



Dopamine: Functions, Signaling, and Association with Neurological Diseases

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Received: 21 August 2018 / Accepted: 2 November 2018 / Published online: 16 November 2018
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Abstract

The dopaminergic system plays important roles in neuromodulation, such as motor control, motivation, reward, cognitive function, maternal, and reproductive behaviors. Dopamine is a neurotransmitter, synthesized in both central nervous system and the periphery, that exerts its actions upon binding to G protein-coupled receptors. Dopamine receptors are widely expressed in the body and function in both the peripheral and the central nervous systems. Dopaminergic signaling pathways are crucial to the maintenance of physiological processes and an unbalanced activity may lead to dysfunctions that are related to neurodegenerative diseases. Unveiling the neurobiology and the molecular mechanisms that underlie these illnesses may contribute to the development of new therapies that could promote a better quality of life for patients worldwide. In this review, we summarize the aspects of dopamine as a catecholaminergic neurotransmitter and discuss dopamine signaling pathways elicited through dopamine receptor activation in normal brain function. Furthermore, we describe the potential involvement of these signaling pathways in evoking the onset and progression of some diseases in the nervous system, such as Parkinson's, Schizophrenia, Huntington's, Attention Deficit and Hyperactivity Disorder, and Addiction. A brief description of new dopaminergic drugs recently approved and under development treatments for these ailments is also provided.

Keywords Dopamine pathway · Neurotransmitter · Central nervous system · Neurodegenerative diseases

Abbreviations

AD	Alzheimer's disease
ADHD	Attention deficit/hyperactivity disorder
ALDH	Aldehyde dehydrogenase
BDNF	Brain-derived neurotrophic factor
CaMKII	Calcium/calmodulin-dependent kinase II
cAMP	Cyclic 3,5 adenine-monophosphate

CDK5	Cyclin-dependent kinase 5
CK1	Casein kinase 1
CK2	Casein kinase 2
COMT	Catechol- <i>O</i> -methyl transferase
CREB	cAMP Response element-binding protein
CSF	Cerebral spinal fluid
DAG	Diacylglycerol
DARPP-32	cAMP-Regulated phosphoprotein 32-kDa
DAT	Dopamine transporter
DJ-1	PARK7 (Parkinson disease protein 7)
DOPAC	3,4-Dihydroxyphenylacetic acid
DOPAL	3,4-Dihydroxyphenylaldehyde
ELKs	Glutamine, leucine, lysine, and serine-rich protein
ERK	Extracellular-signal regulated kinases
FDA	US Food and Drug Administration
GABA	γ -Amino butyric acid
GIRK	G protein inwardly rectifying potassium channel
GPCR	G protein-coupled receptor
GRK	G protein-coupled receptor kinase
GSK3	Glycogen synthase kinase 3

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GSTM2	Glutathione transferase
GTP	Guanosine triphosphate
HVA	Homovanillic acid
HD	Huntington's disease
HTT	Huntingtin gene
IGF	Insulin growth factor
IP3	Inositol trisphosphate
JNK	c-Jun kinase
L-DOPA	Levodopa
LB	Lewy bodies
LRRK2	Leucine-rich repeat kinase 2
MAPK	Mitogen-activated protein kinase
MAPT	Microtubule-associated protein
MAT	Monoamine transporter
MAO	Monoamine oxidase
mTORC2	mTOR complex 2
NAC	Nucleus accumbens
NET	Norepinephrine transporter
NMDA	Glutamate <i>N</i> -methyl-D-aspartate
Parkin	PRKN
PD	Parkinson's disease
PDPK1	Phosphatidylinositol-dependent kinase 1
PIP2	Phosphatidylinositol-2-phosphate
PIP3	Phosphatidylinositol-3-phosphate
PKA	Protein kinase A
PKC	Protein kinase C
PLC	Phospholipase C
PP1	Protein phosphatase 1
PP2A	Protein phosphatase 2A
PP2B	Protein phosphatase 2B
RGS	Regulators of G protein signaling
RIM	Rab3a-interacting molecule
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
SNCA	α -Synuclein
STEP	Striatal-enriched tyrosine phosphatase
SZ	Schizophrenia
TAAR	Trace amine-associated receptors
VMAT2	Vesicular monoamine transporter
MTA	Ventral tegmental area

Background

Initially, studies on neural cell communication focused exclusively on electrophysiological aspects but, in the beginning of twentieth century, scientists such as John N. Langley and Thomas R. Elliot introduced the concept of chemical release upon nerve stimulation (Elliott 1905; Sourkes 2009; Starke 2014). These ideas were confirmed later by the work of Otto Loewi, Henry Dale, Ulf von Euler, and others, who demonstrated that acetylcholine and adrenaline acted as chemical transmitters in the parasympathetic

and sympathetic nervous systems (Loewi 1921; Dale 1935, 1937; von Euler 1946). Subsequently, the physiological roles of another chemical transmitter, dopamine, were described by Carlsson et al. (1957). Chemical transmitters such as acetylcholine and dopamine belong to a class of molecules termed neurotransmitters that are the primary mode of cell-to-cell communication in the nervous system and associated with many diseases.

Typically, neurotransmitters are synthesized endogenously and act as signaling molecules (Wurtman et al. 1980). Neurotransmitters are stored in vesicles in presynaptic terminals and released into the synaptic cleft in response to an action potential or after a graded potential threshold is met (Kanner and Schuldiner 1987; Attwell et al. 1993; Steinhardt et al. 1994). Once released, they can elicit a physiological response in postsynaptic or nearby cells. In general, neurotransmission occurs quickly and the compound is rapidly (i) metabolized by enzymes (Kanner and Schuldiner 1987), (ii) taken back up by presynaptic neuron (Iversen 1971), or (iii) bound to postsynaptic neurons or target cells' receptors (Garris et al. 1994).

Many compounds are released by cells, but *bona fide* neurotransmitters must meet a distinct set of criteria (Sourkes 2009): (i) the compound should be synthesized in presynaptic neurons; (ii) when the presynaptic neuron is activated, the release of this compound should lead to an effect on postsynaptic neuron(s) or target cell(s); (iii) when administered exogenously, similar outcomes to endogenous stimulation would occur; and (iv) a mechanism of neurotransmitter removal, from synaptic cleft after signaling, should be in place.

Neurotransmitters can be subdivided according to their molecular identity: small organic molecules, peptides, monoamines, nucleotides, and amino acids (Kandel et al. 2013). A functional classification may also be utilized, since these molecules can act as excitatory or inhibitory transmitters and can also bind to fast response ionotropic receptors or slower response metabotropic receptors (Kandel et al. 2013). For instance, glutamate-containing synapses are mainly fast excitatory and frequently observed in memory storage elements (Dingledine et al. 1999). In contrast, γ -aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system (CNS) and binds to ionotropic (GABA_A) and metabotropic (GABA_B) receptors (Werhahn et al. 1999). Acetylcholine is the neurotransmitter that signals from neuron to muscle at the neuromuscular junction, and is also present in many brain regions where it binds to muscarinic (metabotropic) or nicotinic (ionotropic) receptors (Fambrough et al. 1973; Whitehouse et al. 1986; Jones et al. 2012). Recently, a number of reports have indicated that neuron terminals can co-release different neurotransmitters which may present synergistic functions (Bartfai et al. 1988; Hnasko and Edwards 2012).

The monoamine transmitters share many biochemical characteristics, i.e., they are small charged molecules, normally cannot cross the blood–brain barrier (Kortekaas et al. 2005), synthesized from amino acids by short metabolic routes and regulated by one rate-limiting enzymatic reaction (Stahl 1985). In general, monoamine neurotransmitters exert their actions on neuronal circuitry by binding to metabotropic receptors, and have a slower modulation compared to the fast neurotransmission mediated by glutamate and GABA (Beaulieu and Gainetdinov 2011), with the exception of serotonin which can also bind to ionotropic receptors (MacDermott et al. 1999; Lee et al. 2010).

One group of monoamines, the catecholamines, are derived from the amino acid tyrosine and include the three essential neurotransmitters: norepinephrine, epinephrine, and dopamine (Fernstrom and Fernstrom 2007). Norepinephrine typically regulates sleep patterns, focus, and alertness (Spector et al. 1965; Mitchell and Weinshenker 2010), while epinephrine controls the adrenal glands, sleep, alertness, and the fight-or-flight response (Aston-Jones 2005; Chrousos 2009). As a major monoamine neurotransmitter, dopamine has essential roles regulating motor neurons (Harrington et al. 1996), spatial memory function (Luciana et al. 1998), motivation (Salamone and Correa 2012), arousal (Andreatic et al. 2005; Zion et al. 2006), reward and pleasure (Schultz 1998; Berridge and Kringelbach 2008), as well as in lactation (Demarest et al. 1984), sexual behavior (Krüger et al. 2005), and nausea (Nakagawa et al. 2008).

Dopamine-producing neurons were first mapped by Annica Dahlström and Kjell Fuxe in 1964 (Dahlström and Fuxe 1964; Andén et al. 1966). In humans, projections of dopaminergic neurons extending from the *substantia nigra pars compacta* to the dorsal *striatum*, known as the nigrostriatal pathway, control movement and motor skill learning (Hikosaka et al. 2002). The loss of these dopaminergic neurons is most often associated with the symptoms of Parkinson's disease.

In the present review, we focus on the roles of dopamine signaling in normal physiological processes (homeostasis) and related pathologies, and further demonstrate the clinical relevance of this molecular network to the diagnostics and therapeutics of a range of human maladies.

Dopamine

Synthesis and Metabolism

The majority of dopamine synthesis occurs directly from tyrosine but, since L-phenylalanine can be converted to tyrosine by phenylalanine hydroxylase, dopamine can also be indirectly synthesized from phenylalanine (Nagatsu et al. 1964; Fernstrom and Fernstrom 2007). Regardless,

the primary metabolic route involves a two-step synthesis in the cytosol. Tyrosine hydroxylase (the rate-limiting enzyme) converts tyrosine to levodopa (L-DOPA) using tetrahydrobiopterin, oxygen (O₂), and iron (Fe²⁺) as cofactors. L-DOPA can then be converted to dopamine by aromatic L-amino acid decarboxylase (DOPA decarboxylase), having pyridoxal phosphate as a cofactor (Christenson et al. 1970). A minor synthesis pathway may also occur, in which p-tyramine can be converted to dopamine through Cytochrome P450 2D6 activity in the *substantia nigra* (Bromek et al. 2011; Ferguson and Tyndale 2011). Following synthesis in dopaminergic neurons, dopamine is sequestered into the acidic lumen of synaptic vesicles via the vesicular monoamine transporter 2 (VMAT2) (Fig. 1a) (Eiden and Weihe 2011). In noradrenergic and adrenergic cells, dopamine can be further converted into norepinephrine and epinephrine by sequential modifications from dopamine β-hydroxylase and phenylethanolamine N-methyltransferase in the presence of O₂, L-ascorbic acid, and S-adenosyl-L-methionine (Udenfriend and Wyngaarden 1956; Weinshilboum et al. 1971).

The acidic environment of the synaptic vesicle lumen stabilizes dopamine and prevents oxidation (Guillot and Miller 2009). In a non-acidic microenvironment, dopamine is sensitive to oxidation or further metabolism by monoamine oxidase B (MAO-B) into 3,4-Dihydroxyphenylacetaldehyde (DOPAL) which is preferentially converted into 3, 4-dihydroxyphenylacetic acid (DOPAC) by the enzyme aldehyde dehydrogenase (ALDH). Catechol-O-Methyltransferase (COMT) can further degrade DOPAC into homovanillic acid (HVA), and can also directly convert dopamine into 3-methoxytyramine (Eisenhofer et al. 2004; Chen et al. 2011). Dopamine and its end products can be quantified in blood and cerebral spinal fluid, although it is difficult to determine their origin because they are produced by CNS and certain peripheral organs, such as kidney and gut (Jose et al. 2002; Anlauf et al. 2003). In pathologies such as Alzheimer's and Parkinson's diseases, the amounts of HVA and 3-methoxytyramine are correlated with disease progression. Hence, these components may be useful biomarkers (Morimoto et al. 2017; Stefani et al. 2017), since they can contribute to the specificity of the diagnosis (Reitz and Mayeux 2014).

