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Review

The role of dopamine in human addiction: From reward to motivated attention

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Abstract

There is general consensus among preclinical researchers that dopamine plays an important role in the development and persistence of addiction. However, the precise role of dopamine in addictive behaviors is far from clear and only a few clinical studies on the role of dopamine in human addiction have been conducted so far. The present paper reviews studies addressing the role of dopamine in humans. There is substantial and consistent evidence that dopamine is involved in the experience of drug reward in humans. Dopamine may also be involved in motivational processes such as drug craving. However, given the inconsistent findings of studies using dopamine receptor (ant)agonists, the role of dopamine in the experience of craving is far from resolved. Recent theories claiming that dopamine signals salience and makes the brain paying attention to biological relevant stimuli may provide an interesting framework for explaining addictive behaviors. There is accumulating evidence that patients with drug and alcohol addiction have an aberrant focus on drug-related stimuli. Although there is some preliminary support for the role of dopamine in these attention processes, more studies have to be carried out in order to test the validity of these theories in human subjects.

Keywords: Dopamine; Addiction; Human; Attention; Craving; Reward

Contents

1. Introduction

In the last decades, there has been a serious debate on the role of dopamine in addiction (Robinson and Berridge, 1993; Wise, 2004a,b), but it is now generally accepted that dopamine is pivotal in the development and persistence of addiction. However, its precise role is far from clear. Several studies have shown that dopamine is important in experiencing reward and in motivational aspects of drug use: craving. In addition, the results of recent preclinical studies also suggest a role of dopamine in the attentive processing of drug-related cues. Most

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studies addressing the role of dopamine were conducted in non-human populations. Less attention has been paid to human studies that address dopamine's role in addictive behaviors. Some clinical studies have used dopamine receptor antagonists or agonists in the treatment of addiction or addiction-related symptoms such as craving. In addition, the introduction of new imaging techniques such as Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT) has made it possible to study the dopamine system in living human subjects. These techniques can be used to image neurotransmitter systems in the brain; for example, dopamine D2-like receptors can be visualized with [^{11}C] raclopride PET or [^{123}I] iodobenzamide ([^{123}I] IBZM) SPECT, and gamma-aminobutyric acid (GABA) receptors with [^{11}C] flumazenil PET. Using these unique abilities of SPECT and PET, it is possible to study the role of specific neurotransmitter systems that are involved in addictive behaviors. In the present paper there is a focus on the role of dopamine. Other neurotransmitter systems and the interaction of dopamine with other neurotransmitters will not be discussed. For a discussion of these relations is referred to work of others (e.g., Kalivas et al., 2005; Kalivas, 2004).

The main focus of the present paper will be to discuss the role of dopamine in (a) the experience of reward, (b) craving, and (c) attentional processing of drug-related stimuli in humans. Generally, two lines of research will be discussed: direct evidence for the involvement of dopamine studies using neuroimaging techniques and indirect evidence using pharmacological challenges that modulate the central dopaminergic system.

