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·Review·

Brain dopaminergic system changes in drug addiction: a review of positron emission tomography findings

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Dopamine (DA) is considered crucial for the rewarding effects of drugs of abuse, but its role in addiction remains unclear. Positron emission tomography (PET) is the first technology used for *in vivo* measurement of components of the dopaminergic system in the human brain. In this article, we review the major findings from PET imaging studies on the involvement of DA in drug addiction, including presynaptic DA synthesis, vesicular monoamine transporter 2, the DA transporter, and postsynaptic DA receptors. These results have corroborated the role of DA in addiction and increased the understanding of its underlying mechanisms.

Keywords: dopamine; dopaminergic system; drug addiction; positron emission tomography

Brain Dopaminergic System

Dopamine (DA) is a catecholamine neurotransmitter in the nervous system. It has many functions in the brain, including punishment, reward, voluntary movement, mood, attention, motivation, sleep, working memory, and learning[1]. DA is synthesized by the hydroxylation and decarboxylation of L-tyrosine in DA neurons and, before being released into the synapse in response to an action potential, it is stored within presynaptic vesicles (Fig. 1). The action of DA occurs by binding to postsynaptic DA receptors, resulting in the formation of second messengers. There are five subtypes of DA receptors, which can be grouped into two classes or families: D1-like and D-2 like[1, 2]. The D1-like receptor family comprises the D1 and D5 receptors, encoded by genes with no introns, acting by way of Gs-proteins and activating adenylyl cyclase, thus increasing cAMP production[3, 4]. The D2-like receptor family comprises the D2, D3, and D4 receptors, encoded by genes containing introns. D2-like receptors act *via* Gi-proteins, inhibit adenylyl cyclase activity, and thus decrease cAMP activity[3, 5].

The action of DA in the synapse is terminated primarily by reuptake to the presynaptic membrane through the dopamine transporter (DAT)[6]. Otherwise, DA is partially removed by oxidation by monoamine oxidase orcatechol-O-methyltransferase in the synaptic cleft (Fig. 1).

The dopaminergic neurons, whose primary neurotransmitter is DA, interconnect many areas of the brain to form a system which originates in the substantia nigra (SN) pars compacta, ventral tegmental area (VTA), and hypothalamus. The dopaminergic system is typically divided into four major pathways: mesocortical (from the VTA to the frontal cortex), mesolimbic (from the VTA to the nucleus accumbens), nigrostriatal (from the SN to the striatum), and tuberoinfundibular (from the hypothalamus to the pituitary gland). The mesostriatal and mesocortical pathways are currently recognized to contribute most to drug addiction[7].