Dopamine is sensitive to spontaneous, metal-catalyzed, and enzyme-catalyzed oxidation into electron-deficient quinones if it is not sequestered into vesicles or metabolized by MAO-B or COMT (Damier et al. 1996; Chen et al. 2011; Segura-Aguilar et al. 2014). Dopamine quinones are short-lived toxic species that readily form covalent bonds with cellular macromolecules (Stokes et al. 1999). The dopamine quinone can also undergo intramolecular cyclization to aminochrome which polymerizes and forms neuromelanin, the dark pigment contained in the dopaminergic neurons found in the *substantia nigra pars compacta*

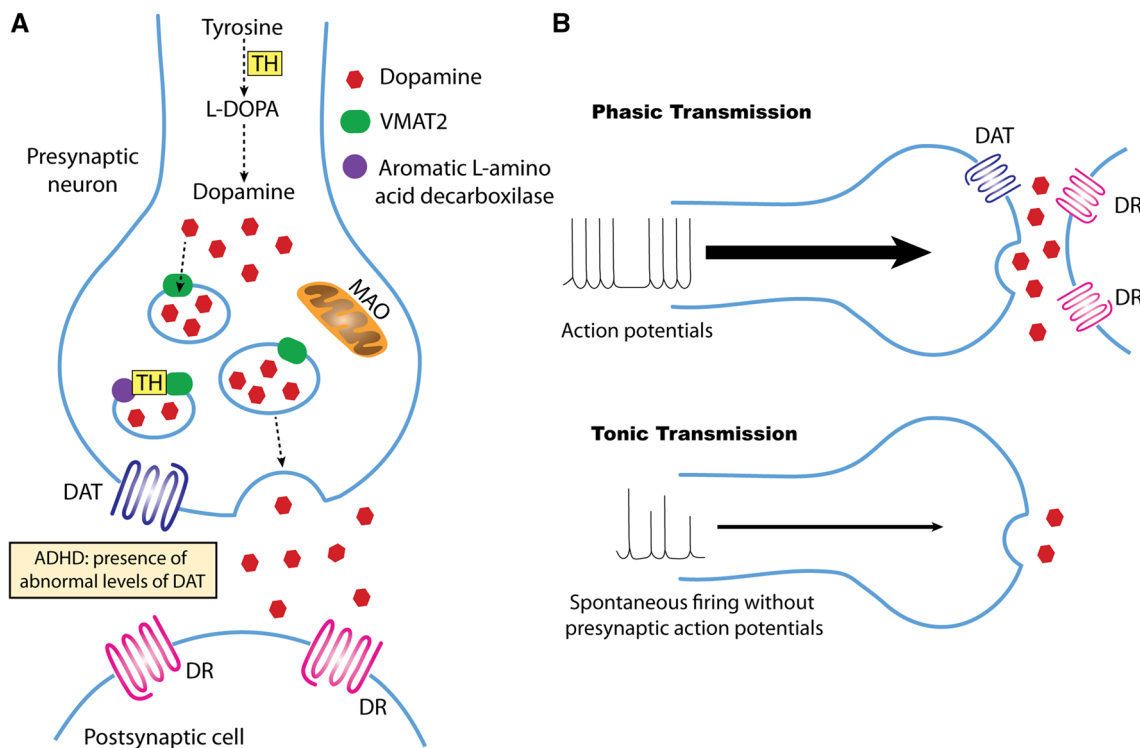


Fig. 1 Dopamine synthesis and phasic/tonic transmissions. **a** Primary metabolic route involving a two-step synthesis. First tyrosine hydroxylase (TH) converts tyrosine to L-DOPA which can then be converted to dopamine. Dopamine is transported from the cytosol by a vesicular monoamine transporter (VMAT2) into synaptic vesicles where it is stored until release into synaptic cleft. Dopamine degradation pathways with Monoamine oxidase (MAO) present in outer mitochondrial membrane. Dopamine receptors are present in both post and presynaptic neurons (including dopamine transporter, DAT). Moreover,

there is an association between the presence of atypical levels of DAT and the onset of ADHD. **b** Dopamine phasic transmission is triggered by action potentials that reach the dopaminergic neuron synapse, resulting in a fast and transient dopamine release in the synaptic cleft due to synchronized burst firing. Tonic transmission occurs by slow and irregular firing in the neuron without presynaptic action potentials, being regulated by the activity of other neurons and neurotransmitter reuptake or degradation. Modified from (Bilder et al. 2004)

(Segura-Aguilar et al. 2014). **Neuromelanin is formed in dopaminergic neurons of substantia nigra pars compacta due to the levels of VMAT-2 which are lower than mesolimbic system (Segura-Aguilar et al. 2014), leading to an inverse relationship between VMAT-2 expression level and neuromelanin content in human midbrain dopaminergic neurons (Liang et al. 2004).**

In healthy subjects aminochrome is not toxic in dopaminergic neurons by the action of DT-diaphorase which can catalyze the reduction of aminochrome to Leukoaminochrome (Lozano et al. 2010; Segura-Aguilar et al. 2014; Huenchuguala et al. 2016; Herrera-Soto et al. 2017) and glutathione transferase (GSTM2) which can convert aminochrome to 4-Glutathionyl-5,6-dihydroxy indoline preventing neurotoxicity (Hauser and Hastings 2013; Huenchuguala et al. 2016; Segura-Aguilar and Huenchuguala 2018). GSTM-2 is only expressed in astrocytes, but dopaminergic neurons can internalize it, which may protect them from aminochrome over accumulation. In fact, free aminochrome could induce mitochondrial dysfunction leading to cell death and

dopaminergic neurons loss (Arriagada et al. 2004; Aguirre et al. 2012; Huenchuguala et al. 2017).

Dopamine as a Neurotransmitter

Extracellular dopamine levels are modulated by two main mechanisms: phasic and tonic transmission (Fig. 1b) (Floresco et al. 2003). Phasic dopamine release is driven directly by action potentials in the dopamine-containing cells that result in fast and transient increase of dopamine concentrations near the presynaptic terminal. Conversely, tonic transmission occurs when dopamine is released, independently from presynaptic action potentials, and is regulated by the activity of other neurons and neurotransmitter reuptake (Floresco et al. 2003). Tonic release generates milder and less spatially restricted increases in extracellular dopamine compared to phasic release (Venton et al. 2003). One interesting aspect of those firing mechanisms is related to the effect of DAT on dopamine extracellular levels. Phasic dopamine burst can reach a

peak of 1.6 mM saturating D2 receptors, while DAT activity maintains dopamine extracellular levels by reuptake and the concentrations vary in a millisecond scale. In contrast, the dopamine tonic transmission reaches a nanomolar concentration, varying in seconds to minutes scale, and is not disproportionately affected by DAT activity. Although the tonic concentration is lower, this is sufficient to stimulate presynaptic D2 receptors present on afferent terminals (Grace 1991; Floresco et al. 2003; Grace et al. 2007).

Synaptic vesicles containing dopamine are stored in the presynaptic terminal until release into the synaptic cleft (Harrington et al. 1996; Miller et al. 1999). In most cases, dopamine release occurs through exocytosis led by changes in membrane potential (Agnati et al. 1995; Eiden et al. 2004; Liu et al. 2018). Rather than fast synaptic transmission, dopamine is mainly released by volume transmission, diffusing through a larger area, to mediate effects in a variety of cells (Agnati et al. 1995). However, it has been shown that, in the *striatum*, sparse release of dopamine occurs in hotspots of axons generating a localized signal with rapid kinetics, where scaffolding proteins such as Bassoons, glutamine, leucine, lysine, and serine-rich protein (ELKS) and Rab3a-interacting molecule (RIM) form varicosities with active zone-like sites which are essential for dopamine release by presynaptic neurons (Liu et al. 2018).

After dopamine enters the extracellular space, it can bind to postsynaptic receptors located on dendrites and soma or presynaptic autoreceptors (D2 and D3 receptors) located on the presynaptic neuron (Levesque et al. 1992; Gardner et al. 1996, 1997). After the postsynaptic neuron elicits an action potential, dopamine quickly becomes unbound (Floresco et al. 2003). Then, dopamine is taken back up by presynaptic cells, a process mediated by the dopamine transporter (DAT) or by monoamine transporters (MATs) (Fig. 1a) (Harrington et al. 1996; Miller et al. 1999).

Regarding its physiological role, dopamine cannot be simply classified as an excitatory or inhibitory neurotransmitter, since it can bind to different G protein-coupled receptors (GPCRs) and differentially modulate adenylate cyclase depending on the type of dopamine receptor involved (Beaulieu and Gainetdinov 2011). In general, activation of D1-like receptors leads to an increase in 3'-5'-cyclic adenosine monophosphate (cAMP) levels due to greater adenylyl cyclase activity (Aosaki et al. 1998; Missale et al. 1998; Vallone et al. 2000). Contrarily, the recruitment of D2-like receptors leads to inhibition of adenylate cyclase and decreased cAMP levels (Chio et al. 1994). Noteworthy, dopamine may act both as an inhibitory and excitatory neurotransmitter in presynaptic neurons expressing D1-like receptors, depending on the downstream opening of potassium or sodium channels. Therefore, the effects of dopamine depend on target cell receptors, second messenger responses, ion channel

activation in the postsynaptic plasma membrane, and protein expression profiles (Beaulieu and Gainetdinov 2011).

Curiously, dopamine can also bind to trace amine-associated receptors (TAAR) (Borowsky et al. 2001), a family of intracellular receptors which modulate dopaminergic activity in a manner not fully understood (Lindemann et al. 2008). TAAR1 is a distinct GPCR mainly activated by tyramine, a trace amine, and is coupled to $G\alpha_s$, causing increases in cAMP levels and Ca^{2+} release from the endoplasmic reticulum (Zucchi et al. 2006; Xie and Miller 2007; Lindemann et al. 2008). Interestingly, TAAR1 activation decreases dopamine reuptake, efflux, and inhibits dopaminergic neuronal firing (Ledonne et al. 2011; Revel et al. 2011). Recently, it has been demonstrated that TAAR1 can dimerize with D2-like receptors in vitro (Espinoza et al. 2011). Asif-Malik et al. showed that D2/TAAR1 heterodimers may potentiate presynaptic auto-inhibition and also block dopamine D2 receptor postsynaptic signaling. Both processes can then control neurochemical actions of cocaine addiction through Glycogen synthase kinase-3 (GSK3) pathway (Asif-Malik et al. 2017).