2. Dopamine and reward

There is an obvious relation between the rewarding effects of drugs and their self-administration. When drugs yield pleasurable effects in subjects, the chance of taking that drug again increases. This phenomenon of repeated use is guided by the principles of instrumental conditioning. It is known that all drugs of abuse have rewarding properties. Self-reported subjective drug effects such as pleasure and euphoria have been reported for all drugs of abuse (e.g., Fischman and Foltin, 1992). Early pharmacology approaches in addiction research were mainly focused on the role of dopamine in the rewarding effects of self-administration of addictive drugs (Wise and Bozarth, 1987). Preclinical studies suggested that the dopaminergic system is involved in the experience of these pleasurable feelings (Wise and Bozarth, 1987). In addition, several human imaging studies have demonstrated that endogenous dopamine release in the striatum is correlated with the experience of pleasure (hedonic effects) evoked by several categories of drugs, i.e., drug-induced euphoria (Drevets et al., 2001; Laruelle et al., 1995; Volkow et al., 1997, 1999a,b). For example, Barrett et al. (2004) showed that the hedonic effects of cigarette smoking, are associated with increased dopaminergic activity in the dorsal striatum. Furthermore, using SPECT in combination with the dopamine D2/D3 radiotracer [^{123}I] IBZM, Abi-Dargham et al. (2003) showed that the magnitude of the decrease in dopamine D2 receptor availability was significantly associated with the self-reported positive reinforcing effects of amphetamine. Furthermore, Oswald et al. (2005) found that amphetamine administration resulted in striatal dopamine release, which was positively correlated with self-reported drug-liking. There are also studies showing drug-induced dopamine release in the striatum, but which failed to find associations with subjective drug liking. For example, Boileau et al. (2003) found that an oral dose of alcohol promotes dopamine release in the brain, with a preferential effect in the ventral striatum and Leyton et al. (2002) found that amphetamine released dopamine in the ventral striatum, but a relation with subjective hedonic effects in these studies was not found.

Summarizing, most studies investigating the role dopamine in the experience of pleasure in humans are compatible with the view that dopamine release and high levels of extracellular dopamine in the ventral striatum are associated with the pleasurable effects of drugs of abuse.

3. Dopamine and craving

The pleasurable effects of drugs by themselves cannot explain the total spectrum of addictive behaviors. Both addicted and non-addicted persons may experience pleasurable effects equally (Volkow et al., 2003). The focus in addiction research has made a shift from the rewarding aspects of drug use towards the motivational aspects of addictive behavior (Robinson and Berridge, 1993; Wise, 2004a). The motivational properties of drugs may last for several years after the determination of drug use, and may even last a lifetime (Hser et al., 2001). Stimuli in the environment associated with drug use are still able, probably by means of Pavlovian conditioning principles, to trigger motivational circuits and elicit a high motivation to use these drugs: so-called cue-elicited craving. This conditioned craving contributes to the continuation of drug use in active drug abusers and to relapse in detoxified abusers (Everitt, 1997). Several decennia ago, Perez-Cruet (1976) and Schiff (1982) already demonstrated a role for dopamine in classical drug conditioning, suggesting a broader role of dopamine in addiction than its role in reward only. More recent work in addiction research showed that classical conditioned drug related stimuli are able to induce dopamine release in the mesolimbic region (e.g., Di Ciano et al., 1998; Duvauchelle et al., 2000; Gratton and Wise, 1994). These findings suggest that in conditioned subjects dopamine has a role the earlier, motivational phase, i.e., before the use of the drug and before the experience of pleasure per se. This motivational phase can be labeled as the desire phase of drug use: craving. Several theories suggest that dopamine is strongly associated with conditioned craving (Di Chiara, 1998; Robinson and Berridge, 1993). The role of dopamine in craving has been confirmed in several studies using laboratory animals (Di Chiara et al., 1992; Robinson and Berridge, 1993). Several human studies have addressed the question whether dopamine could play a role in the experience of craving modulation or whether dopamine has an effect on cue-elicited drug craving. The use of dopamine receptor agonists in the treatment of cocaine dependence has

yielded mixed results (Soares et al., 2003). Based on a meta-analysis of 17 studies, Soares et al. concluded that the use of dopamine agonists in cocaine addiction could not be supported. Fewer studies focused specifically on drug craving and also yielded contradictory results. For example, Jarvik et al. (2000) found that cigarette craving scores decreased significantly across increasing dosages of the dopamine receptor agonist bromocriptine. However, there are also several studies that showed that bromocriptine does not have an effect on craving (e.g., Ciraulo et al., 2005; Handelsman et al., 1995; e.g., Handelsman et al., 1997; Kranzler and Bauer, 1992).

