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Blunted Dopamine Transmission in Addiction: Potential Mechanisms and Implications for Behavior

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Positron emission tomography (PET) imaging consistently shows blunted striatal dopamine release and decreased dopamine D2 receptor availability in addiction. Here, we review the preclinical and clinical studies indicating that this neurobiological phenotype is likely to be both a consequence of chronic drug consumption and a vulnerability factor in the development of addiction. We propose that, behaviorally, blunted striatal dopamine transmission could reflect the increased impulsivity and altered cost/benefit computations that are associated with addiction. The factors that influence blunted striatal dopamine transmission in addiction are unknown. Herein, we give an overview of various factors, genetic, environmental, and social, that are known to affect dopamine transmission and that have been associated with the vulnerability to develop addiction. Altogether, these data suggest that blunted dopamine transmission and decreased D2 receptor availability are biomarkers both for the development of addiction and resistance to treatment. These findings support the view that blunted dopamine reflects impulsive behavior and deficits in motivation, which lead to the escalation of drug use.

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Introduction

Drug addiction is a pathology that can be defined as a progressive loss of control over drug seeking and taking that becomes compulsive and persisting despite adverse consequences.[1,2] The neurobiological circuits underlying addiction have been extensively discussed elsewhere[3-5] and the general consensus is that drugs of abuse are originally processed as a reward, but that chronic consumption usurps the brain reward system, through their effects on several neurotransmitters. One of the main neurotransmitter systems involved in the development of addiction is mesolimbic dopamine transmission, which consists in the projections of dopamine neurons from the ventral tegmental area to the ventral striatum or nucleus accumbens (NAc) and cortical areas.

It is recognized that dopamine does not simply signal "reward," but instead modulates the reinforcing effects of a reward, which can be either natural, such as sex and food, or the reward associated with drugs and alcohol.[3,4,6,7] Dopamine neurons fire in anticipation of or in response to a reward, which results in higher levels of dopamine being released in the striatum, the NAc in particular. Striatal dopamine increases the likelihood that the behavior that previously successfully resulted in a reward would be repeated. Salamone et al[6,8] have extensively shown that dopamine transmission in the NAc increases the willingness to exert effort for a reward and that, conversely, dopamine antagonism results in an animal being less likely to exert such effort. Dopamine has also been described as mediating "incentive salience," which signals the extent to which the reward or associated cues are wanted.[9] In a

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series of studies in nonhuman primates, Schultz et al[10,11] demonstrated that dopamine serves as a reward prediction error, and codes for reward as it differs from prediction, and as such modulates reward-based learning. Thus, dopamine can be broadly viewed as regulating the reinforcement value of a reward, or the extent to which a given reward is worth the effort required, thereby mediating the behavioral economics of motivated behavior.

Because most drugs of abuse share the ability to increase dopamine transmission within the striatum, extensive work has been done to understand the implication of this neurotransmitter system in addiction. Human imaging studies are in agreement with animal data, and show that mesolimbic dopamine transmission is altered in subjects with substance use disorders.

Principles of Positron Emission Tomography

Most human positron emission tomography (PET) and single photon emission tomography (SPECT) imaging studies in addiction have focused on the imaging of dopamine receptors and dopamine levels in the striatum. PET and SPECT use radionuclide-labeled molecules that are ligands (often agonists or antagonists) for receptors or transporters. Radiotracers have been developed to image various cellular targets in the brain, ranging from receptors to markers of inflammation.[12,13] The radiotracers most frequently used to study dopaminergic transmission in addiction are ligands of the dopamine D2 receptor family (type 2, 3, and 4 dopamine receptors), which include [18F]fallypride and [11C]raclopride, although other D2 receptor tracers can also be used for this purpose. The radiotracer binds to the receptor and provides a measure of receptor "availability," measured as the binding potential relative to nonspecific binding (BPND). BPND is the ratio of receptor binding to a reference region and provides an indirect measure of receptor density in the brain.[14]