It is interesting to note that experiments with selective transporter blockers and transporter knockout mice demonstrated that dopamine reuptake dopamine may also occur via reuptake by noradrenergic transporter (NET) (Morón et al. 2002; Carboni and Silvagni 2004; Carboni et al. 2006; Valentini et al. 2006). Additionally, in vitro models of cell lines transfected with cloned receptors have shown dopamine binding to α_2 adrenergic receptors (Aguayo and Grossie 1994; Newman-Tancredi et al. 1998; Zhang et al. 1999, 2004; Rey et al. 2001; Cornil et al. 2002, 2008), these studies suggest a direct action of dopamine on adrenergic receptors (Aguayo and Grossie 1994; Cornil et al. 2002, 2008; Zhang et al. 2004). Although there are considerable differences regarding the anatomical distribution and functional aspects of noradrenergic and adrenergic receptors, there is an overlap in their target regions (Cornil et al. 2008). The most common systemic interactions in these regions are modulations of noradrenergic cells on firing dopaminergic neurons and the associated release of dopamine (Xu et al. 1993; Gresch et al. 1995; Pan et al. 2004). The actions of dopamine on adrenergic receptors have also been reported in vivo (Cornil et al. 2008), for instance, noradrenergic neurons can reuptake dopamine in the cortex by NET activity (Di et al. 1992; Morelli et al. 1992; Tanda et al. 1995). Furthermore, hippocampal noradrenergic fibers can also release dopamine contributing to the extracellular homeostasis (Devoto and Flore 2006; Devoto et al. 2015). In conclusion, there is a vast heterogeneity regarding dopaminergic systems regulating and interacting with other pathways which exert many physiological roles across the CNS (Devoto and Flore 2006).

Dopamine Signaling in Normal Brain Function

To exert its actions, dopamine has to bind to a particular set of receptors, located at the plasma membrane of respective target cells. Dopamine receptors belong to the superfamily of GPCRs. The first indication of their existence was described in 1972 and they were identified in 1975 (Kebabian et al. 1972; Burt et al. 1975; Seeman et al. 1975). Five different subtypes of dopamine receptors have been described so far: D1, D2, D3, D4, and D5. All dopamine receptors are metabotropic and lead to the formation of second messengers, which trigger or block the activation of specific cell signaling pathways (Baik 2013a; Beaulieu et al. 2015).

Dopamine Receptors

Dopamine receptors are widely expressed in the CNS, but are also found peripherally in blood vessels, kidneys, heart, retina, and adrenals controlling catecholamine release and the renin–angiotensin system (Fig. 2a) (Missale et al. 1998). D1 and D2 are the most abundantly

expressed dopamine receptors in the brain (D1 being the highest), and the two are rarely co-expressed in the same cells (Missale et al. 1998; Baik 2013a).

Based on their structure and pharmacological properties, dopamine GPCR receptors have been subdivided in two major groups: D1-like receptors, which includes D1 and D5; and D2-like receptors comprising D2, D3, and D4 (Baik 2013a). D1-like receptors are mostly found in the caudate–putamen (*striatum*), nucleus accumbens, *substantia nigra pars reticulata*, olfactory bulb, amygdala, and frontal cortex (Savasta et al. 1986; Wamsley et al. 1989). D2-like receptors are mainly expressed in *striatum*, the lateral part of the *globus pallidus*, core of the nucleus accumbens, ventral tegmental area, hypothalamus, amygdala, cortical areas, hippocampus, and pituitary (Wamsley et al. 1989; Yokoyama et al. 1994). D1 and D5 receptors are located in postsynaptic dopamine-mediated cells, whereas D2 and D3 can be localized both post- and presynaptically (Beaulieu and Gainetdinov 2011; Baik 2013a). D4 receptors are largely expressed in the retina (Cohen et al. 1992). D1 and D5 receptors are coupled to $G_{\alpha_{s,olf}}$ protein, stimulating the production of the second messenger cAMP. On the other hand, D2, D3, and D4 receptors are coupled to $G_{\alpha_{i,o}}$ protein, which inhibits the production of intracellular cAMP (Kebabian 1978).

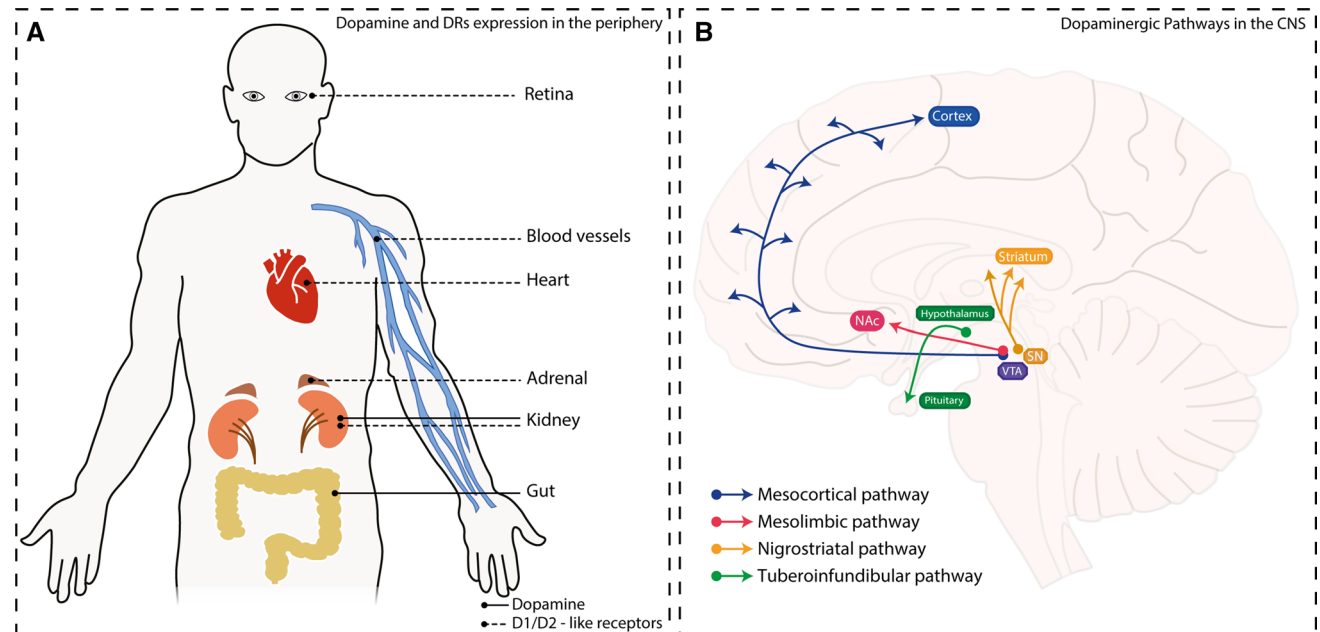


Fig. 2 Distribution of dopamine, dopamine receptors, and dopaminergic pathways in central and peripheral systems. **a** Expression of dopamine and dopamine receptors (D1/D2-like receptors) in the periphery. Dopamine (continuous black arrow) is produced in kidney and gut while dopamine receptors (dashed black arrow) are located mainly in retina, blood vessels, heart, adrenal, and kidney. **b** Distribution of the four main dopaminergic pathways in the central nervous system.

VTA is the source of mesocorticolimbic system: dopaminergic neurons project to cortex via mesocortical pathway (blue) and, to nucleus accumbens via mesolimbic pathway (red). Dopamine neurons in the *substantia nigra* project to the *striatum* and form the nigrostriatal pathway (yellow). The tuberoinfundibular pathway (green) is formed by dopaminergic neurons that project from hypothalamic nuclei (arcuate nucleus and periventricular nucleus) to the pituitary

Binding assays and agonist/antagonist studies have demonstrated some differences in the affinity of dopamine to D1-like and D2-like receptors. **D2-like receptors have from 10- to 100-fold greater affinity to dopamine than D1-like receptors**, with the **D1 receptor having the lowest affinity within the D1-like family** (Missale et al. 1998; Beaulieu and Gainetdinov 2011; Tritsch and Sabatini 2012). It is believed that these differences in dopamine affinity are due to differential roles of these receptor families, considering that dopamine neurons may have tonic and phasic patterns of neurotransmitter release (Grace et al. 2007; Baik 2013a). This means that D1-like receptors are thought to be preferentially activated by high concentrations of dopamine phasic release, whereas D2-like receptors would be responsible for detecting tonic low levels of dopamine (Goto et al. 2007; Grace et al. 2007; Baik 2013a). Nevertheless, these studies have not been able to measure whether dopamine tonic levels binding to D2-like receptors can activate intracellular signaling responses in vivo. Therefore, more studies are still necessary to clarify this hypothesis (Baik 2013a).

D1- and D2-like receptors are also different in their genetic structure. The **D1 and D5 receptor genes have no introns in their coding regions**, while the **D2, D3, and D4 genes have six, five, and three introns, respectively** (Gingrich and Caron 1993). The genetic organization of the D2-like receptor family enables the generation of receptor splice variants. Splice variants for D3 and D4 receptors have been described but are poorly characterized (Giros et al. 1991; Van Tol et al. 1991). **Alternative splicing is particularly important for the D2 receptor**, and it leads to the generation of two distinct receptor isoforms: **D2S (D2-short) and D2L (D2-long)** (Dal Toso et al. 1989; Giros et al. 1989; Shioda 2017). These two D2 variants are identical, except for an insertion of 29 amino acids in the D2L intracellular domain which is thought to help determine second messenger specificity (Giros et al. 1989; Baik 2013a). **D2S is mostly expressed in presynaptic regions, being involved in autoreceptor functions**, whereas **D2L apparently is at postsynaptic regions** (De Mei et al. 2009). Accordingly, the two D2 isoforms have distinct anatomical, physiological, signaling, and pharmacological properties (Beaulieu and Gainetdinov 2011).

D1, D2, and D3 receptors are known to control locomotor activity (Missale et al. 1998). However, D2 and D3 receptors have more complex roles than D1 receptors due to the existence of different variants and their pre- and postsynaptic locations (Missale et al. 1998; Beaulieu and Gainetdinov 2011). **Activation of presynaptic D2-like autoreceptors usually decreases dopamine release, which leads to decreased locomotion**, at the same time that **activation of postsynaptic receptors increases locomotor activity** (Beaulieu and Gainetdinov 2011). Presynaptic autoreceptors, mainly D2S receptors, are also involved in feedback mechanisms that adjust

neuronal firing rate, synthesis as well as phasic release of dopamine in response to changes in extracellular levels of the neurotransmitter (Missale et al. 1998). All dopamine receptors are involved, in a certain level, with defined actions of dopamine. Nevertheless, the specific physiological roles of D3, D4, and D5 receptors have not been fully characterized yet (Missale et al. 1998; Beaulieu and Gainetdinov 2011).

Furthermore, it has been found that dopamine receptors may dimerize with each other or with receptors from structurally divergent families (Angers et al. 2002; So et al. 2005; Milligan 2009; Perreault et al. 2014). These protein dimers, such as D2-D4, D1-NMDA (*N*-methyl-D-aspartate), and others (Perreault et al. 2014), have unique pharmacological properties, engage different signaling pathways, and can work as distinct functional units (Missale et al. 2010).

Dopamine Signaling Pathways

Upon receptor binding, dopamine elicits intracellular responses which depend on the type of dopamine receptor that was activated. Dopamine downstream signaling mainly involves G proteins (Fig. 3); however, dopamine receptor signaling can also engage G protein-independent signaling pathways (Luttrell and Lefkowitz 2002).

G proteins are mostly composed of three subunits: α , β , and γ . Upon dopamine binding to the GPCR, the α -subunit attaches to guanosine triphosphate (GTP) and then dissociates from the $\beta\gamma$ complex. Both the α /GTP-subunit and the $\beta\gamma$ complex can activate a number of downstream effectors. When GTP hydrolysis occurs, the trimeric G protein re-associates and its activity temporarily ceases. GPCRs undergo constant regulation upon activation, and their sensitivity changes depending on the intensity and timing of the activating signal (Pierce et al. 2002).

It is commonly accepted that D1-like receptors are coupled to $G_{\alpha_{s/olf}}$ protein, activating the protein adenylyl cyclase to produce higher levels of the second messenger cAMP, which stimulates the activity of the protein kinase A (PKA). In the opposite sense, D2-like receptors, which are coupled to $G_{\alpha_{i/o}}$ protein, inhibit adenylyl cyclase and reduce the intracellular concentration of cAMP which blocks PKA activity (Kebabian and Greengard 1971; Kebabian and Calne 1979; Missale et al. 1998). PKA has several targets such as cAMP response element-binding protein (CREB), glutamate receptors, GABA receptors, ion channels (e.g., calcium and potassium), all of them being affected by dopamine's action on dopamine receptors (Greengard 2001).