Regarding the use of dopamine receptor antagonists in addiction, similar contradicting findings emerge from the literature. A study of Berger et al. (1996) shows that the dopamine receptor antagonist haloperidol reduces cue-elicited craving in a population of cocaine-dependent patients. Similar results were obtained by other studies with other addictions and other dopamine antagonists, for example smoking and olanzepine (Hutchison et al., 2004). However, it must be noticed extra-dopaminergic neurotransmitter systems, e.g., serotonergic systems, are involved in the effects of atypical neuroleptics (Marek et al., 2003). In contrast to this, other studies using the typical antipsychotic haloperidol did not result in reductions in craving in heroin-dependent patients (Franken et al., 2004a) or in smokers (Mahler and de Wit, 2005). In line with the results with typical neuroleptics, also more atypical antipsychotics yield inconclusive results. Studies of Hutchison et al. (2004, 2001) showed that olanzepine attenuates craving for tobacco in smokers and urge to drink in heavy drinkers. In contrast, in a study of Smelson et al. (2004) no indications were found that risperidone decreased cocaine craving. In addition, there are also reports that dopamine antagonists actually increase smoking behavior (Caskey et al., 1999; Dawe et al., 1995).

Summarizing, studies that addressed the involvement of dopamine in the experience of craving are inconclusive. Several factors may influence these contrasting results in clinical pharmacological studies using dopaminergic agents. Results may depend on the paradigm used (cue-elicited craving versus more long-term craving), the craving questionnaires that were used (craving measured as the desire escape from a negative state versus desire to experience the pleasurable effects), drug of abuse, personality of the drug user (see e.g., Reuter and Netter, 2001), or different stages of dependence or abstinence. There is clearly a need for new theories that can incorporate the mixed findings.

One new and interesting theory that accounts for a dual role of dopamine in drug craving is that of Pilla et al. (1999) and Childress and O'Brien (2000). These researchers propose that craving is the result of two separate neurobiological pathways. The first craving pathway (chronic craving) is the result of a reduced dopamine activity (reduced dopamine D2 receptor density in the striatum and orbitofrontal cortex). This reduction results in a chronic state of anhedonia. Drugs are used to stimulate the dopamine activity in the striatum and orbitofrontal cortex in an attempt to alleviate this chronic anhedonic state. It can be regarded as a 'need for dopamine', which is experienced as chronic craving (Dackis et al., 1987). The second craving pathway (instant craving) results from a temporary enhanced cue-elicited dopaminergic activity in the striatum, amygdala, and cingulate cortex. Although implications of this two-pathway model for humans have been suggested by others (Childress and O'Brien, 2000), few tests of this model have been conducted in humans yet. Pilla et al. (1999) suggested that the partial dopamine D3 agonist BP 897, acting either as an agonist (reducing chronic craving) or as an antagonist (reducing cue elicited acute craving) and may be an effective drug dealing with both types of craving. It can be hypothesized that when dopamine activity is low, such as during the post-withdrawal anhedonia and chronic craving, partial agonists function as an agonist and decrease this form of craving. However, when instant craving is elicited by drug related cues, partial dopamine agonists may antagonize the heightened activity of dopamine, and decrease instant craving. Currently, BP 897 entered phase II clinical studies (Garcia-Ladona and Cox, 2003).

There is some evidence from neuro-imaging studies for the dual craving pathways. Heinz et al. (2004) found that alcoholics who displayed less availability of dopamine D2-like receptors in the ventral striatum have higher craving severity and greater cue-induced activation of the medial prefrontal cortex and anterior cingulate as assessed with PET and Functional Magnetic Resonance Imaging (fMRI), respectively. Both PET and postmortem studies showed reduced levels of striatal dopaminergic D2 receptors among cocaine and methamphetamine users (Kish et al., 2001; Volkow et al., 2001, 1993). Recent PET studies in humans show that dopamine is released in the human striatum during the anticipatory or appetitive phase of motivated behavior (Koepp et al., 1998). Leyton et al. (2002) found that amphetamine-induced drug wanting was correlated with dopamine release in the ventral striatum. Oswald et al. (2005) demonstrated that d-amphetamine induced striatal dopamine release was correlated with the desire to take drugs. Summarizing, the role of dopamine in human craving is unclear. This may be the result of different definitions of craving or different phases of abstinence among others. Testing of a clear theoretical model that makes some predictions about the different forms craving, such of that of Pilla et al. (1999; but see also Verheul et al., 1999) may advance this field of research.

