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FEATURE REVIEW

Dopamine in drug abuse and addiction: results from imaging studies and treatment implications

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The involvement of dopamine in drug reinforcement is well recognized but its role in drug addiction is much less clear. Imaging studies have shown that the reinforcing effects of drugs of abuse in humans are contingent upon large and fast increases in dopamine that mimic but exceed in the intensity and duration those induced by dopamine cell firing to environmental events. In addition, imaging studies have also documented a role of dopamine in motivation, which appears to be encoded both by fast as well as smooth DA increases. Since dopamine cells fire in response to salient stimuli, the supraphysiological activation by drugs is likely to be experienced as highly salient (driving attention, arousal conditioned learning and motivation) and may also reset the thresholds required for environmental events to activate dopamine cells. Indeed, imaging studies have shown that in drug-addicted subjects, dopamine function is markedly disrupted (decreases in dopamine release and in dopamine D2 receptors in striatum) and this is associated with reduced activity of the orbitofrontal cortex (neuroanatomical region involved with salience attribution and motivation and implicated in compulsive behaviors) and the cingulate gyrus (neuroanatomical region involved with inhibitory control and attention and implicated in impulsivity). However, when addicted subjects are exposed to drug-related stimuli, these hypoactive regions become hyperactive in proportion to the expressed desire for the drug. We postulate that decreased dopamine function in addicted subjects results in decreased sensitivity to nondrug-related stimuli (including natural reinforcers) and disrupts frontal inhibition, both of which contribute to compulsive drug intake and impaired inhibitory control. These findings suggest new strategies for pharmacological and behavioral treatments, which focus on enhancing DA function and restoring brain circuits disrupted by chronic drug use to help motivate the addicted subject in activities that provide alternative sources of reinforcement, counteract conditioned responses, enhance their ability to control their drive to take drugs and interfere with their compulsive administration.
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Dopamine (DA) is the neurotransmitter that has been classically associated with the reinforcing effects of drugs of abuse. This notion reflects the fact that most of the drugs of abuse increase extracellular DA concentration in limbic regions including nucleus accumbens (NAc).[1,2] Increases in DA secondary to phasic DA cell firing play an important role in coding rewards and reward-associated stimuli,[3] and apparently do not code specifically for reward but for saliency, which in addition to reward includes aversive, novel and unexpected stimuli.[4] It is also proposed that DA encodes for the motivation to procure the reward rather than encoding for the reward itself.[5] These modern views about the role of DA in reinforcement provide a different perspective about drugs of abuse, implying that drugs are reinforcing not just because they are pleasurable but because by increasing DA they are being processed as salient stimuli that will inherently motivate further procurement of more drug (regardless of whether the drug is consciously perceived as pleasurable or not) and will facilitate conditioned learning.[6]

We have used positron emission tomography (PET) an imaging technology that allows measurement of neurochemical and metabolic processes in the living human brain, to investigate the nature of (1) acute brain changes in DA activity induced by drugs of abuse and (2) long-term brain changes in DA activity

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and the functional consequences of these changes in drug-addicted subjects. This paper reviews these findings along with their therapeutic implications.

Acute effects of drugs of abuse on DA in the human brain and its role in their reinforcing effects

To investigate the increases in DA induced by drugs of abuse and the associated reinforcing effects in humans, we chose to study cocaine since it is considered one of the most reinforcing of the drugs of abuse. Cocaine increases extracellular DA by blocking the DA transporters (DAT). We compared the acute effects of cocaine with methylphenidate (MP), a stimulant that like cocaine increases DA by blocking DAT. These two stimulant drugs have similar affinities *in vitro* (Ki for inhibition of DA uptake correspond to 640 and 390 nM, respectively).[7] However, MP has much lower levels of abuse[8] and has well-accepted clinical use for the treatment of children with attention deficit hyperactivity disorder (ADHD).

We used PET imaging to compare these two drugs to investigate how DA in the human brain was involved in the reinforcing effects of stimulant drugs and to determine what other variables modulated the addictive liability of this class of drugs. This work was also intended to help us understand why cocaine is much more abused than MP. The brain effects we investigated were pharmacokinetics (rate of onset and offset) and potency (ability to block DAT and increase extracellular DA). The behavioral effects were assessed using self-report measures of 'high' and other drug-induced experiences, which have been shown to be reliable and consistent across studies and predict self-administration of drugs in humans.[9] The other variable we investigated was 'expectation effects'.

Pharmacokinetics

Cocaine and MP were labeled with carbon-11 for PET imaging. Then, we used serial PET images to compare their regional distribution and pharmacokinetics (temporal course) in the human brain and to assess the relationship between their pharmacokinetics in brain and the temporal patterns of the self-report of 'high'.[10] Our PET studies revealed that both drugs entered the brain rapidly after i.v. administration (in less than 10 min) and had similar regional distribution, with the highest uptake in basal ganglia where they competed for binding to DAT. However, they differed in some pharmacokinetics properties; while they both entered the brain rapidly the rate of clearance was significantly slower for MP (half-life 90 min) than for cocaine (half-life 20 min) (Figure 1). The initial uptake of these two drugs in basal ganglia (and presumably in the NAc) paralleled the temporal changes for the perception of the 'high'. For cocaine, the reduction in the 'high' followed its fast clearance from brain, while for MP the 'high' declined rapidly despite the persisting presence of high levels of MP in brain (Figure 1). This led us to conclude that the initial fast uptake of these stimulant drugs into the brain, not their steady-state presence, is necessary for drug-induced reinforcement (the experience of 'high'). We also noted that the rate of clearance of cocaine from the brain corresponded well to the frequency of administration reported by abusers during cocaine binging (every 20–30 min). From these observations, we speculated that the slow rate of clearance of MP might constrain the frequency (number of administrations per unit of time) at which it would be administered, since the slow clearance of MP might lead to DAT saturation at this frequency of administration. MP's longer half-life may also result in longer duration of side effects that with repeated administration could become aversive and counterbalance its pleasurable effects. These factors may contribute to the lower levels of abuse of MP than cocaine.

