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Review article

The role of impulsivity in psychostimulant- and stress-induced dopamine release: Review of human imaging studies

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ABSTRACT

Drug addiction is a debilitating disorder and its pivotal problem is the high relapse rate. To solve this problem, the aim is to prevent people from becoming addicted in the first place. One of the key questions that is still unanswered is why some people become addicted to drugs and others, who take drugs regularly, do not. In recent years extensive research has been done to untangle the many factors involved in this disorder. Here, we review some of the factors that are related to dopamine, i.e., impulsivity and stress (hormones), and aim to integrate this into a neurobiological model. Based on this, we draw two conclusions: (1) in order to understand the transition from recreational drug use to addiction, we need to focus more on these recreational users; and (2) research should be aimed at finding therapies that can restore inhibitory control/frontal functioning and improve stress resiliency in addicts.

1. Introduction

Drug addiction is a chronic relapsing disorder. It is one of the most prevalent psychiatric disorders worldwide (Sinha, 2011). Drug addiction has far-reaching consequences for our society, since addicts often experience social problems such as difficulties in finding jobs and adequate housing (EMCDDA, 2009). It also has a major impact on societal costs: according to a report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) public expenditure on preventing and solving problems related to illicit drug use in the European Union was estimated in 2007 to be between €13 and €36 billion (EMCDDA, 2007) with most of it being spend on health interventions (EMCDDA, 2015). Additionally, the chronic, relapsing nature of drug addiction contributes to this high disease burden (Sinha, 2011).

Over the last decade, major research efforts have been devoted to the problem of drug addiction. For example, some studies have tried to untangle factors involved in the various stages of addiction such as stress in relapse (reviewed in Sinha, 2001, 2007). Studies have also focused on the question of why some people become addicted to drugs and other people do not and found that impulsivity is an important personality trait herein (Kreek et al., 2005; Oswald et al., 2007). Moreover, research has come a long way in identifying brain mechanisms contributing to drug addiction. Dopamine plays a pivotal role in all of these factors and has been the main concern of many addiction studies (reviewed in Volkow et al., 2002a, 2011, 2012, 2013), although research has also implicated other neurotransmitter systems, such as GABA and glutamate in drug addiction (e.g. Ramaekers et al., 2013; Urban and Martinez, 2012).

Based on the various foci that these researchers take, they have proposed models that try to explain the relationships among (some of) the many factors involved in drug addiction. One of the most comprehensive models was proposed by Koob and Le Moal (1997) and represents a general framework of three stages in addiction (i.e. preoccupation-anticipation, binge-intoxication and withdrawal-negative affect) connected with each other through what they call “spiralling distress”. This framework incorporates symptoms of drug addiction (e.g. compulsive drug taking) as well as changes in brain reward systems (Koob and Volkow, 2010). Moreover, dysregulation of the brain stress system plays a crucial role in their model. It is involved in the withdrawal-negative affect stage, in relapse as well as in the transition from initial drug use to addiction through the process of

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allostasis (Koob and Le Moal, 2001). On the other hand, Trifilieff and Martinez (2014) proposed a model that explains the role of impulsivity in drug addiction. They state that impulsivity can be a precipitating factor in drug addiction as well as a perpetuating factor and is related to reduced striatal dopamine concentrations.

However, to our knowledge none of the models incorporates both the role of stress as well as the role of impulsivity in psychostimulant addiction, while all seem to be related to striatal dopamine concentrations. Moreover, most models focus on either chronic drug users or healthy controls, but do not explain the neurobiological changes during transition from occasional psychostimulant use to addiction in humans. We therefore review imaging studies in healthy controls, recreational drug users as well as addicts and try to integrate this into a more extended neurobiological model of psychostimulant addiction by focussing on acute effects. First, we review the acute effects of psychostimulants on dopamine in healthy controls, recreational drug users and addicts. Second, we present investigations on the effects of stress on dopamine with and without a psychostimulant in the same three groups. Finally, we review the relationship between impulsivity and dopamine. We conclude by presenting a model that integrates the results of the reviewed studies, which can be used as a working hypothesis to shape future studies.

2. Acute effects of psychostimulants on dopamine

Psychostimulants is a drug class that consists of several pharmacological entities. All drugs in this class have in common that they have stimulating effects such as increased alertness and reduced fatigue (Koob and Le Moal, 2005). The psychostimulants that we focus on are cocaine, amphetamine, methamphetamine and methylphenidate, because they are well studied and commonly used drugs of abuse with a direct effect on the mesocorticolimbic dopamine pathway. Other psychostimulants such as caffeine and nicotine are not included, because they have different mechanisms of action (Koob and Le Moal, 2005).