Moreover, PKA targets a protein named dopamine and cAMP-regulated phosphoprotein 32-kDa (DARPP-32) that is expressed in medium spiny neurons. DARPP-32 amplifies PKA signaling and can integrate or modulate signaling pathways of diverse neurotransmitters, including dopamine itself (Svenningsson et al. 2004). PKA

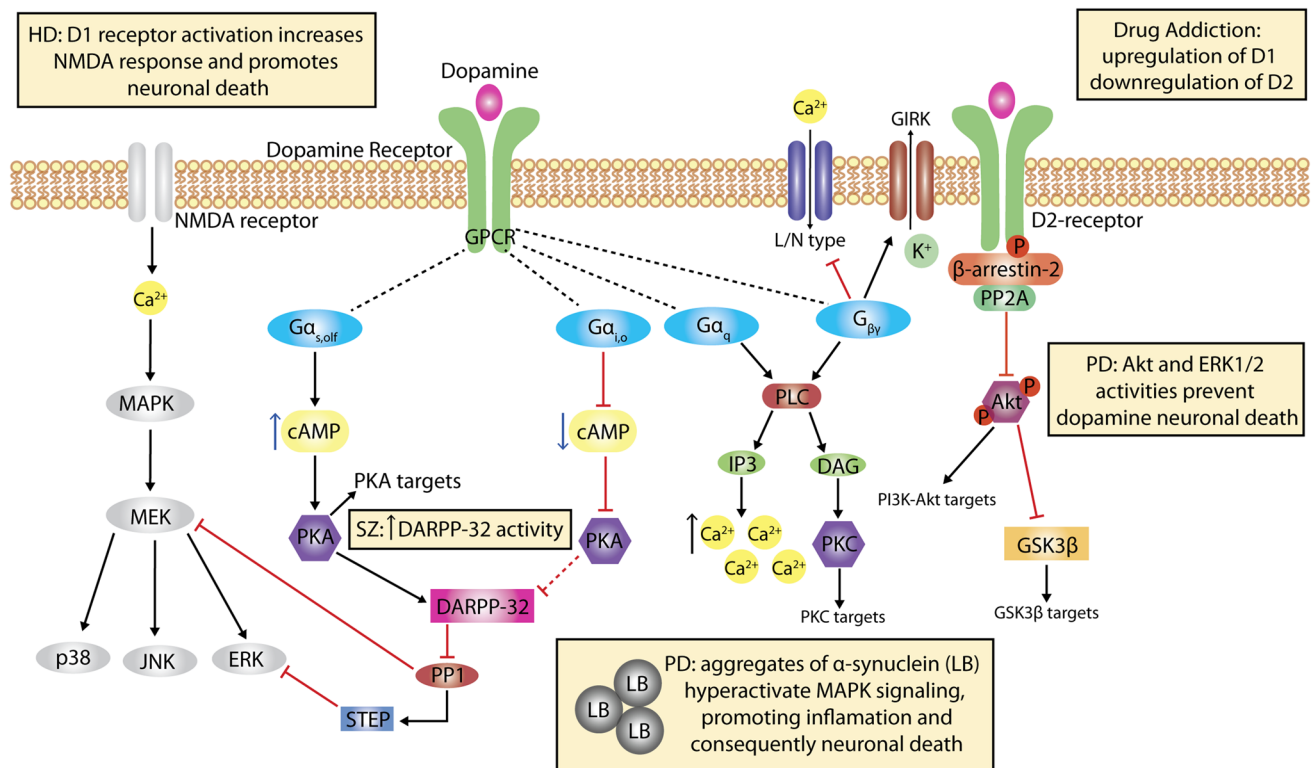


Fig. 3 Dopamine receptor signaling pathways and associated diseases. The main aspects of dopamine signaling and involved disorders discussed in this review are summarized. Dopamine receptors are in the super family of GPCRs associated with different types of G proteins. D1-like (D1 and D5) receptors are associated with $G_{\alpha_{s/olf}}$, whereas D2-like (D2, D3, and D4) are associated with $G_{\alpha_{i/o}}$ having DARPP-32 as their main modulator. These receptors also elicit G_{α_q} , $G_{\beta\gamma}$, and crosstalk to other pathways such as MAPK-MEK-ERK. Furthermore, under specific conditions, D2 receptors may activate Akt-GSK3 pathway. In HD and Drug Addiction, there is upregulation of dopamine D1 receptors that leads to downstream effects, such

as neuronal death. PD is characterized by aggregates of alpha-synuclein that promote inflammation and apoptosis. However, some studies correlated the activation of Akt and ERK signaling pathways to the prevention of dopaminergic neuronal death in PD. The presence of abnormal levels of DAT and the involvement of D4 and D5 dopamine receptors are related to the development of ADHD. In SZ, studies reported the increase of DARPP-32 activity. For all these diseases, the most relevant dopamine signaling pathways are associated with the onset and progression of these illnesses; however, various aspects of the neurobiology still need to be elucidated to promote the development of dopamine-target therapies

phosphorylates DARPP-32 at Thr34 and promotes the inhibitory activity of DARPP-32 toward protein phosphatase 1 (PP1) (Hemmings et al. 1984a, b). PP1 is responsible for histone dephosphorylation (mainly the H3), and by inhibiting PP1, DARPP-32 tips the pathway equilibrium toward a phosphorylated state and enhances the efficacy of PKA-mediated signaling (Greengard 2001; Stipanovich et al. 2008). Therefore, once PKA is activated through DARPP-32, it enhances gene expression in response to D1 receptor stimulation (Stipanovich et al. 2008). Following D2-like receptors stimulation, the phosphorylation of DARPP-32 at Thr34 is normally reduced due to decreased PKA activation (Bateup et al. 2008). Dephosphorylation of DARPP-32 at Thr34 can also be promoted by calmodulin-dependent protein phosphatase 2B (PP2B, also known as calcineurin), which is activated by increased concentrations of calcium (Ca^{2+}) due to D2-like receptor activation (Halpain et al. 1990; Nishi et al. 1997).

Furthermore, PKA-mediated phosphorylation of DARPP-32 at Thr34 can be impacted by other phosphosites in DARPP-32. Casein kinase 1 (CK1) phosphorylates DARPP-32 Ser137 which reduces Thr34 phosphorylation by PKA (Desdoutis et al. 1995). On the other hand, casein kinase 2 (CK2) phosphorylates DARPP-32 at Ser97/102, and this enhances the phosphorylation of DARPP-32 by PKA (Girault et al. 1989). It has been recently shown that, in experiments using striatal slices, activation of glutamate receptors may counteract D1 receptor/PKA signaling by inducing DARPP-32 dephosphorylation at Ser97 (CK2 site). This study showed that glutamate exerts this action by activating protein phosphatase 2A (PP2A), which then dephosphorylates DARPP-32 at Ser97, reducing PKA-dependent DARPP-32 signaling (Nishi et al. 2017).

Interestingly, DARPP-32 may also act as a PKA inhibitor when it is phosphorylated at Thr75 by cyclin-dependent kinase 5 (CDK5), and in this context does not inhibit PP1

(Bibb et al. 1999). Therefore, DARPP-32's actions as a modulator of dopamine receptors are complex and can be activated in response to multiple hormones, neuropeptides, and neurotransmitters (Greengard 2001). Still, despite of being an important modulator and/or effector of dopamine receptors signaling, DARPP-32 is not the only modulator of dopamine-mediated activities (Beaulieu and Gainetdinov 2011).

In addition to regulating adenylyl cyclase activity via $G_{\alpha_{s/olf}}$ or $G_{\alpha_{i/o}}$, dopamine receptors may also couple to G_{α_q} protein and modulate phospholipase C (PLC) (Felder et al. 1989; Jose et al. 1995; Sahu et al. 2009). PLC catalyzes the production of both inositol trisphosphate (IP3) and diacylglycerol (DAG), which increase intracellular levels of calcium and activate protein kinase C (PKC), respectively. The increase of intracellular calcium leads to activation of enzymes that are also involved in the regulation of various signaling pathways, such a PP2B and calcium/calmodulin-dependent kinase II (CaMKII) (Berridge 2009, 2016).

PLC stimulation by dopamine engages both adenylyl cyclase-dependent and non-dependent pathways because activation of PKC and CaMKII can affect glutamate receptors and PKA simultaneously (Beaulieu et al. 2015). Considering that CDK5 has an important role in DARPP-32 regulation, calcium levels and phosphorylation by PKC may regulate its activity (Halpain et al. 1990; Nishi et al. 1997; Sahin et al. 2008). High intracellular calcium concentrations caused by opening NMDA receptors or other mechanisms may increase CDK5 activity by cleavage of the p35 co-activator and lead to impaired PKA signaling (Lee et al. 2000; Beaulieu et al. 2015). On the other hand, dopamine signaling may be also driven by G_{α_q} protein, acting through PKC and leading to a potentiation of PKA signaling (Beaulieu et al. 2015).

There are three main possible cell components that may trigger PLC activity upon dopamine stimulation: D5 receptor, which couples to G_{α_q} protein (Sahu et al. 2009; So et al. 2009); D1-D2 receptors heterodimers, which also elicits G_{α_q} protein (Lee et al. 2004; Rashid et al. 2007); and $G_{\beta\gamma}$ protein subunit activated by D2-like receptors (Hernandez-Lopez et al. 2000; Beaulieu and Gainetdinov 2011). Although some studies have shown that PLC is activated by dopamine receptors, the exact mechanism by which this interaction happens and how it is regulated remains mostly unsolved (Beaulieu and Gainetdinov 2011; Lee et al. 2014; Beaulieu et al. 2015).

The $G_{\beta\gamma}$ subunit of G protein has been shown to participate in the modulation of some ion channels such as the G protein inwardly rectifying potassium channels (GIRKs) (Kuzhikandathil et al. 1998), inhibiting neuronal activity, and the L and N types of calcium channels, decreasing the entrance of calcium in the cell upon D2 stimulation (Yan et al. 1997; Missale et al. 1998). On the other hand, PLC activation by D2 receptors seems to increase calcium

intracellular concentrations (Undie et al. 1994; Hernandez-Lopez et al. 2000). Dopamine receptors may also interact with sodium channels (Hu et al. 2005; Ma et al. 2015), GABA receptors (Liu et al. 2000), and Na^+/K^+ ATPase (Bertorello et al. 1990; Missale et al. 1998). In addition, there is evidence that brain-derived neurotrophic factor (BDNF) receptors may be transactivated by D1 and D2 receptors in neurons (Swift et al. 2011). Regarding dopamine pathway modulators, DARPP-32 may interact with a variety of different proteins, hormones, and neurotransmitters as previously shown (Greengard 2001). Therefore, even though distinct dopamine receptors may activate different signaling pathways, they share a number of common molecules that help control the complexity of signaling (Baik 2013a). Moreover, the neuronal cell populations, the location across the CNS, the physiological status, and the crosstalk among these various proteins, enzymes, and receptors must be taken into consideration when evaluating dopamine signaling cascade effects and functions, since they may result in different types of physiological responses (Missale et al. 1998, 2010).