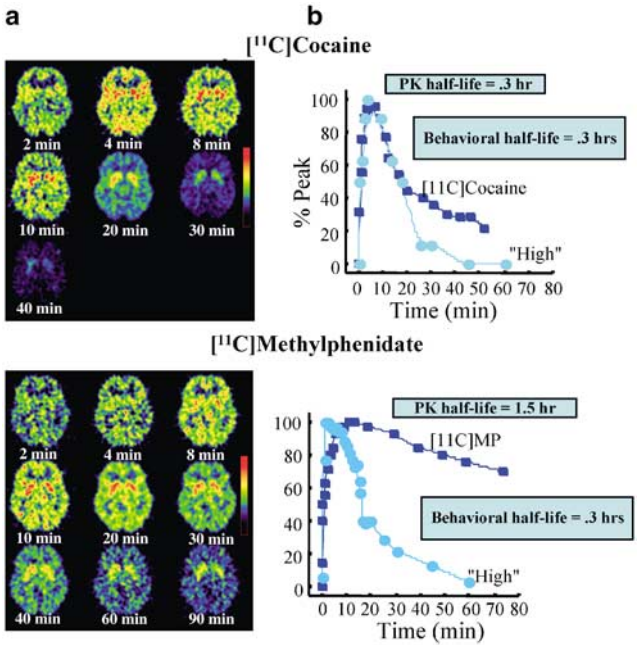

Figure 1 (a) Images for [11C]cocaine and for [11C]methylphenidate at the level of the basal ganglia at different times after radiotracer administration. The colors reflect the concentration of the radiotracer and correspond to red > yellow > green > blue > purple. (b) Time-activity curves for [11C]cocaine and for [11C]methylphenidate plotted with the corresponding temporal patterns for the subjective experience of 'high' after pharmacological doses of intravenous cocaine and of intravenous MP. The peak corresponds to the normalized maximum for the self-report of 'high' reported by each subject. Note the rapid uptake of these two drugs into the brain but the much faster clearance for cocaine than for MP. Note the parallelism between the 'high' after cocaine and the kinetics of [11C]cocaine in basal ganglia. Note the dissociation between the 'high' from MP, which falls rapidly after peaking and the slow clearance of [11C]methylphenidate from basal ganglia.

Dopamine and drug reinforcement

We compared the potency of cocaine and MP to block DAT in the living human brain, since these are the

targets considered to be responsible for their reinforcing effects.[7,11] Although these two drugs have similar affinities *in vitro*,[7] differences in their brain bioavailability could affect their *in vivo* potencies. These studies showed that the ED_{50} dose required to block 50% of the DAT was lower for MP (0.075 mg/kg) than for cocaine (0.13 mg/kg).[12–14] To induce a 'high', both of these drugs had to block more than 50% of the DAT, and above that threshold the degree of 'high' was dependent on the level of DAT blockade. Thus, we concluded that differences in the *in vivo* potency of these two drugs for blockade of DAT (ie, lower for cocaine than MP) could not be responsible for the differences in their rate of abuse in humans (ie, higher for cocaine than MP).

Although DAT blockade is the initial pharmacological effect of both cocaine and MP, the subsequent increase in DA and activation of DA receptors are responsible for their behavioral effects.[15] To measure the increases in synaptic DA induced by drugs, we used PET and [^{11}C]raclopride, a DA D2 receptor radioligand that competes with endogenous DA for occupancy of the DA D2 receptors and can be used to assess relative changes in synaptic DA.[16] This requires two PET scans with [^{11}C]raclopride—one after pretreatment with placebo and one after pretreatment with the drug being evaluated. The difference between these conditions is used to assess relative changes in synaptic DA induced by the drug.[16] We first compared the ability of i.v. cocaine and that of i.v. MP to increase synaptic DA in the baboon brain and showed similar decreases in striatal [^{11}C]raclopride binding after these two drugs indicating that they are equipotent.[17] We then assessed the role of the drug-induced DA increases in its reinforcing effects by measuring the relationship between MP-induced increases in extracellular DA and the self-report of 'high' in healthy controls.[18] i.v. MP decreased [^{11}C]raclopride binding in a dose dependent manner and it induced a 'high' in most subjects. The subjects having the greatest DA increases were those that perceived the most intense 'high' and subjects in whom MP did not increase DA in striatum did not perceive a 'high' (Figure 2).

These findings are consistent with other studies in the literature. A comparable study with i.v. cocaine in cocaine abusers also reported significant decreases in striatal [^{11}C]raclopride binding.[19] Intravenous amphetamine also increases DA in human brain and these increases have also been shown to be associated with the subjective perception of reinforcement.[20,21] Along with these studies, our findings provide evidence that increases in striatal DA induced by stimulant drugs are associated with their rewarding effects (as reflected by the self-report of 'high' or 'euphoria') in humans. Thus, the contention that DA encodes for motivation but not for reward is not corroborated by these imaging studies evaluating the effects of stimulant drugs in the human brain. Instead, these human studies with PET suggest that DA increases may encode for both (see below). This discrepancy

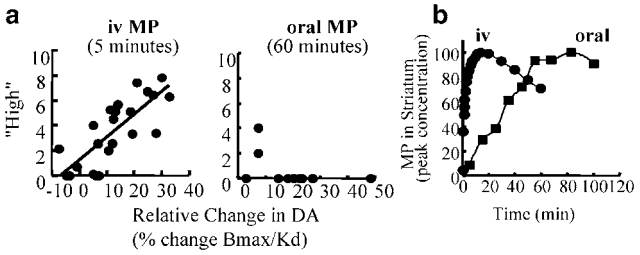

Figure 2 (a) Relationship between changes in DA as assessed by decreases in striatal [^{11}C]raclopride binding after intravenous and after oral MP. The relationship was significant for intravenous but not for oral MP. Also except, for one subject, oral MP did not increases the self-reports of 'high'. (b) Time-activity curves for the uptake of [^{11}C]methylphenidate in the baboon brain after intravenous and after oral administration. The curves have been normalized to maximal uptake. Note that peak uptake after intravenous administration occurs within 10 min whereas after oral administration it does not occur after 60 min.