4. Dopamine and attention

4.1. Attention to drug-related stimuli

Recently it has been suggested by several authors (see e.g., Nieoullon and Coquerel, 2003) that dopamine has a far wider and less specialized role than previously hypothesized in the reward theories. It is known from preclinical studies that dopamine is involved in several cognitive processes such as attention (e.g., Nieoullon, 2002; Nieoullon and Coquerel, 2003) and memory (e.g., Berke and Hyman, 2000). Studies on the pharmacological underpinnings of attention in humans showed that dopamine is involved in attention processing, especially selective attention (Clark et al., 1987). Pharmacological trials

have demonstrated that both dopamine receptor agonists and antagonists are able to affect selective attention (Ahveninen et al., 2000; Kahkonen et al., 2001; Servan-Schreiber et al., 1998; Vitiello et al., 1997). In addition, it is known that persons with a deficient dopaminergic system, such as patients with Parkinson's disease, display deficits in selective attention (Robbins, 1991; Stam et al., 1993; Yamaguchi and Kobayashi, 1998).

Recently, there are some new theories postulating that dopamine may play a role in attentional signaling of reward (Schultz, 1997, 1998). This may have also clinical relevance for understanding several psychopathological states such as schizophrenia (Kapur, 2003) and addiction (Robinson and Berridge, 1993). The role of dopamine as signaling rewarding stimuli in addiction has been put forward in the "Incentive Sensitization Theory" of Robinson and Berridge (1993). Their theory postulates that addictive drugs enhance the mesolimbic dopamine transmission, and thereby attribute incentive salience. Dopamine is thought to transform the perception of stimuli by attributing them with salience. One of the hypotheses of the "Incentive Sensitization Theory" is that dopamine triggers the brain's attention towards drug-related cues. It is hypothesized that activation of dopaminergic activity in the corticostriatal reward circuit by cues which signal reward could contribute to one of the characteristics of addiction, i.e., the excessive focus on activities, which lead to further drug use. This notion of Robinson and Berridge's theory, which is heavily based on observation from preclinical studies, has been applied to the human context by other authors (Franken, 2003; McCusker, 2001; Ryan, 2002). For example, in Franken (2003) drug use and relapse is explained in terms of an attentional bias, which is supposed to be present in drug abusing patients. Attentional bias is the exaggerated amount of attention that is paid to drug-related stimuli at the expense of other (neutral) stimuli. But, how does this attention bias contribute to drug use and relapse? Attentional bias may contribute to addictive behaviors in several ways. Attentional bias may be responsible for the observation that drug abuse patients signal drug cues more easily. It is acknowledged that the perception of drug-related cues is related to conditioned responses (e.g., craving) that may trigger relapse (O'Brien et al., 1998). Further, once a drug cue is detected it is difficult to draw attention away from this cue, which also may trigger drug use. Lastly, because of the limited capacity of attention (MacLeod, 1991; Williams et al., 1996), the automatic focusing on drug related cues would result in a subsequent failure in the processing of competing stimuli, such as avoidance strategies that were learned by the patient in clinical relapse prevention programs. Because attentional bias is—at least in part—involuntary and unintentional, attentional bias is compatible with the existence of an "automatic" pathway to continued drug use and may provide important clues for the future development of treatment interventions.