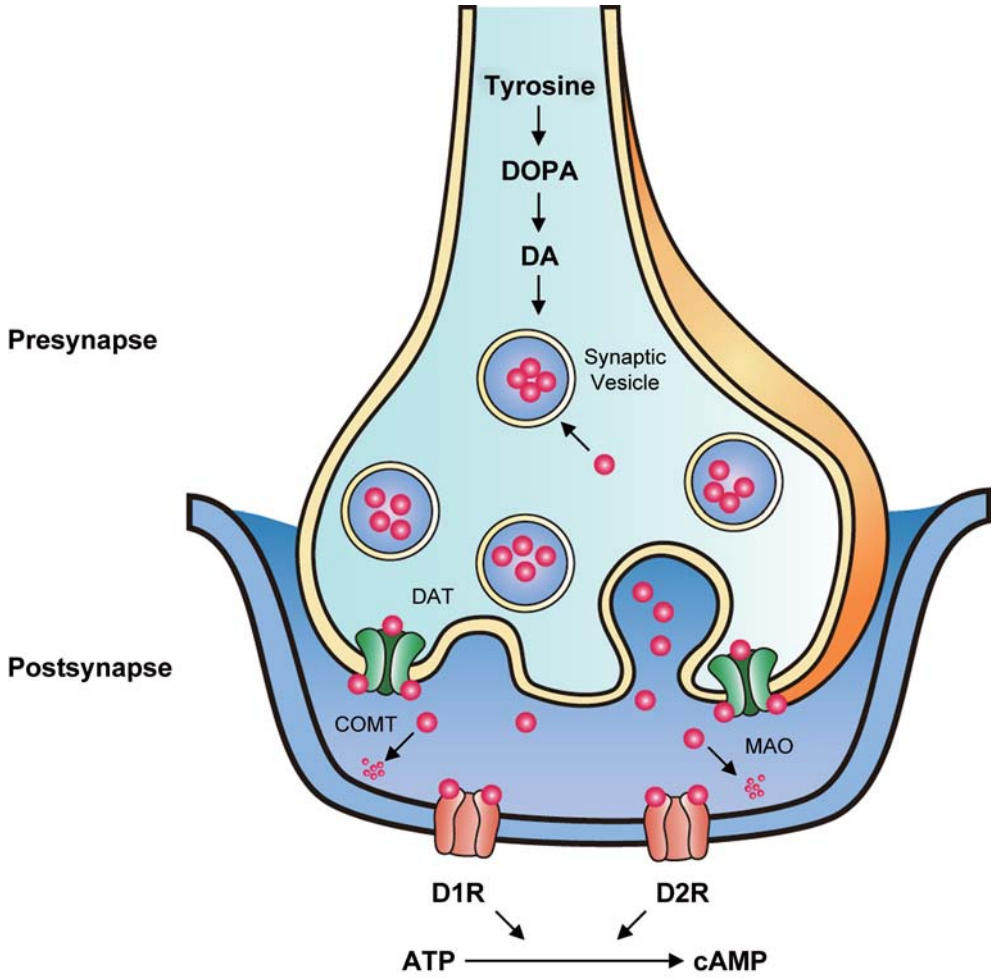

Fig. 1. Schematic representation of a dopaminergic synapse. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; COMT, catechol-O-methyltransferase; D1R, dopamine receptor 1; D2R, dopamine receptor 2; DA, dopamine; DAT, dopamine transporter; DOPA, dioxyphenylalanine; MAO, monoamine oxidase.

Drug Addiction

The term addiction is derived from the Latin verb *addicere*, which referred to the Roman court action of binding a person to another. From the 17th century, addiction has been used to refer to psychoactive substances (e.g. alcohol, tobacco, heroin) which cross the blood-brain barrier, temporarily altering the chemical milieu of the brain[8]. Currently, addiction is identified as continued involvement with a drug, despite the negative consequences associated with it — such as compulsive drug seeking and taking, loss of control over drug-taking, or emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) — when access to the drug is prevented or terminated[9]. Recently, "behavioral addiction" has also been proposed, but is beyond this review and has been described in detail elsewhere[10-18].

The neuronal basis of addiction has been guided by the premise that the motivation of an addict to take drugs results from the desire to experience the hedonic (i.e., rewarding) effects or from the desire to avoid the anhedonia and aversive consequences of withdrawal[19]. There are mounting studies suggesting that the rewarding properties of addictive drugs depend on their ability to provoke DA release in the brain[20-22].

Over the past few decades, the progressive development of functional neuroimaging technology, especially positron emission tomography (PET), has made possible

the elucidation of brain functions associated with addiction[23-25].

PET Imaging of Alterations of the Brain Dopaminergic System in Drug Addiction

PET is a technique that measures the radioactivity released by specific radioligands, and can therefore be used to generate cross-sectional brain images with anatomical or detailed functional information about changes in neurotransmitter responsiveness or receptor expression[26]. The commonly-used isotopes ^{11}C, ^{13}N, ^{15}O, and ^{18}F have short half-lives, making possible repeated studies within a short time-span. Moreover, the quantity of PET tracers injected is too low (in the nanomolar range) to cause harm.

The dopaminergic system has been identified as a key substrate for the rewarding effects of abused drugs and PET was the first technology that enabled the direct measurement of components of the DA system in the living human brain[27]. PET imaging studies have also shown that in drug-addicted individuals, DA function is markedly disrupted[25, 28]. In this article, we review PET radiotracers that are currently available for imaging the dopaminergic system in drug addiction and the main findings of *in vivo* imaging studies.