could reflect the definition of reward and reinforcement. The animal studies that showed no involvement of DA with reward equated food's rewarding effects with its palatability[22] but these are likely to include other variables such as caloric intake, satiation of hunger and conditioned responses. Also natural reinforcers, which induce DA increases within the physiological range that habituate with repeated consumption are likely to lead to different responses from the supraphysiological DA increases induced by drugs of abuse that do not habituate.[23]

Although it is recognized that the speed at which stimulant drugs enter the brain is key to their reinforcing effects (as discussed above), the mechanism(s) underlying the dependency on rate is not understood. One hypothesis is that slow brain uptake of the drug leads to adaptation processes triggered by DA autoreceptor stimulation that decrease DA release (DA autoreceptors inhibit DA release) and thus interferes with the overall ability of the drug to increase extracellular DA.[24] To evaluate this possibility, we compared DA changes induced by MP when it was administered orally (a route of administration that leads to very slow MP delivery into the brain with peak uptake occurring about 60–90 min after administration) with DA changes induced by intravenous MP (a route that leads to very fast MP delivery in brain with peak brain uptake occurring about 10 min after administration). We selected oral (20 mg) and i.v. (0.5 mg/kg) doses that produce equivalent DAT blockade according to our PET assay (about 70%). The results are summarized in Figure 2. Even though the DA increases were comparable for oral and i.v. (approximately 20% changes in specific binding of [^{11}C]raclopride in striatum), oral MP did not induce significant increases in self-reports of 'high' (2.5 ± 4)[25] whereas i.v. did (7.0 ± 4).[18] And, for oral MP there was no correlation between the DA increases and the self-reports of 'high' as it was for i.v. MP (Figure 2).

The results from these studies were clear: the slow brain uptake of oral MP and initial low increases in synaptic DA did not inhibit DA release (as predicted by the DA autoreceptor inhibition hypothesis). Instead, it appears that the difference in the behavioral effects of i.v. and oral MP is due to a difference in the rate of increase in DA; for i.v. MP these occurred within 10 min of administration whereas for oral MP they occurred gradually over 60 min. Thus, it is the change ('delta') per unit time that seems to be associated with the perception of euphoria.

However, we recognized a limitation of this study, because changes in extracellular DA measured with [^{11}C]raclopride reflect the average increases that occur over a 30 min period and because i.v. MP has a much faster rate of brain uptake than oral MP, the initial peak DA increase is likely to be much higher for i.v. than for oral MP. Thus, we speculated that the more intense 'high' reported after i.v. than oral MP reflects much faster and initially greater DA increases. Another limitation is that our DA measurements were made in the dorsal striatum and not in the NAc, which is the structure associated with drug reinforcement in laboratory animals.

These imaging studies corroborated the relevance that drug-induced increases in extracellular DA have on their rewarding effects, and they highlighted the importance of fast DA kinetics. It therefore appears that the reinforcing effects of drugs of abuse are due to their ability to mimic but surpass in intensity and duration the DA increases triggered by phasic DA cell firing. Large, rapid increases may be the mechanism through which DA encodes the saliency of an event. In these studies, we focused on the effect of stimulant drugs on brain levels (and kinetics) of DA, but we realize that the reinforcing effects of drugs of abuse reflect not only DA direct's effects but also its interactions with other neurotransmitters such as glutamate and GABA, which in turn may modulate the magnitude of the DA responses to the drug.[26]

Expectation effects

The reinforcing effects of drugs of abuse are linked to the ability to increase DA, but they are also modulated by nonpharmacological variables such as conditioned responses.[27] These nonpharmacological variables shape the expectation that the subject has of the drug effects, which, in turn, modulates the responses to the drug.[28] For example, in drug abusers, the subjective responses to the drug are more pleasurable when subjects expect to receive the drug than when they do not.[29]

The effects of expectation on brain responses to drugs of abuse have been studied in laboratory animals. Cocaine-induced increases in DA in NAc, are larger when animals are given the drug in an environment where they had previously received it than in a novel environment,[30] and when animals self-administer the drug than when cocaine administration is involuntary.[31] Also, cocaine induced changes in brain function (measured by metabolism),[32] are different when animals self-administer cocaine than when administration is involuntary,[33] and when cocaine is given in a conditioned environment *vs* their home cage.[34]

To evaluate the effects of expectation on the responses of the human brain to drugs of abuse, we used another radiotracer (FDG), which provides an assay of the brain's metabolism instead of the brain's biochemistry as with [^{11}C]raclopride. Our subjects were cocaine abusers,[35] and we measured changes (both increases and decreases) in regional brain metabolism rather than changes in DA in the striatum, since this allowed us to evaluate downstream effects of the brain response to the drug as well as response at the primary sites of action. We used MP rather than cocaine because its pharmacokinetic properties make it more appropriate for PET-FDG imaging (MP's longer half-life than cocaine is better suited for the 30 min average of activity measured by FDG).

The effects of MP were measured when cocaine abusers were expecting as well as when they were not expecting to receive a stimulant drug. As shown in Figure 4, the increases in metabolism induced by MP were about 50% larger throughout most of the brain when the drug was expected than when unexpected. The largest increases in metabolism were in two brain regions (cerebellum and thalamus). In contrast, when MP was unexpected it produced greater increases than when it was expected in the left lateral orbitofrontal cortex (OFC). Along with the expectation-enhanced increases in overall brain metabolism, the increases in self-reports of 'high' were also increased about 50% more when subjects expected to receive MP than when they did not. MP-induced increases in self-reports of 'high' were significantly correlated with the metabolic increases in thalamus.