Dopamine-Mediated Activation of MAPK Signaling

Given its complexity, it is possible that many of the consequences of dopamine receptor stimulation require specific conditions that only occur under co-activation of other types of receptors and signaling pathways (Beaulieu and Gainetdinov 2011). One co-activated pathway converges on the extracellular-signal regulated kinases (ERK), which have been shown to act as integrators of dopamine's action (Beaulieu and Gainetdinov 2011; Beaulieu et al. 2015). ERK 1/2 are activated by D1- and D2-like receptors, and these proteins have a role in cell death and development, as well as in synaptic plasticity, potentially leading to different physiological responses (Chang and Karin 2001; Beom et al. 2004; Chen et al. 2004; Thomas and Huganir 2004).

A number of studies have shown that ERK activation by D1 receptors is also driven by the interaction with glutamate NMDA receptors (Valjent et al. 2000, 2005). Upon activation, NMDA activates Ras–Raf–MEK–ERK signaling pathway; however, without D1 stimulation, this activity is counteracted by striatal-enriched tyrosine phosphatase (STEP), which dephosphorylates ERK (Paul et al. 2003). PP1, which is inactivated by PKA–DARPP-32, dephosphorylates STEP and controls its activity. D1 receptor stimulation elicits PKA function and results in PP1 inactivation, persistence of STEP phosphorylation, increased ERK phosphorylation, and prevention of dephosphorylation of upstream proteins of ERK cascades (Valjent et al. 2000, 2005; Beaulieu and Gainetdinov 2011). Therefore, D1 receptor stimulation is not able to mediate ERK phosphorylation itself, but requires endogenous glutamate to activate MAPK signaling (Pascoli et al. 2011). Furthermore, D1 receptor actions, promoting

the activation of ERK pathway, involve a complex regulation including phosphatases and kinases, in addition to the cross talk with glutamate receptor signaling (Baik 2013a). In this sense, intracellular levels of calcium seem to be involved in ERK regulation by D1 receptors. It has also been shown that D1 receptor activation may phosphorylate NMDA receptor subunits, increasing calcium intracellular influx through NMDA receptor (Pascoli et al. 2011; Flores-Barrera et al. 2014; Murphy et al. 2014). Higher levels of calcium may then activate a variety of signaling cascades including CaMKII, which also activates Ras–Raf–MEK–ERK pathway (Dolmetsch et al. 2001; Colbran and Brown 2004). The interaction between D1-like and NMDA receptors to trigger ERK activation has been highly associated with responses in the *striatum* to drugs of abuse (Missale et al. 2010; Cahill et al. 2014).

The mechanism of ERK activation by D2-like receptors is not completely defined and seems to be indirectly regulated by $G\alpha_q$ and $G\alpha_i$ proteins (Choi et al. 1999; Beaulieu and Gainetdinov 2011; Baik 2013a). D2 receptors have also been shown to activate ERK signaling in heterologous cell culture systems instead of brain cells (Welsh et al. 1998; Choi et al. 1999). It has been proposed that ERK pathway may be activated through D2/ β -arrestin stimulation, but other studies report that only GPCRs exert this role (Kim et al. 2004; Quan et al. 2008). Therefore, it is noteworthy that Ras–Raf–MEK–ERK cascade activation, mediated by dopamine receptors, is complex and may be modulated by other pathways (Beaulieu et al. 2015). Furthermore, it may lead to distinct physiological outcomes depending on the anatomical localization and physiological state of the dopaminergic neurons (Baik 2013a).

Regulators of G Protein Signaling and G Protein-Coupled Receptor Kinases Involved in Dopamine Signaling

The dopamine signaling cascade may also be modulated by proteins that interfere with the G protein receptor activity (Beaulieu and Gainetdinov 2011) such as the regulators of G protein signaling (RGS) (Hollinger and Hepler 2002; Chasse and Dohlman 2003; Woodard et al. 2015) and the G protein-coupled receptors kinases (GRKs) (Gurevich et al. 2016; Komolov and Benovic 2018; Rajagopal and Shenoy 2018).

RGS proteins compose a family of more than 35 intracellular proteins that promote inhibitory effects on GPCRs and consequently decrease their downstream effects by catalyzing the conversion of the GTP-bound to the activated α -subunit of the G protein (Burchett 2000; Hollinger and Hepler 2002). All RGS have a well-preserved common domain for $G\alpha$ -subunit binding (so-called RGS domain), but widely vary in size and organization of other functional domains as well as their location (Hollinger and Hepler 2002; Heximer and Blumer 2007). It is noteworthy

that RGS accelerates GTP hydrolysis only in $G\alpha_{i/o}$ and $G\alpha_q$ proteins (Berman and Gilman 1998). In regards to GPCRs that regulate dopamine receptors, mainly the D2-like class, there is evidence that RGS9-2 is the subtype that plays a major role in this pathway, being highly expressed in the *striatum* (Kovoor et al. 2005; Seeman et al. 2007). Also, RGS are important to stop signaling in an early phase of the slow synaptic transmission elicited by dopamine D2 receptors (Beaulieu et al. 2004; Cerver et al. 2010; Beaulieu and Gainetdinov 2011).

The GRKs control the intensity of GPCR signaling to prevent a hyper-activation of the pathway, thereby acting as inhibitors of dopamine signaling (Ferguson 2001; Gurevich and Gurevich 2006; Gurevich et al. 2016). It is important that the cell has such a mechanism to promote desensitization when the receptor is persistently activated by its ligand, as well as when there is no stimulation for a long period, i.e., GRKs can allow the receptor to be re-exposed to the ligand at the membrane (Carman and Benovic 1998; Beaulieu and Gainetdinov 2011; Rajagopal and Shenoy 2018).

GRKs phosphorylate receptors in response to continuous stimulation (Pitcher et al. 1998). As a result, the receptor becomes a target to a multifunctional scaffolding protein named arrestin, which attaches to this complex, blocking (“arresting”) further activation of GPCRs (Lohse et al. 1990; Gurevich and Gurevich 2006). Also, this complex signals for the internalization of the receptor, preventing it from being persistently stimulated by the ligand and then promoting downregulation of the pathway (Laporte et al. 2002; Luttrell and Lefkowitz 2002; Rajagopal and Shenoy 2018). Additionally, a GPCR–arrestin complex may elicit a variety of other scaffolding proteins that act as signs to activate G protein-independent pathways, such as ERK, JNK, p38, and Akt—a process dependent on GRKs activity (DeWire et al. 2007; Gurevich and Gurevich 2014; Rajagopal and Shenoy 2018).

In mammals, seven different types of GRKs have been described, which are mainly grouped in three classes: GRK1-like, which includes GRK1 and GRK7; GRK2-like containing GRK2 and GRK3; and GRK4-like incorporating GRK4, GRK5, and GRK6 (Premont et al. 1995; Pitcher et al. 1998; Premont and Gainetdinov 2007; Mushegian et al. 2012). GRK1-like proteins are expressed only in the visual system and are not involved in dopamine receptor signaling (Premont and Gainetdinov 2007). Conversely, GRK2- and GRK4-like components are broadly expressed in the whole body and may be regulators of all the GPCRs, including dopamine receptors (Erdtmann-Vourliotis et al. 2001; Bychkov et al. 2012). In vitro experiments have shown that GRK2 and GRK3 may phosphorylate D1, D2, and D3 receptors (Tiberi et al. 1996; Kim et al. 2001; Sedaghat et al. 2006). Knockout animals for GRK6 are hypersensitive to dopaminergic agonists possibly due to increased activity of

D2 receptors. So, these receptors are physiological targets of GRK6 modulation and may also be involved in the activation of Akt pathway (Gainetdinov et al. 2003; Seeman et al. 2005). The arrestins also have isoforms that are specific for the visual system (arrestin-1 and arrestin-4) (Luttrell and Lefkowitz 2002). Conversely, β -arrestin-1 (arrestin-2) and β -arrestin-2 (arrestin-3) are ubiquitously expressed in the majority of tissues and, therefore, may have a role in regulating GPCR-related signaling (Luttrell and Lefkowitz 2002; Gurevich and Gurevich 2006). In particular, β -arrestin-1 is much more expressed in the brain, reaching up to twenty times the concentration of β -arrestin-2 (Arriza et al. 1992; Gurevich et al. 2002).

Nonetheless, the precise map of interaction among each type of dopamine receptor–GRK–arrestin is not fully characterized yet, and further studies are necessary (Gurevich et al. 2016). GPCRs seem to be continuously regulated by GRK–arrestin, and some receptors interact exclusively with a specific subset of GRKs or arrestins (Premont and Gainetdinov 2007; Deming et al. 2015). Recently, it was found that some types of GRKs do not phosphorylate the activated dopamine receptor, but still elicit its internalization and activation of signaling pathways (Li et al. 2015), which suggests even greater complexity in this pathway. Ultimately, the mechanisms of GPCR regulation by GRKs may depend on tissue location and the pattern of expression of GRK/arrestin in each particular situation (Beaulieu and Gainetdinov 2011).

Activation of Akt–GSK3 Pathway by Dopamine

Following β -arrestin attachment to the phosphorylated dopamine receptor, besides the desensitization and/or internalization of the receptor, it may also affect other signaling pathways (DeWire et al. 2007). A major pathway that may be regulated is the phosphatidylinositol-3 kinase (PI3K)–Akt (also called protein kinase B)–glycogen synthase kinase 3 (GSK3) (Beaulieu et al. 2004; Beaulieu 2011).

The PI3K–Akt signaling pathway regulates biological processes including cell survival, proliferation, differentiation, glucose metabolism, and gene transcription (Liu et al. 2009; Martini et al. 2014). Growth factors, cytokines, and other molecules can bind to receptor tyrosine kinases (RTKs) and some GPCRs to modulate signal transduction through the PI3K–Akt pathway (Cross et al. 1995; Scheid and Woodgett 2001; Altar et al. 2008; Liu et al. 2009; Martini et al. 2014). The binding of agonists typically results in the recruitment of kinases to the intracellular domain of the receptor that phosphorylate PI3K. This leads to increased conversion of phosphatidylinositol-2-phosphate (PIP2) in the cellular membrane to phosphatidylinositol-3-phosphate (PIP3) which provides a docking site for Akt. Membrane

bound Akt is fully activated by sequential phosphorylation of Ser308 and Thr473 by PDPK1 and mTORC2, respectively.

Dopamine inhibits the PI3K–Akt pathway through the D2 receptor (Gurevich et al. 2002; Beaulieu et al. 2007, 2009; Beaulieu 2011). Dopamine binding to the D2 receptor triggers the formation of a complex consisting of β -arrestin-2, Akt, and PP2A (Beaulieu et al. 2005; Beaulieu 2011). This allows PP2A to inactivate Akt via dephosphorylation (Beaulieu et al. 2004, 2005; Ugi et al. 2004). Inactivated Akt cannot phosphorylate its substrates including the two GSK3 isoforms GSK3 α and GSK3 β , which causes them to be constitutively activated (Cross et al. 1995; Liu et al. 2009; Martelli et al. 2010; Kaidanovich-Beilin and Woodgett 2011). Enhanced activation of GSK3 acts as a positive feedback loop to promote the stabilization of the signaling complex elicited by β -arrestin-2 and has downstream effects on other GSK3 substrates (O'Brien et al. 2011).

The D2 receptor modulation of PI3K–Akt is a signaling mechanism independent from cAMP/PKA activity. Interestingly, the relationships of the D2 receptor with these cascades are dissociable, and β -arrestin-2 only activates downstream effectors under specific conditions (Peterson et al. 2015). Furthermore, the kinetics of the two different cascades differ, with the β -arrestin-2 effects usually taking 30–60 min to occur (Beaulieu et al. 2004, 2005). This suggests that the β -arrestin-2/Akt axis may be involved in late responses elicited in slow synaptic transmission induced through D2 receptors (Beaulieu and Gainetdinov 2011).