PET Studies of Presynaptic DA Synthesis

Addictive drugs exhibit a wide range of structures and actions, but the unifying principle appears to be that they each acutely enhance DA neurotransmission by means that dissociate it from normal drive by environmental cues[29, 30]. The function of DA synthesis in the presynaptic neuron can be currently measured in preclinical animal studies and in human subjects. Thus, if DA synthesis by the presynaptic DA neurons in drug-addicted individuals were impaired, this would be expected to translate into a blunted DA response.

L-dopa (*L*-dihydroxyphenylalanine) is the immediate precursor of DA. Although DA in the circulation does not cross the blood-brain barrier, *L*-dopa is carried into the brain by the large neutral amino-acid transport system, is then converted into DA by *L*-aromatic amino-acid decarboxylase, and is stored in intraneuronal vesicles from which DA is released when the neuron fires[31]. ^{18}F- or ^{11}C-labeled *L*-dopa is an analog of *L*-dopa, and this positron-emitting compound is used clinically to trace the dopaminergic pathway and to evaluate presynaptic function. Uptake of *L*-dopa labeled with a positron-emitting radionuclide reflects the synthesis rate of DA in the terminals, under the conditions of PET[32, 33]. Studies with PET and radionuclide-labeled *L*-dopa and their main findings are summarized in Table 1.

In cocaine addiction, PET imaging with [^{18}F] dopa (6-[^{18}F] fluoro-*L*-dopa) shows a delayed decrease in DA terminal activity in the striatum of detoxified cocaine abusers compared with controls[34, 35]. Also, a decrease in presynaptic DA activity during cocaine abstinence or withdrawal is associated with relapse[36, 37].

Methamphetamine (MA), another prevalent psychostimulant drug of abuse, induces more deleterious changes in the brain than cocaine when a toxic dose is used[35]. This is evident from the significant reductions in striatal [^{18}F] dopa uptake in MA-treated mice, suggesting the neurodegeneration of dopaminergic cells and DA synthesis in MA abuse[35].

In alcohol addiction, although there is no difference in the net influx of striatal [^{18}F] dopa (an index of DA synthesis) between detoxified alcoholic patients and control subjects[33], findings from several studies have shown that low DA synthesis correlates with alcohol craving, negative mood states, and a high risk of relapse[33, 38]. Further, among late-onset (type 1) alcoholics, [^{18}F] dopa uptake is elevated in the putamen and caudate, which is correlated with poor performance on the Wisconsin Card Sorting Test. This study suggests that the magnitude of the change in presynaptic DA function correlates with the patients' degree of inability to modify their behavior[39].

In smokers, significantly higher [^{18}F] dopa uptake occurs in the putamen and caudate than in non-smokers, which suggests that smoking is related to greater DA activity in the human basal ganglia, and nicotine-induced DA activity may be a mechanism relevant to dependence on cigarette smoking[40].

Ecstasy (+/-3,4-methylenedioxymethamphetamine, MDMA) is a popular recreational drug with known neurotoxicity. Its potential long-term effects on dopaminergic function have been verified recently by an *in vivo* PET study in human subjects. In the study by Tai *et al.*[41] [^{18}F] dopa uptake in the putamen was 9% higher in ex-users of ecstasy than in controls, even after >3 years of abstinence.