These findings provide evidence that in cocaine abusers, expectation amplified the effects of MP in brain and its reinforcing effects and they highlight the notion that the response to a drug is not just a function of its acute pharmacological effects. They also suggest that the thalamus, a region involved with conditioned responses, may mediate the enhancement of the reinforcing effects of stimulant drugs by expectation. These findings also corroborate in humans the involvement of the OFC in unexpected reward.[3] Since both the thalamus and the OFC receive direct as well as indirect projections from DA cells, these regional brain responses could reflect downstream dopaminergic effects, or these effects could also reflect conditioned changes in excitatory glutamatergic or inhibitory GABAergic input into these brain regions.

DA, saliency and motivation

To evaluate the role of DA in saliency and motivation, we performed two different studies designed to measure the magnitude of the DA increases induced by oral MP when given by itself *vs* when given with a salient stimuli while in parallel assessing the subjective motivational responses. In one study, we used

food-deprived subjects, and the salient stimuli were displays of food that could not be consumed.[36] In the second study, the salient stimuli was a monetarily remunerated mathematical task.[37] In both experiments, MP made the stimulus more salient as evidenced by the increases in the self-reports of 'desire for the food' for the food stimulation study and by increases in the report of the stimulus as 'interesting', 'exciting' and 'motivating' for the mathematical task study. Moreover, the increases in these self-reports were associated in both studies with the increases in DA in striatum. These two studies corroborate the relevance of DA in encoding saliency and not necessarily reward itself; since in the case of the food stimulation experiment the subjects did not consume the food so the presentation of the stimuli was not a rewarding one. Nor did subjects report euphoria (reinforcement) to the relatively low oral dose of MP used (20 mg in this study with the average weight of subjects about 70 kg), which would mimic increases in tonic DA rather than phasic increases (as discussed above).

The findings for the two studies suggest that a potentially important effect of oral MP (that has not been extensively investigated) is that of enhancing the saliency value of environmental stimuli. Understanding this effect may help us understand when MP might produce a therapeutic effect and when it may not. For example, the enhancement of saliency (ie, of the assigned classroom activities in school) may be crucial for the clinical effects of MP in the treatment of children with ADHD, but this same property may be detrimental when MP is used to treat addicted subjects in an outpatient setting, since it could enhance the saliency of environmental stimuli linked to the drug and thus increase drug craving. These studies also provide evidence of the relevance of tonic increases in DA (elicited by oral MP) for encoding motivation. For both studies, the drug-induced increases in DA were perceived as increasing motivation; in one study, this was manifested by increasing the motivation to consume the food (which was paradoxical, since MP is considered an anorexigenic drug) and in the other study by increasing the motivation to perform the mathematical task.

Recent views of the role of DA emphasize DA's role as either encoding reinforcement (or predicting reward) *vs* encoding motivation. From these results it appears that DA encodes for both; reward may be predominantly encoded by fast and large increases in DA whereas motivation may be encoded both by fast as well as smooth DA increases.

Long-term effects of drugs of abuse on DA in the human brain; involvement in addiction

Drug-induced increases in extracellular DA during intoxication do not explain addiction, since this occurs in nonaddicted as well as in addicted subjects. Moreover, the magnitude of the drug-induced DA increases appears to be smaller in addicted than in nonaddicted subjects.[38] Since drug addiction requires chronic drug administration, it is likely that addiction results from neurobiological changes associated with repeated drug use. In cocaine abuse, chronic and intermittent drug-taking induces supraphysiological perturbations of the DA system (marked DA increases followed by DA decreases), which we speculate must disrupt the circuits regulated by DA. Three DA circuits are likely to be involved in addiction; (1) the mesolimbic circuit (including NAc, amygdala and hippocampus) for drug reward and for drug-related memories and conditioned responses;[1,39,40] (2) the mesocortical circuit (including cingulate gyrus and OFC) for the compulsive drug administration and poor inhibitory control in addiction;[41] and (3) the nigrostriatal circuits (includes the dorsal striatum) for habit formation.[42] Although here we focus on the relevance of the DA system in the addictive state, of course we realize the complexity of the addiction processes, and that the disruption of other neurotransmitters (such as glutamate, GABA, norepinephrine and serotonin) are certainly involved.[43]

Dopamine neuronal function

We evaluated the function of DA neurons in addicted and normal subjects by measuring the rate of DA release in striatum after MP administration using PET and [^{11}C]raclopride.[16] Since MP is a DAT blocker, for an equivalent level of DAT blockade, differences in extracellular DA between subjects would be predominately a reflection of differences in DA release.[44] As shown in Figure 3, compared to controls the cocaine-addicted subjects had a marked decrease in DA cell

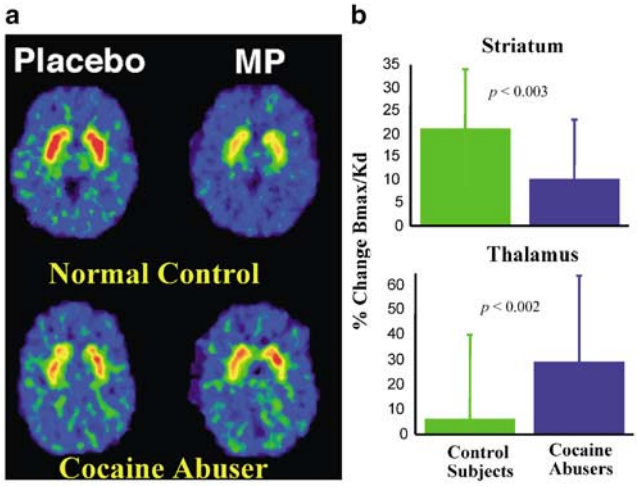

Figure 3 (a) Images obtained with [^{11}C]raclopride at the level of the basal ganglia after placebo and after MP in a control and in a cocaine abuser. (b) Changes in [^{11}C]raclopride binding in striatum and in thalamus in controls and in cocaine abusers. Note the blunted response to MP in striatum in the cocaine abusers and the decreases in [^{11}C]raclopride binding in thalamus in the cocaine abusers but the lack of an effect in the controls.