The systems involved with D2 receptor-mediated activation of GSK3 appear to be wide-ranging and include synaptic NMDA receptor activity (Li et al. 2009), circadian responses (Doi et al. 2006; Yujnovsky et al. 2006), prevention of long-term depression in synapses (Peineau et al. 2007), and reward behaviors (Miller et al. 2014). The importance of GSK3 feedback to the D2 receptor has also been demonstrated in vivo. Animals with a selective reduction of GSK3 activity in forebrain neurons, but not in dopaminergic neurons, displayed reduced striatal D2 function (Gomez-Sintes et al. 2014).

Dopaminergic Pathways and Their Roles in the Central Nervous System

The dopaminergic system plays important roles in neuromodulation, such as movement and motor control (Paus 2001), spatial memory function (Luciana et al. 1998), motivation (Depue and Collins 1999), arousal (Andretic et al. 2005), reinforcement, reward (Berridge and Kringelbach 2008), sleep regulation (Grossman et al. 2000), attention (Aston-Jones 2005), affect (Berridge and Kringelbach 2008), cognitive function (Paus 2001), feeding, olfaction, hormone regulation (Li et al. 1999), and influences the immune (Basu

and Dasgupta 2000), cardiovascular (Goldberg et al. 1978; Contreras et al. 2002), gastrointestinal (Willems et al. 1985), and renal systems (Aperia 2000). In the retina, amacrine cells release dopamine extracellularly during daylight, enhancing the activity of cone cells and increasing sensitivity to color and contrast while suppressing rod cell activity (Hampson et al. 1992). Dopamine also has other functions including nausea (Nakagawa et al. 2008), maternal and reproductive behaviors (Krüger et al. 2005), and lactation (Demarest et al. 1984).

In humans, midbrain dopaminergic neurons from the ventral tegmental area (VTA) project to the prefrontal cortex via the mesocortical pathway and to the nucleus accumbens via the mesolimbic pathway (Fig. 2b) (Horvitz 2000; Wise 2009). Together, these pathways form the mesocorticolimbic system, which plays a role in reward and motivation (Kelley and Berridge 2002). The VTA region is also the origin of dopaminergic projections to the amygdala, hippocampus, cingulate gyrus, and olfactory bulb (Fallon and Moore 1978; Loughlin and Fallon 1983; Gasbarri et al. 1997; Hasue and Shammah-Lagnado 2002; Otmakhova et al. 2013). Electrophysiology studies on localized brain stimulations have implicated the mesolimbic dopaminergic system in positive reward and appetite-motivated behaviors (Wauquier and Rolls 1976; Ikemoto and Panksepp 1999; Carlezon Jr and Thomas 2009). However, aversive stimuli and stress may also lead to dopamine release by this same system, which might correspond to a generalized behavioral arousal involving the “seeking of safety” behavior (Ikemoto and Panksepp 1999). The mesolimbic system has also been recognized for its role in the determination of personality traits (Depue and Collins 1999), including novelty (Otmakhova et al. 2013) or sensation seeking (Bardo et al. 1996), extraversion (Depue and Collins 1999), and impulsivity (Buckholtz et al. 2010).

In animal experimental models, microinjections of dopamine into the nucleus accumbens increase locomotor activity (Pijnenburg and Van Rossum 1973), exploratory behaviors (Mogenson and Nielsen 1984), conditioned approach responses (Parkinson et al. 1999), and anticipatory sexual behaviors (Damsma et al. 1992). Experimental modulation of dopamine on the ventral pallidum and olfactory tubercle has similar effects, but with more intense responses (Ikemoto 2007). Still, lesions in ventral pallidum reduce natural and artificial reward responses. Moreover, when a GABA-A receptor antagonist is injected into the VTA, locomotion is increased (Arnt and Scheel-Krüger 1979; Mogenson et al. 1980; Stinus et al. 1982). This phenomenon occurs because GABAergic neurons inhibit dopaminergic neurons and the antagonist blocks this inhibition (Arnt and Scheel-Krüger 1979; Mogenson et al. 1980; Stinus et al. 1982). Therefore, enhanced dopaminergic function in mesolimbic system increases behavioral activity, while lesions of this system can eliminate exploratory and appetitive behaviors.

Regarding maternal behavior, mesolimbic dopaminergic neurons are important downstream targets of oxytocinergic regulation, since oxytocin-producing neurons from medial preoptic area project directly to the VTA (Numan and Smith 1984; Numan and Sheehan 1997). The administration of oxytocin receptor antagonists into the VTA impairs maternal behavior (Pedersen et al. 1994). Moreover, dopamine itself in this pathway is important for full expression of maternal behaviors, since dopamine-depleting 6-OHDA lesions (Hansen et al. 1991; Hansen 1994) or peripheral injections of D1 and D2 receptor antagonists significantly disrupt maternal care (Giordano et al. 1990; Hansen et al. 1991; Stern and Taylor 1991). In experimental models, presenting a pup to a lactating dam increases extracellular dopamine levels and FOS-immunoreactivity in the nucleus accumbens in the dam (Fleming et al. 1994). Also, dopamine release levels in this nucleus are associated with natural variations of mothers licking and grooming, where dams who present higher levels of dopamine release have higher expression of these behaviors toward pups (Champagne et al. 2004). These effects are implicated in incentivization and mediate appetite-driven behaviors toward a wide range of reinforcers and stimuli, including those related to mother–infant interactions such as pup odors, sounds, and suckling (Robbins and Everitt 1996; Ikemoto and Panksepp 1999; Numan 2007).

Dopamine acts at D1 but not D2 receptors in the context of maternal behavior (Numan et al. 2005). More specifically, it has been demonstrated that dopamine in the nucleus accumbens elicits D1 activity through adenylyl cyclase and not PLC to promote the onset of maternal care (Stolzenberg et al. 2010). However, whether this pathway is involved in the maintenance of this behavior in rats is not known. The mesolimbic dopamine pathway is also crucial to the consolidation of maternal memory, when the mothers show enhanced maternal responsiveness toward their infant if they have already had previous maternal experiences. D1 and D2 dopamine receptors, especially in the nucleus accumbens shell, play an important role in this context (Parada et al. 2008).

Dopamine neurons in the substantia nigra that project to the striatum form the nigrostriatal pathway (Fig. 2b), which has a role in the control of motor function and learning capabilities (Hikosaka et al. 2002). This pathway controls procedural aspects of movements and motivated behaviors, since it projects to more dorsal basal ganglia areas where behavioral and cognitive habits are learned and stored (Carli et al. 1985; Graybiel 1997; Haber 2003). The nigrostriatal dopaminergic system is also involved in central pain modulation, in which inhibition is modulated by D2 receptors, without the involvement of D1-like receptors (Michael-Titus et al. 1990; Magnusson and Fisher 2000).

Dopamine modulates the body movements by two main pathways: direct and indirect (Graybiel 1997, 2000; Cenci

2007). The modulation of the direct pathway involves the activation of subthalamic nucleus which can activate the dopaminergic neurons of nigrostriatal pathway (Horvitz 2000). In the *striatum*, inhibitory neurons expressing D1 receptors are activated by dopamine, which results in the inhibition of the medial part of the *globus pallidus* and allows for thalamocortical signaling (Surmeier et al. 2007; Gerfen and Surmeier 2011). Moreover, the *substantia nigra* communicates with subthalamic nucleus in a feedback loop manner, avoiding permanent activation of nigrostriatal pathway (Carlsson and Carlsson 1990). The modulation of the indirect pathway also occurs, but in this case the targets are inhibitory neurons present in *striatum* expressing D2 receptors (Calabresi et al. 2000, 2014). D2 receptor stimulation inhibits the striatal neurons, which disinhibits the external *globus pallidus* and results in thalamocortical signaling (Kravitz et al. 2010; Cachope and Cheer 2014). Together, the direct and indirect pathways allow for fine regulation of motor control by dopamine.

In the *incerto-hypothalamic* system, dopaminergic neurons project to several regions of the hypothalamus and participate in the blockage of gonadotrophin releasing hormone (GRH), which is responsible for the development of reproductive system and the regulation of other pituitary hormones (Bjo et al. 1975; Watabe-Uchida et al. 2012). In animal experimental models, it has been demonstrated that *incerto-hypothalamic* dopaminergic neurons block thyroid-stimulating hormone (TSH) secretion (Brown et al. 1972). However, the dopaminergic system stimulates the secretion of growth hormone, which functions as a co-gonadotrophic hormone (Cunha-Filho et al. 2002).

The *tuberoinfundibular* dopaminergic pathway is constituted of projections from the arcuate nucleus and the periventricular nucleus of the hypothalamus to the pituitary gland (Fig. 2b), and regulates the secretion of prolactin from the anterior pituitary gland (Demarest et al. 1983, 1984). Dopamine, which exerts the most important hypothalamic regulation over prolactin secretion, is produced by neurons in the arcuate nucleus and secreted into the hypophyseal portal system of the median eminence, which supplies the pituitary gland (Gudelsky and Porter 1980; Gudelsky 1981). During lactation, working primarily via changes in the inhibitory control of prolactin by dopamine must be removed in order for the dam to present appropriate physiological responses to pup suckling (Ben-Jonathan and Hnasko 2001).

In this way, suckling reduces the release of dopamine in the tuberoinfundibular system and may then increase circulating prolactin levels, which stimulates milk synthesis (Demarest et al. 1983; Voogt et al. 2001). Moreover, prolactin secretion is self-regulated by a short loop feedback mechanism where increased levels of prolactin increase tuberoinfundibular system activity (Moore 1987). During lactation in rats, prolactin does not increase the activity

of the dopamine system. This mechanism allows for the increased levels of prolactin necessary during the lactation period, and is thought to be driven by changes in tyrosine hydroxylase activity in late gestation (Grattan and Averill 1995; Arbogast and Voogt 1996; Andrews et al. 2001; Romano et al. 2013).

The D2 subtype of the dopamine receptor is predominant in the *lactotroph*; however, the mechanisms elicited upon receptor activation in this prolactin producing cell are not completely clear. Neither decreased cAMP levels nor PLC inhibition seem to be exclusive or of primary importance for dopamine activity in this case (Crowley 2015). On the other hand, it is believed that dopamine acts by blocking the entrance of Ca^{2+} in the *lactotrophs*, which is essential for prolactin exocytosis. Also, the withdrawal of dopamine in these cells promoted by the suckling stimulus would activate several aspects of Ca^{2+} intracellular signaling, including PLC activity (Martinez et al. 1992; Gregerson et al. 1994).

Together with the four main pathways, nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular, there is another diencephalic dopaminergic cluster in the dorsal posterior hypothalamus named A11 region (Skagerberg et al. 1982; Lindvall et al. 1983; Qu et al. 2006; Barraud et al. 2010). Those neurons, approximately 300 in rats (Skagerberg et al. 1982) or 130 in mice (Qu et al. 2006), project to neocortex (Manger et al. 2004) which might be related to changes in the perception of ascending sensory information (Clemens et al. 2006); serotonergic dorsal raphe (Peyron et al. 1995), promoting cardiovascular and sympathetic activity; they also descend as the source of spinal dopamine through the dorsolateral funiculus (Holstege et al. 1996) and via an extensive set of collaterals (Clemens et al. 2006). However, they are most concentrated in the superficial sensory-related dorsal horn and intermediolateral nucleus (Skagerberg et al. 1982; Lindvall et al. 1983; Clemens and Hochman 2004).