Table 1. PET imaging of presynaptic DA synthesis in drug addiction

Ref.	Radioligand	Drug	Subjects	Controls	Main findings
[34]	[^{18}F] dopa	Cocaine	11 cocaine addicts	8 normal participants	(↓) [^{18}F] dopa uptake negatively correlated with days off cocaine
[35]	[^{18}F] dopa	Cocaine	10 male mice treated with cocaine (30 mg/kg) for 7 days	10 male mice treated with saline for 7 days	(↓)
[35]	[^{18}F] dopa	MA	10 male mice treated with MA (30 mg/kg) for 7 days	10 male mice treated with saline for 7 days	(↓)
[33]	[^{18}F] dopa	Alcohol	12 detoxified male alcoholics	13 age-matched healthy men	(-) [^{18}F] dopa uptake positively correlated with alcohol craving
[38]	[^{18}F] dopa	Alcohol	11 detoxified male alcoholics	13 normal controls	(-)
[39]	[^{18}F] dopa	Alcohol	10 type 1 alcoholics	8 normal controls	(↑) [^{18}F] dopa uptake in putamen and caudate negatively correlated with Wisconsin Card Sorting Test performance among alcoholics
[40]	[^{18}F] dopa	Nicotine	9 smoking men	10 normal controls	(↑)
[41]	[^{18}F] dopa	MDMA	14 ex-MDMA users (abstinent >3 years)	12 normal controls	(↑)

(↓) striatal radioligand uptake decreased, (↑) increased, or (-) did not significantly differ from healthy controls; MA, methamphetamine; MDMA, ecstasy (+/-3,4-methylenedioxymethamphetamine).

PET Studies of Vesicular Monoamine Transporter 2

Vesicular monoamine transporter 2 (VMAT2) is a protein responsible for transporting monoamine neurotransmitters from the cytoplasm into synaptic vesicles[42], so it plays an important role in regulating the presynaptic DA concentration. The most-used ligand in VMAT2-binding studies *in vivo* is ^{11}C-labeled dihydrotetrabenazine (DTBZ). Binding of [^{11}C] DTBZ to VMAT2 is commonly considered to be a stable marker of DA neuronal integrity and an *in vivo* marker of DA nerve terminals[43]. PET imaging studies of VMAT2 in drug addiction and the main findings are summarized in Table 2.

Postmortem studies comparing the VMAT2 density in cocaine abusers with healthy subjects using radiolabeled DTBZ found significantly reduced [^{3}H] DTBZ binding in the striatum of cocaine abusers[44]. A recent *in vivo* PET study with [^{11}C] DTBZ confirmed the previous *in vitro* findings, suggesting compensatory down-regulation of the DA storage vesicles in response to chronic cocaine abuse and/or a loss of dopaminergic terminals[45].

Animal studies and preclinical investigations have established that drugs of abuse produce long-term changes in DA neuronal integrity. In a PET imaging investigation of “heavy” MA users, the striatal [^{11}C] DTBZ binding was decreased by 10%, even after at least 3 months of abstinence, reflecting the long-lasting effect of MA on VMAT2[46]. And in the study of Boileau *et al.*[43], who used human subjects to measure striatal [^{11}C] DTBZ binding after an acute oral dose of amphetamine (AMPH), a slight decrease of [^{11}C] DTBZ binding was also found.

However, in a subsequent study, the striatal [^{11}C] DTBZ binding in early-abstinence MA abusers (mean, 19 days; range, 1–90 days) was increased[47]. One potential explanation for this increase is that [^{11}C] DTBZ binding not only reflects DA synaptic integrity, but also indicates changes in the endogenous vesicular DA storage levels with unchanged VMAT2 protein expression[47]. This hypothesis was verified by Kilbourn *et al.*[48], who conducted a systematic study in rats, in which *in vivo* PET analysis of [^{11}C] DTBZ binding was examined as a function of DA

Table 2. PET imaging of vesicular monoamine transporter 2 in drug addiction

Ref.	Radioligand	Drug	Subjects	Controls	Main findings
[43]	[^{11}C] DTBZ	AMPH	9 non-drug-using subjects with low-dose AMPH (0.4 mg/kg)	Same subjects before drug use	(↓)
[46]	[^{11}C] DTBZ	MA	16 MA users	18 normal controls	(↓)
[47]	[^{11}C] DTBZ	MA	16 recently withdrawn MA users (mean 19 days)	14 normal controls	(↑)

(↓) striatal radioligand uptake decreased or (↑) increased compared with healthy controls; MA, methamphetamine; AMPH, amphetamine.