activity.[38] MP-induced decreases in striatal [^{11}C]raclopride binding (reflecting increase in DA) in cocaine abusers were 50% lower than in controls. The self-reports of 'high' induced by i.v. MP were also more intense in controls than in cocaine abusers. In contrast to this, MP induced intense cocaine craving in cocaine abusers but not in controls. This indicates that addiction is not associated with an enhanced drug-induced increase in DA in striatum or an enhanced pleasurable response to the drug. These findings support the 'incentive sensitization' hypothesis of drug addiction, which proposes that in addiction there is increased wanting for the drug that is not necessarily linked to increased liking.[27] The decreases in DA release in striatum, which encodes reward, saliency and motivation might underlie the decreased sensitivity to 'natural' reinforcers in addicted subjects.[45,46] This finding suggests the possibility that the addicted subjects may take the drug to compensate for the decreased stimulation of DA-regulated reward pathways.

Interestingly, in cocaine abusers but not in controls MP induced significant decreases in binding of [^{11}C]raclopride in thalamus (Figure 3). This thalamic response was associated with the increases in drug wanting and was observed in addicted subjects but not in controls suggesting that it reflects an adaptation from chronic drug use. Since [^{11}C]raclopride binds to both D2 and D3 receptors and the thalamus has a high concentration of D3 receptors,[47] which have high affinity for DA, the thalamic response in addicted subjects could reflect an upregulation of D3 receptors in addiction. More work is required to evaluate both the role of the thalamus, which is a brain region that is not traditionally associated with reinforcing effects of drugs and that of DA D3 receptors in drug addiction.

Dopamine transporters

Imaging studies have also evaluated the density of DAT, which is crucial for regulating synaptic levels of DA. Apparently, DAT density is characterized by plasticity and (as might be expected) appears to be increased in response to increases in DA (which it regulates). The findings in the literature differed across the various drugs of abuse investigated. For example in cocaine abusers, DAT appears to be increased shortly after cocaine discontinuation but the levels normalize with detoxification.[48] In alcoholics, studies have reported lower DAT that recover rapidly during the first 4 days of abstinence.[49] Metamphetamine abusers have long-lasting decreases in DAT,[50–52] which appear to reflect neurotoxic effects rather than changes linked to the addiction process itself. These decreases recover very slowly after months of detoxification.[53] These heterogeneous findings indicate that DAT changes are unlikely to underlie the common phenomenology of compulsive drug intake and poor control that characterizes drug addiction.

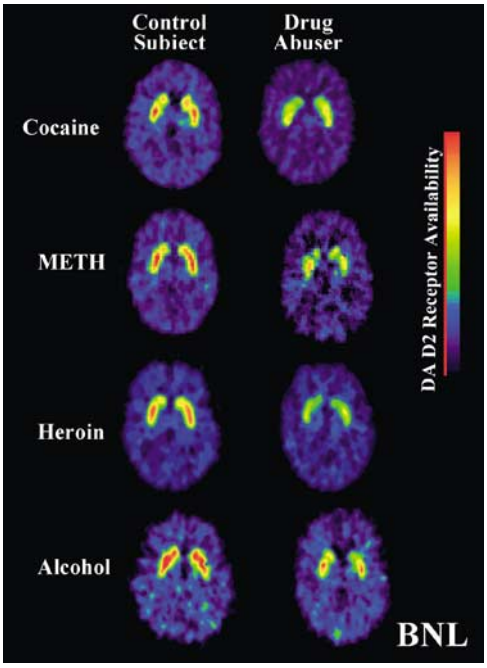

Figure 4 Images obtained with [^{11}C]raclopride (to measure DA D2 receptor availability) at the level of the basal ganglia in subjects addicted to different types of drugs of abuse including alcohol and the images for age- and gender-matched controls. Note the decreases in DA D2 receptors in drug abusers when compared with controls. The scale is to the right and the different colors reflect the levels of DA D2 receptor availability. METH corresponds to methamphetamine.

Dopamine D2 receptors

DA D2 receptors are one class of receptors that convey the reinforcing effects of drugs of abuse. Their relevance has been confirmed by studies that show decreases in the reinforcing effects of alcohol and morphine in DA D2 receptor knockout mice[54,55] and decreases in the reinforcing effects of drugs with pretreatment with DA D2 receptors blockers.[56]

PET studies measuring DA D2 receptors have consistently shown long-lasting decreases in DA D2 receptors in drug-addicted subjects (including alcoholics) when compared with controls (Figure 4).[41] We have postulated that the decreases in DA D2 receptors in the addicted subjects, coupled with the decreases in DA release, might result in a decreased sensitivity of reward circuits to stimulation by natural rewards (their reinforcing effects appear to also involve DA D2 receptors) and a decrease in motivational salience for nondrug-related environmental stimuli. This could put subjects at greater risk for seeking drug stimulation as 'self-medication' to temporarily activate these desensitized reward circuits.

It is likely that changes in DA receptors with addiction are not specific to DA D2 receptors. Indeed, imaging studies have also shown a reduction in DA D1 receptors in the ventral striatum of human

cigarette smokers relative to nonsmokers.[57] However, adequate PET tracers for DA D3 and DA D4 receptors have not yet been developed, so even though these receptors are implicated in addiction, currently it is not feasible to image and quantify them in human subjects.