The loss of A11 neurons causes a disinhibition of sensory inputs and favors the occurrence of abnormal visceral or muscular sensations (Clemens et al. 2006). Impairment of A11 neurons are related with restless legs syndrome, which is conceptualized as abnormal limbs sensations that diminish with motor activity, has a circadian period and peaks at the evening, leading to disrupted sleep (Winkelman 1999; Bara-Jimenez et al. 2000; Clemens et al. 2006). The spinal cord of rats, cats, monkeys, and humans express dopamine receptors D₁, D₂, and D₃ (Lindvall et al. 1983; Holstege et al. 1996), while the contribution of these receptors to spinal reflex are not fully understood. It has been demonstrated that dopamine and D₂ agonists can depress the monosynaptic reflex amplitude, dependent on D₃ receptors, since this effect was absent in D₃ knockout mice (Clemens and Hochman 2004). Hence, A11 modulatory neurons could hypothetically inhibit spinal somatosensory and sympathetic autonomic

circuits, possibly leading to an imbalance of the descending control of the sympathetic pre-ganglionic and further focal akathisia, therefore contributing to restless legs syndrome (Clemens et al. 2006).

Diseases Involving Dopamine Signaling

In the brain, dopamine signaling is involved in functions such as voluntary movement, working memory, attention, and learning. Dopamine also plays a significant role in the periphery regulating important physiological processes such as hormonal regulation, immune system, among others (Missale et al. 1998; Iversen and Iversen 2007; Beaulieu and Gainetdinov 2011). Since so many vital functions are dependent on the activation of dopamine receptors, it is not surprising that malfunctions of dopaminergic signaling have been implicated in the progression of various human disorders (Kim and Choi 2010; Beaulieu and Gainetdinov 2011). Here, we present a summary of the major nervous system diseases associated with dysfunctions in dopaminergic signaling pathways.

Parkinson's Disease

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is pathologically caused by the loss of dopamine-producing neurons in the *substantia nigra pars compacta* and the presence of intraneuronal aggregates called Lewy bodies (LB) that are enriched in α -synuclein (SNCA) (Spillantini et al. 1997; Dauer and Przedborski 2003; Dexter and Jenner 2013; Williams-Gray and Worth 2016). PD most commonly affects those 60 years of age and older, has an incidence of ~150–200 cases per 100,000 individuals, and is more prevalent in men than in women (Schrage et al. 2000; Popat et al. 2005; Dexter and Jenner 2013). The disease presents as a cluster of motor symptoms called parkinsonism (bradykinesia, resting tremor, rigidity, and postural instability) that are commonly attributed to the loss of striatal dopamine, as well as non-motor features including depression and cognitive impairment (Gibb and Lees 1988; Gandhi and Wood 2005; Poewe 2008; Kim and Choi 2010; Dexter and Jenner 2013; Kalia and Lang 2015; Postuma et al. 2015; Williams-Gray and Worth 2016).

PD was once considered to be a sporadic disease, but the contribution of both common and rare genetic variation to the disease is now appreciated. Genome-wide association studies have identified that common variation in at least 41 different *loci* modulates the risk of developing PD (Chang et al. 2017). Rare variants in genes including leucine-rich repeat kinase 2 (*LRRK2*), SNCA, PTEN-induced putative kinase 1 (*PINK1*), parkin (*PRKN*), and DJ-1 (*PARK7*) have also been found to cause familial forms of PD (Hernandez et al. 2016).

Many of the genes associated with PD risk are involved in autophagy, lysosomal function, the oxidative stress response, and the maintenance of mitochondrial integrity (Hauser and Hastings 2013; Beilina and Cookson 2016). All of these processes are thought to contribute to the demise of dopaminergic neurons in PD.

The number of dopaminergic neurons in the *substantia nigra* decreases at a rate of ~4% per decade as part of the normal aging process (Fearnley and Lees 1991). However, this decline is accelerated in PD and parkinsonism appears when the number of dopaminergic neurons and striatal dopaminergic terminals decrease to ~70% and ~40–50% of that expected in age-matched controls, respectively (Cheng et al. 2010). The classical model of how parkinsonism arises from the loss of striatal dopamine content is based on the functional connections of the basal ganglia. Decreased dopamine levels reduce activity in the direct pathway and increase activity in the indirect pathway, which results in decreased thalamocortical drive and parkinsonism (Obeso Jose et al. 2009).

Huntington's Disease

Huntington's disease (HD) is an autosomal dominant disorder caused by a CAG repeat expansion on exon 1 of the huntingtin gene (*HHT*) (MacDonald et al. 1993; Ha and Fung 2012; Cepeda et al. 2014; Kim and Fung 2014). This fatal and progressive neurodegenerative disease affects about 5 to 7 per 100 000 individuals, is highest among whites, and, the mean age of onset is around 40 years, although some patients are diagnosed in late life (Wright et al. 1981; Myers et al. 1985; Takano et al. 1998; Walker 2007; Roos 2010; Kim and Fung 2014). HD presents as a movement disorder characterized by chorea, but cognitive deficits and psychiatric disturbances often appear as the disease progresses (Roos 2010; Ha and Jankovic 2011; Ha and Fung 2012; Cepeda et al. 2014).

The most profound neurodegeneration caused by HD occurs in the caudate and putamen, which contain high levels of dopaminergic innervation and dopamine receptors. Thus, dysfunctional dopamine signaling is central to the symptoms of HD (Jakel and Maragos 2000; Cyr et al. 2006; Beaulieu and Gainetdinov 2011). This has been confirmed by imaging studies that have shown significant reductions in striatal D1 and D2 dopamine binding in HD brains compared to healthy controls (Felicio et al. 2009; Nikolaus et al. 2009).

The early stages of HD are characterized by hyperkinetic movements caused by increased thalamocortical glutamatergic signaling driven by the loss of neurons in the indirect pathway; however, hypokinesia occurs in the late stages of the disease when both the direct and indirect pathways are impacted (Cepeda et al. 2014; Dickey and La Spada 2017). D1 and D2 receptor activation lead to different actions in

HD. Studies have demonstrated that dopamine and glutamate signaling pathways have a synergistic action that can enhance toxicity through D1 receptor activation (Tang et al. 2007; Paoletti et al. 2008; Cepeda et al. 2014). It increases NMDA responses that can promote neuronal death (neurotoxicity) such as aberrant Cdk5 activation (Fig. 3), while the activation of D2 decreases NMDA receptor responses and has a neuroprotective role (Bozzi and Borrelli 2006; Paoletti et al. 2008; Cepeda et al. 2014).

Schizophrenia

Schizophrenia (SZ) is a severe mental illness with a heterogeneous combination of symptoms (Perez-Costas et al. 2010; Kahn et al. 2015; Owen et al. 2016). It is characterized by three types of symptoms: positive (hallucinations, disorganized speech, and behavior), negative (impair motivation and social withdrawal), and cognitive (dysfunctions on memory) (Joyce and Roiser 2007; Kahn et al. 2015; Meyer and MacCabe 2016; Owen et al. 2016). SZ affects 1% of world population, is more frequent and severe in men than women, and the onset occurs in late adolescence and is uncommon after age 50 (Castle and Murray 1991; Freedman 2003; Ross et al. 2006; Perez-Costas et al. 2010; Kahn et al. 2015; Meyer and MacCabe 2016).

Albeit the neurobiology of SZ remains to be elucidated, many hypotheses have been proposed to clarify the disease, including the neurodevelopmental hypothesis, the glutamate hypothesis, and the most accepted, dopamine hypothesis (Kambeitz et al. 2014; Hu et al. 2015; Schmidt and Mirnics 2015; Howes et al. 2017; Wang et al. 2017). Strong evidence suggests alteration of dopaminergic neurotransmission, and abnormalities in glutamatergic signaling are involved in the genesis of psychotic and cognitive symptoms (Joyce and Roiser 2007; Owen et al. 2016). Analyses of in vivo imaging studies of synaptic function demonstrated that patients with schizophrenia have shown high levels of D2 dopamine receptor density compared to healthy control subjects, but no alteration in D1 dopamine receptor (Frankle and Laruelle 2002; Nikolaus et al. 2009; Volkow et al. 2009; Beaulieu and Gainetdinov 2011).

Modifications in neuronal circuit function can be regulated by dopaminergic homologous and heterologous receptor interactions between D1–D2 dopamine receptors, as well as by other signaling proteins (Missale et al. 2010; Xu et al. 2017). DARPP-32 is one target for the phosphorylation activity of dopamine receptors, is activated and co-expressed with D1 in the MSNs, and consists of many sites of regulatory phosphorylation (Walaas et al. 1983; Svenningsson et al. 2004; Wang et al. 2017). Moreover, Fienberg et al. (1998) described that a DARPP-32 mutant mice model showed relevant disturbances in molecular and behavioral responses to dopamine, antipsychotics, and abuse drugs,

which indicates the importance of DARPP-32 regulation in dopaminergic function.

In a rodent model, the acute administration of amphetamine promoted an increase of locomotor activity and sensorimotor deficits (via DA D2 receptor), by increasing synaptic monoamines (Sams-Dodd 1998; Ralph et al. 2001; Zheng et al. 2013) and these features are described in some neurological disorders such as SZ (Sams-Dodd 1998; Ralph et al. 2001; Zheng et al. 2013). Moreover, this chronic hyperdopaminergic context may increase the DARPP-32 activity (Fig. 3) because CDK5, p35, and p25 total levels are increased, resulting in high CDK5 kinase activity and subsequently increased phosphorylation of DARPP-32 at Thr75 (Baracskey et al. 2006). Since DARPP-32 is dephosphorylated by calcineurin (PP2B) and, PP2B knockout mice showed cognitive impairment, these results suggest a correlation between DARPP-32 and SZ (Fig. 3) (King et al. 1984; O'Donnell 2013; Wang et al. 2017). In relation to the glutamate hypothesis, the administration of a non-competitive psychotogenic NMDAR antagonist (ketamine) in healthy animals induced dopamine disturbances similar to SZ symptoms and, Stephan et al. (2009) suggest that dopamine dysfunction likely affects NMDA plasticity, that could be related to the SZ (Lieberman et al. 1987; Stephan et al. 2009; Gold et al. 2012; Maia and Frank 2017).

Attention Deficit/Hyperactivity Disorder

Attention deficit/hyperactivity disorder (ADHD) is one of the most prevalent, behavioral, and multifactorial psychiatric disorders in childhood with a complex etiology and strong genetic base (Castellanos and Tannock 2002; Faraone et al. 2003, 2005; Biederman 2005; Matthews et al. 2014). Around 5% of children and 2.5% of adults worldwide have ADHD (Polanczyk et al. 2007; Simon et al. 2009; Nigg 2013). **Some symptoms of ADHD persist into adolescence and adult life in approximately 80% of children diagnosed with the disorder (Faraone et al. 2003).** Despite specific differences, ADHD has similar symptoms to those found in children who survived encephalitis (Hohman 1922; Ebaugh 1923; Stryker 1925; Matthews et al. 2014).

ADHD is characterized by inattention (daydreaming and distraction), impulsiveness, excessive motor activity, and hyperactivity (Lange et al. 2010; Matthews et al. 2014). In animal models of ADHD, the locomotor hyperactivity was associated with dopaminergic dysfunction (Shaywitz et al. 1976; Giros et al. 1996; Cardinal et al. 2001; Castellanos and Tannock 2002; Viggiano et al. 2002). Also, human functional and imaging studies have provided some evidence of dopaminergic dysfunction which supports the possible role of catecholamine dysregulation in the neurobiology of ADHD (Castellanos and Tannock 2002).

In a human study, Faraone et al. (2005) described that specific genes showed important associations with ADHD, and these genes are related to components of the catecholamine signaling system, such as DAT, norepinephrine transporter (NET), D4, and D5 dopamine receptors (Fig. 1a) (Yang et al. 2004; Faraone et al. 2005; Madras et al. 2005). Knockout-DAT mice showed hyperactivity and deficits in inhibitory behavior, two characteristics related to ADHD, and hyperactivity decreased when treated with stimulants (Giros et al. 1996; Gainetdinov et al. 1999). Abnormal levels of DAT have also been detected in brains of ADHD patients, and DAT is a target of anti-hyperactivity drugs such as amphetamine (Madras et al. 2005). Moreover, strong evidence suggests that D4 and D5 receptors are associated with ADHD. D4 receptors are found in main regions associated with the etiology of this psychiatric disorder, such as frontal lobe regions (Noain et al. 2006; Floresco and Maric 2007; Gizer et al. 2009). Furthermore, several meta-analysis studies described the presence of polymorphisms in *DRD4* and *DRD5* dopamine receptors genes associated with ADHD in childhood (Faraone et al. 2005; Li et al. 2006; Gizer et al. 2009).