2.1. Healthy non-drug using humans

Numerous studies have shown that psychostimulants increase striatal dopamine concentrations in healthy non-drug using humans. For example, methylphenidate, cocaine and amphetamine all increase dopamine in striatum and/or substantia nigra/ventral tegmental area (SN/VTA) compared to placebo (Clatworthy et al., 2009; del Campo et al., 2013; Fowler et al., 1989; Oswald et al., 2015; Volkow et al., 1995). Most studies on psychostimulants' mechanism of action are based on methylphenidate administration in healthy volunteers. Methylphenidate increases dopamine in the nucleus accumbens by blocking the dopamine transporter (Volkow et al., 2002a) and this increase correlates with plasma concentrations of *d*-threo-methylphenidate (Volkow et al., 1998). Moreover, the fast uptake of methylphenidate as well as cocaine into the brain was temporally correlated with the subjective feeling high (Fowler et al., 1989; Spencer et al., 2006; Volkow et al., 1995). The *intensity* of the rewarding effects of methylphenidate was positively correlated with dopamine $(D)_2$ receptor occupancy (Volkow et al., 1999). Amphetamines have a slightly different mechanism of action compared to cocaine and methylphenidate. Instead of blocking the dopamine transporter, amphetamine enters the presynaptic cell through the transporter. There it expels dopamine from their vesicles and reverses the action of the dopamine transporter, thereby releasing dopamine into the synaptic cleft (Sulzer et al., 1995). D-Amphetamine decreased (ventral) striatal $D_{2/3}$ receptor availability in humans, which correlated with the intensity of subjective responses such as euphoria and drug wanting (Drevets et al., 2001; Laruelle et al., 1995; Leyton et al., 2002; Martinez et al., 2003). Together these studies demonstrate a positive relationship between psychostimulant-induced dopamine release and subjective drug effects in healthy non-drug using humans.

Thus, psychostimulants increase dopamine, but how does this relate to brain activation during task performance? It is widely accepted that psychostimulants improve cognitive function (Linssen et al., 2014; Repantis et al., 2010). The question is if this improved performance is related to dopaminergic effects. Functional magnetic resonance imaging (MRI) studies showed that methylphenidate significantly increased activation in task-relevant areas (dorsal attention network including parietal and prefrontal cortex) and reduced activation in the default mode network (DMN; insula and posterior cingulate cortex) during performance of a working memory and visual attention task (Tomasi et al., 2011; Tomasi et al., 2009). This increased activation coincided with improved performance, i.e. faster reaction times, but not with increased accuracy compared to a control group who did not receive any drug. The decreased activation in the DMN correlated negatively with striatal dopamine transporter (DAT) availability (i.e., less deactivation was related to more DAT availability). Methylphenidate also increases cerebral blood flow in dopaminergic target areas such as striatum and prefrontal cortex amongst others, measured with a pulsed arterial spin labelling sequence (Schouw et al., 2013a). However, during reward anticipation healthy controls showed blunted striatal activation after a psychostimulant challenge, but increased ventral striatal activation after sensitization through repeated administration compared to baseline/placebo (Knutson et al., 2004; O'Daly et al., 2014; Schouw et al., 2013b). The reverse dichotomy is seen in decision-making: increased amphetamine-induced dopamine release in the right ventral striatum was associated with decreased performance (Oswald et al., 2015), while sensitization led to reduced dorsal striatal activation (O'Daly et al., 2014). A low dose methylphenidate (20 mg) had no effect on cingulate activity during performance of an addiction Stroop paradigm (Goldstein et al., 2010). Based on these studies it seems likely that dopamine is related to cognitive performance. However, it is less clear how they are related since different paradigms show different effects. It has been suggested that different inverted-U shaped relationships might exist between performance on various tasks and dopamine concentrations in the brain (Clatworthy et al., 2009). Nevertheless, it seems that increased striatal DA release as well as increased DAT availability are both related to impaired performance.

Functional connectivity studies measure the interaction between (remote) brain networks and combined with pharmaco-MRI, give an idea about enhanced or diminished brain functions induced by the drug. Methylphenidate reduced functional connectivity between the nucleus accumbens and both basal ganglia and medial prefrontal cortex (Ramaekers et al., 2013). Other studies showed methylphenidate effects on several cognitive and sensory-motor resting state networks with some showing decreased (e.g., right frontal parietal network with striatum) and others increased (e.g., dorsal attention network with thalamus and insula or thalamus/dorsal striatum with precentral gyrus and amygdala/hypocampus) functional connectivity (Farr et al., 2014; Mueller et al., 2014). This implies that methylphenidate reduces control over behaviour through decreased connectivity between striatum and frontal cortex, but increases attention/memory as would be expected from its clinical effect in ADHD (Tomasi et al., 2009).

2.2. Recreational drug users

Not many studies have investigated the acute effects of psychostimulants on dopamine in recreational users. Amphetamine use in combination with 3,4-methylenedioxymethamphetamine (MDMA) may decrease DAT density (Reneman et al., 2002). DAT availability decreased in amphetamine/MDMA users compared to MDMA only users, but not compared to other drug-using controls and healthy controls (Schouw et al., 2013a). Based on these studies, it seems that DAT is not affected in recreational psychostimulant users. However, the dopamine receptor might be affected. Recreational dexamphetamine users demonstrated no change in dopamine release after an ampheta-