Brain glucose metabolism

As described earlier, regional brain glucose metabolism provides an index of brain function, and we used PET to measure this in conjunction with the DA D2 receptors. In some subjects, we obtained both measures and documented that the reductions in striatal DA D2 receptors in the detoxified drug-addicted subjects were associated with decreased metabolic activity in the OFC and in anterior cingulate gyrus (CG) (Figure 5).[58,59] We interpret this association to reflect a disruption of the OFC and CG secondary to the intermittent changes and consequent disrupted DA activity in drug-addicted subjects.

In contrast to the decreases in metabolic activity in OFC and CG of detoxified cocaine abusers, the OFC is hypermetabolic in active cocaine abusers.[60] The increases in OFC in active cocaine abusers were found to be proportional to the self-reports of craving. This led us to postulate that during cocaine intoxication or as the intoxication subsides, the drug-produced increases in DA in striatum are associated with the self-perception of 'high', but also that this activates the OFC, which leads to the craving and subsequent compulsive drug intake characteristic of addiction. Indeed, in a subsequent study, we showed that i.v. MP increased metabolism in OFC only in the cocaine abusers in whom it induced intense craving.[61]

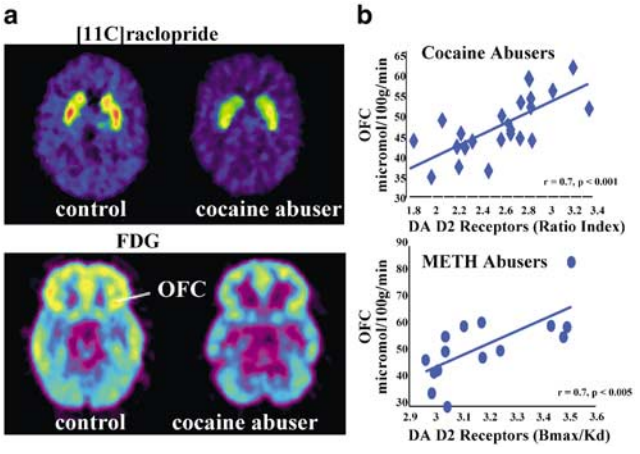

Figure 5 (a) Images obtained with [^{11}C]raclopride (to measure DA D2 receptor availability) and with FDG (to measure brain metabolism) in a control and in a cocaine abuser. Note the reduction in DA D2 receptors in basal ganglia and the reduced metabolism in the orbitofrontal cortex (OFC) in the cocaine abuser when compared with the control. (b) Relationship between DA D2 receptor availability in striatum and regional brain metabolism in OFC in cocaine and in metamphetamine abusers.

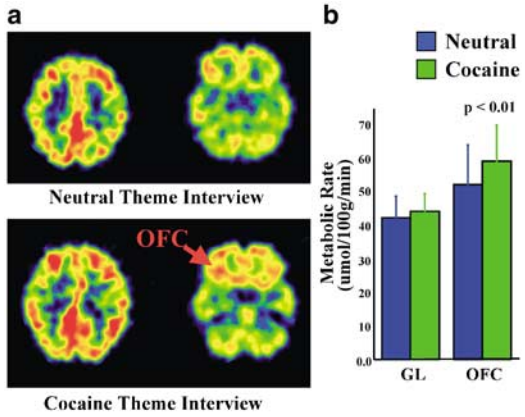

Figure 6 (a) Regional brain metabolic images in a cocaine abuser during a neutral and a cocaine interview. (b) Regional brain metabolic measures for whole brain (global) and for OFC in cocaine abusers tested during a neutral interview and tested during a cocaine interview.

Activation of the OFC in drug abusers has also been reported to occur during craving elicited by viewing a video of drug paraphernalia[39] and by recalling previous drug experiences (Figure 6).[62] Recently, imaging studies using MRI also documented decreased gray matter in the OFC of cocaine abusers indicating that the abnormalities are not only functional but also morphological.[63]

There are several functions of the OFC, which if disrupted might produce some of the behaviors that characterize the addicted state, which we have reviewed elsewhere[41,64] and that include: (1) it processes information related to the relative reinforcing properties of a stimulus in the context of alternative competitive stimuli;[65] (2) it is involved with motivation and 'drive';[66] (3) it is involved with learning stimulus-reinforcement associations and with conditioned responses;[67,68] and (4) it forms part of a circuit that regulates inhibition of emotional responses.[69] Moreover, disruption of the OFC is associated with the emergence of compulsive behaviors[70] and thus its disruption in the drug addict could underlie the compulsive drug administration that characterized addiction. Also, OFC damage in animals results in perseveration and resistance to extinction of reward-associated behaviors,[67] which is reminiscent of what drug addicts report who claim that they cannot stop taking the drug even when it is no longer pleasurable.

DA and vulnerability to drug abuse

One of the most challenging enigmas in drug addiction is why some individuals become addicted and others do not. In laboratory animals, DA function modulates the predisposition to drug self-administration[71] and genetic manipulations of DA D2 receptors markedly affect drug self-administration.[72] Because it

is impractical to study brain DA D2 receptors levels in subjects prior to and after they become addicted, we investigated the significance that the differences in DA D2 receptor levels in nonaddicted individuals have on their responses to drugs.