depletion with alpha-methyl-para-tyrosine (AMPT) and repletion with *L*-dopa. Repeated treatment with AMPT at doses that markedly depleted (-75%) brain DA levels resulted in increased (+36%) *in vivo* [^{11}C] DTBZ binding to VMAT2 in the striatum. This increase in binding was completely reversed by treatment with *L*-dopa to restore the DA levels. But there were no changes in the total number of VMAT2 binding sites, as measured by *in vitro* autoradiography. Further, Boileau *et al*. attributed their findings of a slight decrease in [^{11}C] DTBZ binding caused by AMPH not to changes in presynaptic VMAT2 but an insufficient drug dose to significantly deplete striatal DA[43]. Therefore, more systematic preclinical studies are required to optimally guide the extraction of clinically useful information from [^{11}C] DTBZ PET imaging of the human brain[49].

PET Studies of the Dopamine Transporter

The DAT is a membrane-spanning protein that pumps DA from the extracellular space into the presynaptic neuronal cytosol, from which other transporters sequester DA into vesicles for storage and later release (Fig. 1). DA reuptake *via* the DAT is the primary mechanism by which DA is cleared from synapses and DATs have been used as markers of presynaptic DA terminals[50]. The DAT is also a target for addictive drugs such as cocaine and AMPH. Currently, there are several positron-emitting radionuclide-labeled tracers for PET imaging of the DAT *in vivo*, such as [^{11}C] cocaine, [^{11}C] β-CIT, [^{18}F] FCT, WIN 35,428, and [^{11}C] d-threo-MP. And the neuroimaging studies have demonstrated that chronic use of addictive drugs has long-term impact on DAT levels and activity, resulting in dopaminergic dysfunction by mechanisms not well understood[51] (Table 3).

Cocaine was initially labeled with ^{11}C to track the distribution and pharmacokinetics of this powerful stimulant and drug of abuse in the human brain and body. It was soon discovered that [^{11}C] cocaine is also a sensitive radiotracer for DAT availability[52]. Because the major molecular target of cocaine is the DAT, the question of whether chronic cocaine use alters the DAT has been investigated[53]. Although postmortem studies have shown decreased DAT in cocaine addicts[54], one PET study using [^{11}C] cocaine reported no significant differences in DAT binding between cocaine-dependent individuals who had withdrawn for >5 days and controls[53].

Besides cocaine *per se*, some of its congeners have also been labeled with positron-releasing radionuclides to study the function of the DAT in drug addiction *in vivo*. 2β-carboxymethoxy-3β-(4-iodophenyl) tropane (β-CIT), one of these congeners, has been labeled with ^{11}C for PET studies. In an autoradiographic study on human brain sections and a PET study of monkeys and humans, [^{11}C] β-CIT was found to accumulate markedly in the striatum where DATs are mostly located[55]. In an *in vivo* PET study with [^{11}C] β-CIT, decreased DAT has been found in the putamen in early Parkinson's disease[56], but so far it has not been used in the study of drug abuse.

In 2000, [^{18}F]-(1)-N-(4-fluorobenzyl)-2b-propanoyl-3b-(4-chlorophenyl) tropane ([^{18}F] FCT), a structural congener of cocaine, was found to have a high affinity for the DAT and a relatively low affinity for the serotonin transporter, indicating that it is a suitable tracer for studying the DAT *in vivo* with PET[57]. In the PET study with [^{18}F] FCT in the cocaine self-administration model with monkeys, the laterality of DAT function was changed even before enough cocaine was consumed to produce significant overall changes in receptor and transporter availability[58].

