. Pharmacologic treatment of the underlying disorder in these individuals may reduce drug abuse by reducing the ADHD symptoms rather than by competing at the site of action of cocaine. Pharmacological interventions with drugs that increase DA should have slow rates of brain uptake and clearance, should be minimally cardiotoxic, and must be coordinated with behavioral treatment to focus enhanced saliency on non-drug effects targeted by the psychotherapeutic intervention.

Although neuroleptics interfere with the reinforcing effects of drugs of abuse in laboratory animals (De Wit and Wise, 1977), mixed results have been reported in studies examining the same effects in humans (Brauer et al., 1997). This discrepancy may reflect the fact that doses of neuroleptics administered to animals likely blocked all D2 receptors, while lower doses used in humans occupied a smaller percentage of receptors. Moreover, use of neuroleptics in addicted subjects with low D2 receptors is not well tolerated. Indeed, cocaine-addicted subjects have a higher risk for developing dystonic reactions when treated with these drugs (van Harten et al., 1998), making neuroleptics less than ideal candidates for addiction treatment, except, perhaps in cases when addictions are linked with a psychotic comorbid disorder (Evans et al., 2001; Grabowski et al., 2000).

Promising results from animal studies and preliminary clinical trials with cocaine-addicted and alcoholic subjects suggest that GABA-enhancing drugs can successfully prevent cue- and drug-induced increases in brain DA (Dewey et al., 1998; Di Ciano and Everitt, 2003), and may be useful for aiding abstinence in human addicts (Brodie et al., 2003; Gonzalez et al., 2003; Johnson et al., 2003). Additionally, interference with postsynaptic responses to DA stimulation might be successful in attenuating the reinforcing effects of various types of abused drugs. Selective antagonism of cannabinoid (CB1) receptors has been shown to modulate both DA cells and postsynaptic responses from DA stimulation in laboratory animals (De Vries et al., 2001; Julian et al., 2003; Wallmichrath and Szabo, 2002).

Drugs that allow slight increases in the amount of DA released as a function of DA cell firing may provide a way to increase the sensitivity of drug-addicted individuals to natural reinforcers. Medication-induced patterns of tonic and phasic DA activity should ideally mimic patterns modulated by context and expectation that occur in response to natural reinforcers. Bromocriptine and apomorphine stimulate DA receptors regardless of context and this may explain why they have been of limited value in the pharmacological

treatment of addicted subjects (see review by Kosten et al., 2002). MAO B inhibitors or other drugs that increase the amount of DA release in response to DA cell firing might appropriately and successfully compensate for chronic effects of stimulant abuse and have been effective in treating some nicotine-addicted subjects (George et al., 2003).

Brain imaging studies also suggest that strategies to interfere with conditioned responses may effectively treat addiction. This approach currently is based on behavioral desensitization of addicted subjects to responses linked with conditioned stimuli, but it is reasonable to predict that medications could facilitate these processes by impeding circuits linked to memory processes in the hippocampus and amygdala. Beta-blockers have been shown to inhibit conditioned responses to natural reinforcers and to aversive stimuli (Miranda et al., 2003), but to our knowledge these have not been tested on drug-induced conditioned responses. GABAergic stimulation attenuates Pavlovian conditioned responses and impairs conditioned responses to drugs of abuse (Bailey et al., 2002; Dewey et al., 1998; Franklin and Druhan, 2000; Hotsenpiller and Wolf, 2003). Indeed this may be one of the mechanisms contributing to the therapeutic effectiveness in drug-addicted subjects of some of the GABA-enhancing drugs that have recently been reported.

Because relapse to drug taking usually occurs when individuals are exposed to stressful stimuli, an alternative treatment strategy in drug addiction may be to interfere with the neurobiological responses to stress (Koob, 1999). Antagonism of corticotropin-releasing factor (CRF), which modulates stress responses in the hypothalamic-pituitary-adrenal axis and the amygdala, has been shown in animal studies to interfere with drug relapse (Shaham et al., 1998). Such CRF antagonists may offer a potential medication for prevention of relapse in drug-addicted subjects.

The comorbidity of drug abuse with other mental disorders is high (Kessler et al., 1996; Regier et al., 1990). Thus, treatment of the mental disorder in some instances also requires the concurrent treatment of drug addiction. In some cases, comorbid drug addiction may result from attempts to alleviate the psychiatric disorder through self-medication (as described earlier for comorbid cocaine abuse and ADHD). In other cases, vulnerability to a psychiatric disorder may be increased by brain changes acquired as a result of drug abuse (Volkow et al., 2004). These differing routes leading to drug abuse comorbid with psychiatric disorders suggest different treatment strategies. In patients with drug abuse arising from an attempt to self-medicate, treatment of the disorder may prevent abuse (e.g., treatment of the preexisting condition of ADHD with MP may prevent cocaine abuse (Biederman, 2003; Wilens, 2004)). In instances of comorbidity in which the use of

drugs antecedes mental disease or is not driven by self-medication strategies, the simultaneous treatment of both conditions may be required.

As we acquire basic knowledge about addiction-related brain circuits and how they are affected by environmental variables, dual approaches pairing behavioral interventions with medications will likely offer new and effective treatments for drug addiction and its resulting neurobiological changes. For example, one could conceive of interventions designed to “exercise” brain circuits by specific cognitive and behavioral interventions to remediate and strengthen circuits affected by chronic drug use in an analogous way to some interventions used for reading disabilities (Papanicolaou et al., 2003). Behavioral interventions to activate and strengthen circuits involved in inhibitory control may increase successful abstinence from drug taking. Continuing research in drug addiction must also seek to understand genes involved in the predisposition for drug abuse, which may offer new targets for the development of pharmacological and non-pharmacological interventions. Similarly, a better understanding of the interactions between genes, environment, and neurobiology will help develop behavioral interventions to counteract deleterious effects of stressor(s) on the brain that in turn facilitate drug abuse and addiction.

Finally, it is important to recognize that the conclusions from this review are based mostly on findings from imaging studies of stimulant drugs, particularly cocaine, since this has been the drug most thoroughly investigated with imaging technologies. Some of the findings reported in cocaine-addicted subjects generalize to other addictions (i.e., alcoholics, heroine abusers and methamphetamine abusers) such as the decreases in DA D2 receptors in striatum and the abnormalities in metabolism or cerebral blood flow in orbitofrontal cortex; others may not. More research is required to delineate the unique differences among the various drugs of abuse. This knowledge may help in the design of specific medications, but also help us understand the neurobiological processes that underlie the specificity for an addiction that occurs in most cases to a given drug but not to another, as well as preferences for a particular drug of abuse.

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