For this purpose, we measured the baseline levels of DA D2 receptors in striatum in healthy nondrug abusing subjects and in parallel assessed the behavioral responses to the i.v. administration of MP.[73] Approximately 50% of the subjects described the effects of MP as pleasant and 50% as unpleasant, and this difference was not accounted for by differences in subjects' plasma MP concentration. Interestingly, subjects who described MP as pleasant had significantly lower levels of DA D2 receptors than the subjects who described it as unpleasant. We recently replicated this finding in a different group of subjects also given i.v. MP and showed a negative correlation between self-reports of drug liking and DA D2 receptors.[74] The differences in response to i.v. MP between subjects with high and low DA D2 receptors could be explained if there is an optimal range for DA D2 receptor stimulation to be perceived as reinforcing; too little may not be sufficient but too much may be aversive. This suggests that the relationship between drug-induced DA D2 receptor activation and its rewarding effects may reflect an inverted U-shaped curve. Thus, it is possible that in subjects with high DA D2 receptors a smaller dose of MP may have been perceived as pleasant. If DA D2 levels also modulate sensitivity to physiological rewards, then one could postulate that low DA D2 receptors would predispose a subject to use drugs as a means to compensate for the decreased activation of reward circuits. Alternatively it is possible that low DA D2 receptors could predispose to psychostimulant abuse by favoring initial 'pleasant' drug responses, and/or that high DA D2 receptors may protect against drug abuse by favoring 'unpleasant' drug responses. However, the fact that the subjects who were not addicted had low DA D2 receptors comparable to those of drug-addicted subjects, shows that while low DA D2 receptors may produce a predisposition it is not a sufficient condition for drug addiction.

A limitation for these imaging studies is that they report on correlations between variables, but these do not mean that the association is causal. However, the information from the imaging studies can be used to design preclinical studies to investigate associated variables that may be causally related. Recent work has provided evidence that high levels of DA D2 receptors are causally related to a reduction in alcohol intake.[72] The latter study used an adenoviral vector to deliver the DA D2 receptor gene into the NAc of rats previously trained to self-administer alcohol. A resulting increase in DA D2 receptors within the physiological range ($\pm 50\%$) produced a marked reduction in alcohol intake, which recovered as the DA D2 receptors returned to baseline levels. These results could be taken as indirect evidence of a protective role of high DA D2 receptor levels against alcohol abuse. The expression of DA D2 receptors in the brain, which has been shown to be modulated by both genetic and environmental factors,[75,76] provides a molecular mechanism that can account for the involvement of both genetic as well as environmental factors in the predisposition to drug abuse. It also opens up the possibility for developing strategies to increase the expression of DA D2 receptors as a means of decreasing drug abuse and help treat drug addiction.

Treatment implications

The basic findings on the effects of acute and chronic drugs on brain dopamine function have therapeutic implications. Based on these findings we recently suggested a multiprong approach that includes pharmacological and behavioral interventions for the treatment of drug addiction.[77] Four strategies were delineated to: (a) decrease the rewarding value of drugs, (b) increase the value of nondrug reinforcers, (c) weaken learned positive associations with drug and drug cues, and (d) strengthen frontal control. Here, we will expand on how knowledge of the involvement of DA in drug abuse may offer some direction for the evaluation of old and for the development of new strategies for pharmacological interventions for the treatment of addiction.

These interventions can be divided into those that interfere with the acute effects of the drug and those that compensate for the chronic effects of long-term use linked to its dopaminergic effects. Note again that this discussion is limited to therapeutic interventions that are driven by the imaging findings on DA.

Treatments to interfere with the acute effects of the drug

This can be segregated into four subgroups: (a) drugs that interfere with the binding of the drug to its target, (b) drugs that block the DA receptors, (c) drugs that interfere with the drug-induced DA increases and (d) drugs that interfere with the postsynaptic responses to DA stimulation.

Medications that interfere with the binding of the drug to its target but with different pharmacokinetic properties have been valuable in the management of heroin (methadone) and to a certain extent nicotine addiction (nicotine patch, nicotine gum) (review Kreek *et al*[78]). However, this strategy has not been successful in addictions to stimulant drugs. In the case of cocaine, studies have been done with oral MP or oral amphetamine (AMP), which were given to slowly block the DAT and thus interfere with or minimize the acute effects of cocaine. However, oral MP or AMP in cocaine-addicted subjects did not decrease cocaine consumption when compared with placebo treatment.[79,80] We believe this is explained by the fact that you need to block most if not all DAT to interfere with cocaine's effects[81] and the oral doses required to maintain this level of blockade would be very large (significantly larger than doses that have

been tested) and very likely to have cardiotoxic effects. Also, oral MP and AMP would increase extracellular DA and in so doing would make events more salient.[36,37] In an outpatient setting where subjects are exposed to drug conditioned stimuli, we postulate that the DA increases from MP or AMP could make these stimuli more salient, and could increase craving.

What does this analysis suggest for new drug development? The drugs that target the DAT as potential medications for cocaine addiction should have slow rates of brain uptake as well as slow rates of clearance, and should maintain stable concentrations of DA in brain. Theoretically, these drugs could mute the effects of fast DA increases linked with reinforcing effects from the acute administration of cocaine and the effects of DA decreases that are linked with stimulant self-administration in animals.[82] In addition, the doses used should produce minimal cardiac side effects, either alone or in combination with cocaine. Furthermore, pharmacological interventions with drugs that themselves increase DA (but with slower pharmacokinetic properties) should be coordinated with a behavioral treatment, which could control the enhanced saliency and focus this on nondrug effects targeted by the psychosocial intervention. In this respect, the development of drugs that block the DAT but do not interfere with DA reuptake would solve this problem.

Drugs that block DA receptors such as neuroleptics (primarily DA D2 receptors, but also for some drugs DA D3 and DA D4 receptors) interfere with the reinforcing effects of drugs of abuse in laboratory animals,[83] but in humans some studies report decreases in the reinforcing effects of drugs but others do not.[84] Moreover, schizophrenic patients continue to take drugs of abuse even when medicated with neuroleptics.[85] What is a possible explanation for the discrepancy in the animal and human studies? The neuroleptic doses used in humans are likely to have blocked only 60–80% of the DA D2 receptors[86] whereas the animal studies test doses that are significantly larger than those given to humans and thus are likely to have achieved greater occupancy of D2 receptors. With incomplete D2 receptor occupancy, the DA increases produced by stimulant drugs can still bind to the receptors. Also, drug-addicted subjects appear to be very sensitive to the extrapyramidal side effects of neuroleptics, probably due to the reductions in DA D2 receptors. In these individuals, further blockade of DA receptors puts them at high risk for dystonic reactions,[87] which is a motor consequences of marked reduction in DA neurotransmission. Also, DA D2 receptor blockade in addicted subjects who already have low DA D2 receptor levels is likely to further decrease their sensitivity and motivation for natural reinforcers, which in turn may make them more vulnerable to the use of drugs of abuse since even with blockade drugs of abuse are more effective in activating reward circuits than natural reinforcers. This indicates that neuroleptics are not good candidates for the treatment of addiction except perhaps when linked with a schizophrenic comorbid disorder.[88–89]