Table 3. PET imaging of the dopamine transporter in drug addiction

Ref.	Radioligand	Drug	Subjects	Controls	Main findings
[53]	[^{11}C] cocaine	Cocaine	12 detoxified cocaine abusers (>5 days)	20 normal controls	(-)
[58]	[^{18}F] FCT	Cocaine	12 adult male cocaine-naive rhesus macaques with drug self-administration (9 weeks)	same monkeys before drug use	(-)
[62]	[^{11}C] WIN 35,428	Heroin	11 heroin users abstinent for 6 months, and 10 on methadone maintenance for 6 months	10 normal controls	(↓) ; (↓) (comparison to the abstinent subjects); [^{11}C] WIN 35,428 uptake correlated with subjective anxiety in methadone maintenance subjects
[63]	[^{11}C] WIN 35,428	MA	6 abstinent MA users	10 normal controls	(↓)
[64]	[^{11}C] WIN 35,428	MA	baboons treated with one of three doses of MA [0.5 mg/kg (n = 2), 1 mg/kg (n = 2) and 2 mg/kg (n = 3)]	3 baboons treated with saline	(↓) [^{11}C] WIN 35,428 uptake correlated with MA dose
[65]	[^{11}C] WIN 35,428	MA	11 male MA users	9 normal controls	(↓) [^{11}C] WIN 35,428 uptake associated with duration of MA use and closely related to severity of persistent psychiatric symptoms
[69]	[^{11}C] d-threo-MP	Alcohol	5 alcoholics	16 normal controls	(-)

(↓) striatal radioligand uptake decreased or (-) did not differ significantly from healthy controls; MA, methamphetamine.

Other cocaine analogs, WIN 35,428 and CFT [2β-carbomethoxy-3 beta-(4-fluorophenyl) tropane], have been extensively characterized as selective inhibitors of DA uptake with high affinity for the DAT[59]. Human studies have shown that the extent of [^{11}C] WIN 35,428 binding can be used to differentiate normal people from those with DA system disorders[60, 61]. A PET imaging study with [^{11}C] WIN 35,428 demonstrated that heroin users have a significantly lower DAT uptake than healthy controls[62]. [^{11}C] WIN 35,428 has also revealed a reduction of the DAT in MA abusers and in baboons after MA injection[63-66].

Methylphenidate (MP, Ritalin), a psychostimulant, is commonly used to treat attention deficit hyperactivity disorder and narcolepsy. The psychostimulant properties of MP are linked to its binding to a site on the DAT, resulting in inhibition of DA reuptake and enhanced levels of synaptic DA. The more active d-enantiomer (d-threo-MP) has been labeled with [^{11}C] and animal studies have demonstrated the saturable, reversible, and specific binding of [^{11}C] d-threo-MP to the DAT, suggesting that it is a useful PET tracer for imaging presynaptic dopaminergic neurons[67]. A PET imaging study using pretreatment with MP showed a marked decrease of [^{11}C] d-threo-MP binding in the human brain[68]. However, PET imaging did not find a significant difference of [^{11}C] d-threo-MP distribution between alcoholics and non-alcoholics, which means that prolonged alcohol abuse might have no significant impact on DAT availability[69].

PET Studies of Postsynaptic DA Receptors

The radiolabeled ligands for PET imaging of DA receptors in drug addiction and the main findings are listed in Table 4.

Spiroperidol (spiperone) is a potent D2 receptor antagonist[70]. In 1984, *in vivo* studies in rats and primates showed that ^{18}F-labeled spiroperidol has high specific activity for D2 receptors[71]. Latterly, N-methylspiroperidol (NMSP), the amide N-methyl analog, has also been radiolabeled with ^{18}F. *In vivo* PET imaging in the baboon brain showed that striatal uptake and retention is five-fold higher for [^{18}F] NMSP than for [^{18}F] spiroperidol, which suggested that [^{18}F] NMSP is an ideal choice for studies of the D2 receptor in humans[72]. In PET studies with [^{18}F] NMSP, cocaine abusers show significantly lower D2 receptor availability than normal controls, especially during early detoxification[53, 73], and this may be present even 3–4 months after detoxification[74]. D2 receptor availability was also found to be associated with decreased metabolism in several regions of the frontal lobe, most markedly the orbito-frontal cortex and cingulate gyri[73]. *In vivo* PET imaging in baboons showed that AMPH pretreatment induces decreases in [^{18}F] NMSP in the corpus striatum, suggesting that PET imaging with [^{18}F] NMSP can also be used to monitor drug-induced elevations in endogenous DA levels[75].