There are several clinical studies that affirm the presence of an attentional bias in drug abuse patients (for a review see Franken, 2003). Studies indicating that this attentional bias is a predictor of future drug or alcohol use underline the relevance

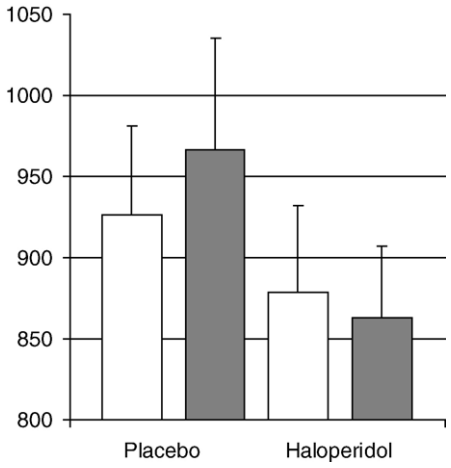

Fig. 1. Mean responding times (in milliseconds) on neutral (white bars) and heroin words (gray bars) by medication condition. Differences between neutral and heroin words indicate attentional focusing on heroin cues (attentional bias). Statistical analyses indicate that individuals in the haloperidol condition were faster to indicate word color of the heroin words, thereby suggesting that, within a heroin dependent population, attention bias for heroin stimuli decreases after ingestion of a dopamine antagonist (Franken et al., 2004a).

of this disturbed attention (Cox et al., 2002; Marissen et al., submitted; Waters et al., 2003). In addition, several studies have found a relation between attentional bias and craving (Field et al., 2004; Franken et al., 2004a,b, 2000b, 2003; cf. Van de Laar et al., 2004), indicating that attentional bias is closely associated with motivational processes.

As far as we know only one clinical study addressed the role of dopamine on "drug attention" directly. In that study (Franken et al., 2004a), the hypothesis that enhanced attention for heroin cues is mediated by the dopaminergic system was tested by using haloperidol as a dopamine receptor antagonist. In a double-blind, randomized, cross-over design, detoxified heroin dependent patients received a single oral dose of 2 mg haloperidol or placebo. Patients performed an Emotional Stroop Task, measuring the attention to heroin cues as compared to neutral cues (attention bias; Franken et al., 2000b), under both medication conditions. In the haloperidol condition, patients showed less attentional bias than in the placebo condition (see Fig. 1). However, no significant effect on subjective craving was found. The finding that haloperidol reduces attention bias in heroin-dependent patients suggests an important role for dopamine in this mechanism underlying drug addiction. This finding is consistent with theories claiming that dopamine triggers the brain's attention towards motivationally significant stimuli.

Surprisingly, only a few experimental studies in humans addressed the salience attribution theory of dopamine. New studies using neuroimaging techniques and pharmacological agents are needed to investigate whether, and if so, how dopamine affects attentive motivational processing.

4.2. Attention to salience

Similar theories have been proposed in other fields of psychopathology. For example, Kapur (2003) stated that psychosis, one of the hallmark symptoms of schizophrenia, is

the result of an "exaggerated release of dopamine, independent of and out of synchrony with the context". This aberrant dopamine release results in an inappropriate attribution of salience, and attention will be focused on irrelevant internal and external stimuli.

Preclinical studies showed that the "signaling reward function" of dopamine is not only relevant for psychopathological states, such as drug addiction and schizophrenia, but may also be relevant to all motivated behavior such as feeding (Bassareo and Di Chiara, 1997; Tanda and Di Chiara, 1998) and sexual behavior in male rats (Phillips et al., 1991). Currently, there is some debate whether dopamine signals only rewarding stimuli or signals salient stimuli in general (Ungless, 2004). Some authors have noticed that enhanced dopaminergic activity in the nucleus accumbens is not only elicited by reward-related stimuli, but also by punishing stimuli (Gray et al., 1997; Horger and Roth, 1996). In contrast, other researchers argued that a reinterpretation of those findings indicate that dopamine may be exclusively responsible for the signaling of reward (Ungless, 2004). A recent preclinical study of Dommett et al. (2005) showed that dopamine cells are activated when biologically important (salient) visual stimuli are presented, leaving this issue unresolved.