Regarding D2 receptor imaging, most radiotracers can also be used to image changes in endogenous dopamine levels in the brain. For example, [11C]raclopride binding is sensitive to variations in the levels of extracellular dopamine, likely because of a competition between dopamine and the radiotracer and receptor internalization.[15-17] A number of PET studies in addiction have used a challenge that increases dopamine levels, such as a psychostimulant (cocaine, amphetamine, or methylphenidate), to measure changes in endogenous dopamine. This allows a comparison between BPND before and after a challenge, referred to as ΔBPND with ΔBPND defined as (BPNDbaseline − BPNDchallenge)/BPNDbaseline. Measured by microdialysis in nonhuman primates, ΔBPND is linearly correlated with changes in extracellular dopamine in the striatum in response to stimulant administration,[18,19] confirming the reliability of this measure to evaluate stimulant-induced dopamine release. Therefore, PET studies using D2 receptor radiotracers provide 2 outcome measures of dopamine signaling: D2 receptor availability (BPND) and induced presynaptic dopamine release (ΔBPND).

PET Measures of Dopamine Transmission in Addiction

Taken together, most PET and SPECT imaging studies show that addiction is associated with an overall decrease in striatal dopamine signaling, measured as a decrease in D2 receptor BPND and stimulant-induced dopamine release from the presynaptic terminals (ΔBPND).[20]

The decrease in striatal D2 receptor binding in addiction is one of the most replicable findings in human imaging research, and has been reported across most types of addictions. Decrease in D2 receptor binding has been described in substance use disorders regarding cocaine,[21-26] alcohol,[27-33] methamphetamine,[34-37] opiates,[38-40] and tobacco.[41-45] However, there are notable exceptions that should be considered. Multiple studies have failed to show alterations in D2 receptor binding in chronic cannabis users (see Ref. 46), although some data suggest slight alterations.[47,48]

Recent studies have not detected decreased D2 receptor binding in the striatum using the agonist radiotracer [11C]PHNO in cocaine abusers.[49,50] However, despite its ability to bind the D2 receptor, [11C]PHNO is a D3 receptor-preferring agonist radiotracer.[51] The studies using [11C]PHNO in cocaine abusers show that binding is increased in D3 rich regions of the striatum, and not decreased in D2 rich striatal subdivisions. These findings indicate that D3 receptors binding may be increased in cocaine dependence, unlike D2 receptors.[49] However, despite these latter exceptions, most of the studies consistently show decreased D2 receptor binding in the striatum of drug abusers, which has been furthermore confirmed in animal models (later).

PET imaging studies in addiction have also shown that stimulant-induced dopamine release (ΔBPND) is blunted in addiction. When compared to healthy controls, lower values for ΔBPND have been reported in abusers of cocaine,[22,52] alcohol,[30,33] opiates,[38] methamphetamine,[37] and nicotine dependence.[53] The mechanisms behind the decrease in striatal dopamine levels in addiction are, thus far unclear. Some studies described decreased [18F]DOPA uptake or striatal vesicular monoamine transporter 2 (VMAT2) binding or both in addiction,[54,55] the latter being supported by postmortem studies.[56-58] Thus, decreased striatal dopamine could originate from impaired synthesis or reuptake of dopamine or both.

Dopamine Signaling and Striatal Subdivisions

PET imaging studies in healthy controls show that dopamine signaling in response to a stimulant challenge is not uniform within the striatum, but varies across its subdivisions. [11C]raclopride displacement in response to a stimulant is higher in the limbic and sensorimotor striatum compared with the associative striatum.[59-62] In accordance, administration of a stimulant in rodents and nonhuman primates leads to higher dopamine release in the ventral striatum compared with the dorsal striatum.[63-65] Neuroanatomical studies of the sensorimotor putamen in nonhuman primates revealed that this brain region shares histochemical features with the ventral striatum,[66,67] which may explain why dopamine signaling is