Raclopride is a synthetic compound that acts as an antagonist on D2 receptors and ^{11}C-labeled raclopride is the most commonly-used tracer in the PET imaging of addiction to cocaine[76], alcohol[69, 77, 78], MA[79], and heroin[80]. In cocaine abusers with intravenous administration of 48 mg cocaine (a typical “street” dose), [^{11}C] raclopride occupancy at D2 receptors was decreased significantly, suggesting that higher DA concentrations compete at the receptor site[76]. Alcoholics showed lower D2 receptor levels in the caudate and putamen during early detoxification and in the caudate during late detoxification, which is in line with the idea that D2 mechanisms are involved in alcohol dependence[69, 77, 78]. Heroin-dependent individuals[80] and MA abusers[79] both showed significantly lower D2 receptor availability than comparison subjects.

[^{18}F]FCP ([^{18}F] 4-fluoroclebopride) is a fluorine-18 labeled benzamide derivative that binds reversibly to D2 receptors[81]. In PET imaging with [^{18}F] FCP, Nader and colleagues[82] found that the baseline D2 receptor availability is negatively correlated with the rate of cocaine self-administration.

[^{18}F] fallypride, an analog of epidepride, is a selective and high-affinity antagonist of D2/D3 receptors. In an [^{18}F] fallypride PET imaging study, nicotine-dependent smokers displayed significantly less availability of D2/D3 receptors within the bilateral putamen, functionally covering parts of the dorsal striatum, compared to never-smoking subjects[83]. [^{18}F] desmethoxyfallypride ([^{18}F] DMFP), another selective D2/D3 receptor antagonist, has also been developed and used to find that a low availability of D2/3 receptors in the ventral striatum and adjacent putamen is associated with a high level of craving for alcohol [33].

For the D1 receptor, [^{11}C] NNC 112, a new benzazepine [(+)-8-chloro-5-(7-benzofuranyl)-7-hydroxy-3-methyl-2,3,4,5-tetra-hydro-lH-3-benzazepine], has been reported to be a useful PET radioligand for the quantitation of D1 receptors in humans[84], and its D1 receptor selectivity has recently been re-evaluated[85]. With PET and the radiotracer [^{11}C] NNC 112, Martinez *et al.*[86] found no difference between cocaine abusers and normal controls. However, within the cocaine abusers, low D1 receptor availability in the ventral striatum was associated with the choice to self-administer cocaine, suggesting that low D1 receptor availability may be associated with an increased risk of relapse. Another radioligand, [^{11}C] SCH23390 [(R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl -2,3,4,5-tetrahydro-1H-3-benzazepine], the first selective D1-like receptor antagonist, is recognized as the standard ligand for PET studies of striatal D1 receptors[87]. A significant reduction in [^{11}C] SCH23390 binding potential has been found in the striatum of smokers compared to nonsmokers, most prominently in the ventral striatum, suggesting a reduction in D1 receptor density in the ventral striatum of cigarette smokers[88, 89].

Conclusions

PET imaging studies have corroborated the role of DA in drug addiction. The increases in DA caused by addictive drugs and the subsequent fast and marked activation of postsynaptic DA receptors are relevant for drug reinforcement. The adaptive changes in the dopaminergic system after long-term drug abuse may lead to the