Summarizing, dopamine, among others, may trigger attention towards conditioned incentives. Although direct evidence is lacking, indirect evidence suggests the involvement of dopamine in the attention systems. According to the current hypotheses, dopamine receptor antagonists may not only modulate drug craving, but also selective attention in humans.

5. Concluding remarks

Since the appearance of imaging techniques, like PET- and SPECT-scanning, much knowledge has been gained regarding the involvement of neurotransmission systems on addictive behaviors in humans. Led by the results of preclinical studies that show the importance of dopamine in substance use and addiction, it is becoming clearer in which way dopamine receptors and endogenous dopamine release may play a role in human addiction. This knowledge will advance further because more sophisticated PET and SPECT techniques to image neurotransmitter release and receptors become available. In this context, the recent successful developments to image not only striatal dopamine D2 receptors but also extrastriatal dopamine D2 receptors as well as the unique opportunity to label in vivo the high-affinity state of the dopamine D2 receptor (Finnema et al., 2005; Aalto et al., 2005) may offer the potential to unravel further the presumed alterations of the central dopaminergic system in addiction.

As reviewed above, the results of neuroimaging and clinical pharmacological studies using dopaminergic agents supported the notion that dopamine may play a role in the experience of the rewarding, pleasurable, effects of substances of abuse in humans. Besides this role, dopamine seems also to be involved in motivational aspects of drug use. However, which exact role is not clear because clinical studies yielded contrasting results. Some studies showed reductions in the experience of craving using dopamine receptor antagonist whereas other studies have yielded positive results in craving reduction using dopamine agonists. A dual craving model proposed by Pilla et al. (1999) and Childress and O'Brien (2000) has been discussed that is compatible with at least some of these inconsistent results. Furthermore, recent theories asserting that dopamine may be responsible for the excessive amount of attention that is paid by drug abuse patients to drug-related cues need to be validated further in future studies. Moreover, dopamine may even play a broader role in the processing of motivational stimuli by attributing salience to these stimuli.

The role of dopamine in attributing salience does not exclude a role for dopamine in reward and drug motivation. Motivational processes and automatic attention towards salience are closely related. It makes sense to state that all emotional stimuli trigger attentional processes reflecting a motivational process moving the subject to approach a pleasant stimulus and avoid an aversive one. From human studies that used electrophysiological measures of attention, such as event-related brain potentials, it has become apparent that motivational relevant stimuli, such as emotional pictures, automatically attract attention (Cuthbert et al., 2000; Lang et al., 1997, 1998; Schupp et al., 2003a,b). This "motivated attention" (Schupp et al., 2004) may be implied in all salience processing. It might turn out that motivated attention and salience processing are two sides of the same coin. Consequently, this might explain the involvement of dopamine in both attentional and motivational processes. Moreover, it would be interesting to investigate the hypothesis that the dopamine system is activated by all salient stimuli, as suggested by preclinical data, within human subjects. Whether and how dopamine modulates the processing of salient cues in general awaits experimental studies. This may make clear whether dopamine's role goes beyond reward and addiction and whether dopamine is also involved in attentive salience processing in general.

Another unresolved issue is how motivational processes in drug-dependent patients can best be assessed. Currently, the most prevailing assessment method is self-report using questionnaires reflecting the desire to use drugs. This self-reported craving is obviously restricted to conscious experience. However, Berridge et al. (Berridge, 2004; Berridge and Winkielman, 2003) showed that in the case of "drug liking" conscious processes are distinct from unconscious processes. In the same vein, motivational processes may also be divided in conscious craving and an unconscious counterpart. Although it is plausible that dopamine plays an important role in motivational processes, it might well be that dopamine is not responsible for the conscious experience of motivation, i.e., the subjective component. This may be an alternative explanation for the inconsistent findings of studies addressing the role of dopamine in drug craving.

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