The potential use of medications that block the ability of drugs of abuse to increase DA as a treatment in addiction, targets neurotransmitters that regulate DA cell firing or that regulate DA release in the NAc such a GABA, opiates, adenosine and glutamate. In particular, GABA enhancing drugs have been shown to interfere with the ability of most of the drugs of abuse to increase DA.[90,91] These drugs have shown promising results in animal studies[92,93]and in preliminary clinical trials in cocaine-addicted subjects[94,95]and in alcoholics.[96] Antagonism of opiate receptors has been shown to be effective in the treatment of alcoholism (review O'Brien *et al*[97]) and has shown some promising results in the treatment of nicotine addiction.[98]

Finally, consider the use of medications that interfere with the postsynaptic responses to DA stimulation. This includes drugs to antagonize the cannabinoid receptors which modulate DA cells but also postsynaptic responses from DA stimulation.[99,100] These drugs have shown promising results in attenuating the reinforcing effects of various types of drugs of abuse in laboratory animals.[101]

Treatments to compensate for changes in DA activity in addicted subjects

Compensatory interventions should aim to mimic the patterns of tonic and phasic DA activity that occurs to natural (nondrug) reinforcers and are modulated by context and expectation. This could provide an explanation of why DA receptor agonists (such as bromocriptine and apomorphine, which stimulate DA receptors regardless of the context) have been of limited therapeutic benefit in addiction (review Kosten *et al*[102]). However, we postulate that drugs that increase the amount of DA that is being released as a function of DA cell firing (such as MAO B inhibitors, which enhance DA release in response to DA stimulation presumably by their inhibition of DA degradation)[103,104] would be promising candidates for pharmacological interventions intended to compensate for chronic effects of stimulant abuse. Indeed, MOA B inhibitors are showing promising results in the treatment of nicotine addiction.[105]

Increases in DA D2 receptors in the brain may provide an effective treatment for stimulant abuse, since this would make the subjective experience of stimulants aversive and would enhance the sensitivity to natural reinforcers, which increase DA much less than drugs of abuse. Currently, there are no available interventions that can noninvasively increase DA D2 receptors in human brain, but animal studies show that increasing DA D2 receptors leads to marked reductions in drug self-administration.[72]

As we start to unravel the differential involvement of the various DA receptor subtypes in compensatory changes in addiction, drugs that target other DA

receptor subtypes may also hold promise in treatment of addiction.

Finally, strategies to interfere with conditioned responses may be valuable. So far, this strategy has been based on behavioral interventions to desensitize subjects to responses linked with conditioned stimuli, but it is possible that medications could be developed to facilitate these processes. For example, drugs that interfere with the responses of circuits linked with memory processes in hippocampus and amygdala (ie, drugs that enhance GABA, inhibit glutamate or antagonize beta-adrenergic neurotransmission) might be effective. For example, beta-blockers have been shown to interfere with the condition responses to natural reinforcers as well as to aversive stimuli, which is an effect mediated by the amygdala.[106] Although propranolol's utility in addiction has been related to its antagonism of the sympathetic hyperactivity during withdrawal[107] it is possible that it could be beneficial in counteracting conditioned response in addiction. Some of the antiepileptic drugs shown to be beneficial in animal models of addiction may also be beneficial not only because of their inhibition of DA release but also because of their inhibition of neuronal responses associated with conditioned responses. Indeed, GABAergic stimulation attenuates Pavlovian conditioned responses[108] and impairs conditioned responses to drugs of abuse.[92,109,110]

As we acquire basic knowledge of brain circuits involved in addiction and on how environmental variables affect them, we will be able to develop behavioral strategies to compensate for these deficits in a manner akin to what is being proposed to promote plasticity of dysfunctional brain circuits and improve reading ability in children with learning disabilities[111–113] or on rehabilitation after brain injury.[114] Dual approaches that pair behavioral strategies with medications to compensate or counteract the neurobiological changes induced by chronic drug exposure or by genetic vulnerabilities are likely to offer in general more robust and longer lasting responses in addiction than either treatment given in isolation.

Summary

Imaging studies have corroborated the role of DA in the rewarding effects of drugs of abuse in humans but also its involvement in motivation. These studies have shown the phasic increases in DA and subsequent fast and marked activation of postsynaptic DA receptors, not the tonic level of DA *per se*, is relevant for drug reinforcement. On the other hand, smooth DA increases have been associated with motivation and the attribution of saliency. Research has also shown that nonpharmacological variables associated with conditioned responses modulate the reinforcing effects of drugs in addicted subjects. Imaging studies have also revealed marked disruptions of DA brain function in addicted subjects. This hypodopaminergic state may lead to deregulation of reward, motivation and inhibitory control circuits. We postulate that the disruption of reward circuits impairs the sensitivity to natural reinforcers and is associated with dysfunction of OFC (which could contribute to the compulsive drug self-administration in addicted subjects) and of the CG (which could contribute to poor inhibitory control).

This basic science research can be used to suggest new treatment strategies for drug addiction. Our findings suggest that interventions designed to enhance DA brain function in drug abusers may help them engage in normal activities, which if made salient would provide them with nondrug alternative sources of reinforcement. Interventions designed to enhance frontal function may help the addicted subject overcome the strong drive to take the drug and may also interfere with the compulsive administration of drugs of abuse.

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