Table 4. PET imaging of postsynaptic DA receptors in drug addiction

Ref.	target	Radioligand	Drug	Subjects	Controls	Main findings
[73]	D2	[^{18}F] NMSP	Cocaine	10 cocaine abusers	10 normal controls	(↓) (detoxified for 1 week); (-) (detoxified for 1 month)
[74]	D2	[^{18}F] NMSP	Cocaine	20 male cocaine abusers	20 normal male controls	(↓)
[75]	D2	[^{18}F] NMSP	AMPH	3 adult female baboons treated with AMPH (1.0 mg/kg)	before drug use	(↓)
[76]	D2	[^{11}C] raclopride	Cocaine	11 male cocaine abusers with intravenous administration of 48 mg cocaine	before drug use	(↓)
[53]	D2	[^{18}F] NMSP	Cocaine	10 cocaine abusers	9 normal controls	(↓)
[69]	D2	[^{11}C] raclopride	Alcohol	10 alcoholics	10 normal controls	(↓)
[77]	D2	[^{11}C] raclopride	Alcohol	9 male alcoholics abstinent for 1-68 weeks	8 normal male controls	(↓)
[78]	D2	[^{11}C] raclopride	Alcohol	14 type 2 alcoholics tested within 6 weeks of detoxification and re-tested 1-4 months later while alcohol-free	11 normal controls	(↓); (-) (between early and late detoxification)
[79]	D2	[^{11}C] raclopride	MA	15 MA abusers	20 normal controls	(↓) [^{11}C] raclopride uptake positively correlated with rate in orbitofrontal cortex in abusers
[80]	D2	[^{11}C] raclopride	Heroin	11 opiate-dependent individuals	11 normal controls	(↓)
[81]	D2	[^{18}F] FCP	Cocaine	12 rhesus macaques with cocaine self-administration	Self control	(↓) (by 15-20% within 1 week initiating self-administration); of (↓) (by 20% during 1 year of drug exposure)
[83]	D2/D3	[^{18}F] fallypride	Nicotine	17 heavy smokers	21 age-matched normal controls	(-); [^{18}F] fallypride uptake positively correlated with nicotine craving in the ventral striatum but negatively correlated in the anterior cingulate and inferior temporal cortex
[33]	D2/D3	[^{18}F] DMFP	Alcohol	12 alcoholics	12 normal controls	(↓) (negatively correlated with alcohol craving)
[86]	D1	[^{11}C] NNC 112	Cocaine	25 cocaine abusers	23 normal controls	(-) [^{11}C] NNC 112 uptake in ventral striatum negatively correlated with cocaine relapse
[88]	D1	[^{11}C] SCH23390	Nicotine	11 smokers	18 normal controls	(↓)
[89]	D1	[^{11}C] SCH23390	Nicotine	12 smokers	12 normal controls	(↓) trend of increase of [^{11}C] SCH23390 uptake after smoking abstinence

(↓) striatal radioligand uptake decreased and (-) not significantly different from healthy controls; MA, methamphetamine; AMPH, amphetamine.

persistent use of drugs and cause relapse. Neuroimaging studies have provided evidence of how the human brain changes as the individual becomes addicted. With the appropriate radiotracers, PET enables visualization of the presynaptic and postsynaptic sites in the dopaminergic system. Imaging these markers provides key insights into the pathophysiology of drug addiction, and understanding of the involvement of DA in drug abuse may also offer directions for the development of new strategies for pharmacological interventions for addiction. The therapeutic interventions that are driven by the imaging findings on DA can be divided into those that interfere with the acute effects of a drug and those that compensate for the chronic effects of long-term use linked to its dopaminergic effects[90].

In the future, the role of PET may become more important in drug-addiction diagnosis and guiding therapy. Enhancements in image resolution and specific molecular tags will permit accurate diagnoses, based on both structural and molecular changes in the brain. For widespread application, advances in molecular imaging should include the characterization of new radiotracers, application of modeling techniques, standardization and automation of image-processing techniques, and appropriate clinical settings in large multicenter trials. The growing field of neuroimaging is helping nuclear medicine physicians to incorporate pathways into personalized patient care.

However, the use of PET to study the role of the dopaminergic system in drug addiction is still in its infancy. Although available PET studies have mainly focused on DA, its interactions with other neurotransmitters such as GABA, glutamate, and serotonin also play important roles in modulating the magnitude of DA responses to drugs. Currently, several imaging modalities complement each other, and image fusion has become common in diagnostics and treatment[91]. In recent years, the multimodality imaging technologies such as PET/CT and PET/MRI have shown promising results, indicating great potential for clinical and preclinical uses[92]. There is no doubt that future PET research on drug addiction will benefit greatly from multimodal imaging approaches. Furthermore, the development of new PET tracers that are sensitive to the targets of DA and other neurotransmitter systems, along with the findings of multimodal imaging studies that are integrated into genetic and neurobiological research, will increase our understanding of the mechanisms underlying drug addiction.

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