Addiction

Addiction is described as one of the most considerable public health and social problems and, succeeded by obesity, is the main cause of avoidable death in United States associated with the use of substances such as tobacco and alcohol (Gardner 2011; Lynch et al. 2013; Nutt et al. 2015). Human addictions are chronic relapsing disturbances characterized by three essential components: the compulsive drug intake, the disability to restrict drug intake, and the arising of the withdrawal syndrome with the presence of anxiety, irritability, and dysphoria (Koob and Le Moal 1997; Koob et al. 1998). Despite more than 40 years of scientific efforts since the discovery of the involvement of dopamine, the neurobiology of addiction remains to be better clarified to promote the development of efficient therapies for this illness (Nutt et al. 2015).

Strong evidence indicates that synaptic alterations in mesolimbic pathways are related to drug and food addiction, and mutual neural substrates for both dopamine-dependent disorders have been described (Kenny 2011; Baik 2013b). Drug addicts and obese people tend to present altered expression of D2 receptors in striatal areas (low D2 receptor levels), and positron emission tomography (PET) studies in obese people suggest a reduced availability on D2 receptors (Wang et al. 2001; Baik 2013b). These data indicate the possible role of dopamine regulation for addiction, however, its neurobiology needs to be better elucidated.

In relation to drug addiction, studies in rats with chronic exposure to drugs of abuse, such as cocaine, showed

adaptations of the dopaminergic system (VTA/NAc) caused by the upregulation of dopamine D1 receptors and the downregulation of dopamine D2 receptors (Henry et al. 1998; Puig et al. 2012; Lynch et al. 2013). Moreover, rats treated with agonists of dopamine D1 and D2 receptors promoted a transient downregulation of autoreceptor sensitivity and a prolonged super sensitivity of D1 receptors indicating relevant dopaminergic alterations in VTA and NAc (Henry et al. 1998).

Dopamine Signaling as Diagnostic and/or Therapeutic Route in Neurological Diseases

Considering the complexity of dopamine functions and its involvement with the development of several diseases, it is not surprising that there are a variety of drugs that aim to treat these illnesses by targeting dopamine receptors directly or indirectly. There is a wide list of selective or non-selective dopamine agonists and antagonists that have been used clinically to improve the symptoms of diseases such as Parkinson's disease, erectile dysfunction, hyperprolactinemia, schizophrenia, bipolar depression, and nausea. Some examples are apomorphine, iloperidone, domperidone, bromopride, clozapine, lurasidone, olanzapine (Beaulieu and Gainetdinov 2011). The majority of these drugs have the D2 receptor as their main target, although there are compounds that may act on D1 and D3 as well (Arnsten and Dudley 2005; Leggio et al. 2016). There is no known drug that targets the D4 receptor that has clinical relevance so far, albeit the search for new compounds in all these categories continues (Beaulieu and Gainetdinov 2011).

Recently, the US Food and Drug Administration has approved a new drug that is a dopamine D2 receptor partial agonist, which also has an agonist activity on 5-HT_{1A} receptors and antagonist on 5-HT_{2A} and α -adrenergic receptors: brexpiprazole (Citrome 2013, 2015; Maeda et al. 2014). It is approved for the treatment of schizophrenia and as an adjunctive treatment for major depressive disorder. Brexpiprazole is also being tested for treatment of agitation associated with Alzheimer's dementia and for post-traumatic stress disorder (Citrome 2015). Another interesting atypical antipsychotic drug that is a partial agonist of the D2 receptor is aripiprazole. High concentrations of aripiprazole decrease firing of dopaminergic neurons while low concentrations increase firing, suggesting that the drug acts on both cAMP/PKA and Akt/GSK3 pathways (Pan et al. 2015; Frankel and Schwartz 2017). Aripiprazole is approved as a therapy for schizophrenia, bipolar disorder, major depression disorder, and, in children, for Tourette's disorder and irritability associated with autistic spectrum disorder (Frankel and Schwartz 2017).

Drugs targeting orthosteric sites of a receptor act in the same site as endogenous ligands and elicit a limited pattern of therapeutic responses because of varying efficiency, specificity, and half-life. Furthermore, they are prone to lead to adverse side effects. Recently, there has been a new approach to the development of drugs that act on dopaminergic pathways in which drugs target post-receptor signaling pathways rather than receptors (Beaulieu et al. 2009, 2015; Freyberg et al. 2010). Here we will focus on presenting an overview of some drugs that are being developed and have the potential to act in this signaling approach, although none of them have been proved yet to reach the same satisfactory therapeutic effects that are observed with full agonists (Beaulieu and Gainetdinov 2011).

One exciting field for modulating receptor function is the development of allosteric drugs for GPCRs, dopamine receptors included (Foster and Conn 2017). These drugs can potentially decrease adverse side effects by binding to sites that are topographically different from the ones that the endogenous ligand binds, and they can also bi-directionally impact downstream pathways. It has been proposed that the use of allosteric modulators could increase selectivity for GPCR subunits and improve therapeutic effects without disrupting the physiologically regulated matrix (Rossi et al. 2017). Interestingly, dopamine receptor heterodimers may also be regulated by allosteric modulators (Trincavelli et al. 2012).

In 2010, the *N*-((trans)-4-(2-(7 cyano-3,4-dihydroisoquinolin-2(1H)-yl)ethyl) cyclohexyl)-1H-indole-2-carboxamide (SB269652) was discovered as the first negative allosteric modulator for D2 and D3 dopamine receptors and may lead to the development of a new class of antipsychotic drugs (Silvano et al. 2010). Accordingly, 3(R)-[(2(S)-pyrrolidinyl carbonyl) amino]-2-oxo-1-pyrrolidine acetamide (PAOPA) is a specific allosteric modulator of D2 receptors that has been shown to decrease schizophrenia-like behaviors in pre-clinical assays, presenting significantly less adverse side effects (Tan et al. 2013). In this sense, allosteric drugs for GPCRs, albeit difficult to develop, are at the moment one of the most valuable pharmaceutical tools to develop different strategies to treat several pathologies. Two drugs in this category have already been approved for marketing purposes (Rossi et al. 2017).

Another class of drugs that focus on dopamine receptor post-receptor signaling that are under development are the biased ligands (also known as functional selective ligands) (Park et al. 2016). These compounds are designed to selectively engage one signaling pathway downstream of a receptor that modulates multiple pathways in response to its endogenous ligand (Beaulieu and Gainetdinov 2011; Beaulieu et al. 2015). D2 receptor-biased ligands are under development as potential therapies for SZ and may

selectively activate cAMP/PKA or β -arrestin-2/Akt downstream effectors (Urs et al. 2017).

Cariprazine is one such drug that the FDA has already approved for clinical use (De Deurwaerdère 2016). Cariprazine may be useful for the treatment of schizophrenia and type I bipolar disorder because it has both antagonist and partial agonist properties at D3 and D2 receptors along with some affinity for the 5-HT_{2B} receptor (Kiss et al. 2010; Veselinović et al. 2013). Its efficacy in other types of neuropsychiatric illness is under investigation (De Deurwaerdère 2016). Pharmacologically, cariprazine is classified as a biased agonist of dopamine receptors since its action on D2 receptors blocks G protein-mediated signaling without recruiting β -arrestin-2 signaling (Gao et al. 2015).

Other possible targets for dopaminergic signaling drug discovery in the future may be the non-coding RNAs because of their role in the maintenance of the neuronal homeostasis and their dysregulation in neurological diseases. The development of drugs that would re-establish non-coding RNA function could renew synaptic transmission (Carrick et al. 2016). In addition, therapies using stem cell-derived dopamine neurons are being developed, especially for the treatment of Parkinson's disease. Taken together, there are a breadth of different therapies under investigation for future neurological disease patients (Gu 2013; Barker et al. 2017).

Dopamine signaling compounds may also be useful diagnostic tools. It has been proposed that gene expression of the D2 receptor and BDNF in the oral cavity could be biomarkers of exercise-induced neuroplasticity in patients with Parkinson's disease. Further studies and validation are necessary before this method can be applied in diagnostic and therapeutic routines (Mougeot et al. 2016). Beyond conventional therapies, researchers keep working to discover new drugs and ways of treating neurological diseases related to dopaminergic functions and signaling, aiming to improve the quality of life and eventually provide a cure for these patients.

Conclusions

Since the discovery of dopamine as a catecholaminergic neurotransmitter, the importance of dopaminergic signaling pathways related to essential physiological and pathological processes in the periphery and central nervous systems has become clear. However, taking in consideration the complexities of dopaminergic signaling systems and their interactions with other critical signaling pathways, our understanding of dopaminergic dysfunction in disease remains to be fully elucidated.

Monoamine neurotransmitters like dopamine exert their actions by binding to metabotropic receptors. Dopamine has essential roles regulating motor neurons, spatial memory

function, motivation, arousal, reward, pleasure, as well as lactation, sexual, and maternal behaviors. The majority of dopamine is synthesized from tyrosine, and dopamine degradation is catalyzed by MAO and COMT. The end products of dopamine metabolism, HVA and 3-methoxytyramine, are useful biomarkers for PD and AD.

Dopamine is transported from the cytosol by VMAT2 into synaptic vesicles. The phasic dopamine release is driven by action potentials, resulting in a fast and transient increase of dopamine in the synaptic cleft. Tonic transmission occurs when dopamine is released, without presynaptic action potentials, and is regulated by other neurons and neurotransmitter reuptake. Thus, dopamine can bind to different GPCRs and differentially modulate adenylyl cyclase. However, the complexity of dopamine signal transduction is not restricted to these pathways, also relating to a wide range of proteins such as ERK, arrestins, Akt, GSK3, PKC, and others. Therefore, dopamine's cellular effects depend on target cell receptors, second messenger responses, ion channels, and protein expression profiles.

VTA dopaminergic projections to the prefrontal cortex and to the nucleus accumbens form the mesocorticolimbic system, playing a role in reward, motivation, and maternal behavior. The nigrostriatal pathway controls motor function and learning of new motor capabilities; this pathway is also involved in central pain modulation. The tuberoinfundibular dopaminergic pathway can suppress the secretion of prolactin from the anterior pituitary gland and is important during lactation.

This review has focused on strong lines of evidence of the involvement of crucial signaling pathways elicited by dopamine receptors in the initiation and progression of multiple diseases of the nervous system. In all conditions that have been mentioned in this review, there is a noticeable correlation between dopamine disturbances and alterations in specific signaling pathways that could lead to the onset of ailments. Moreover, there are many essential aspects of the neurobiology of these maladies that still need to be elucidated. Further understanding all the complex molecular mechanisms that underlie dopamine signaling pathways and these diseases should contribute to the discovery of new therapies that will greatly impact the prognosis and quality of life for patients worldwide.

Acknowledgements This review was supported by São Paulo State Foundation for the Support of Research (FAPESP, Brazil; Grant #2016/02224-1 to JCB, Grant #2017/17998-5 to MOK, and Grant #2017/18019-0 to ARC). DSB is a fellowship recipient of the Agency for the Advancement of Higher Education (CAPES, Brazil). JCB is a recipient of grants from the National Council for Scientific and Technological Development (CNPq, Brazil; Grant #426378/2016-4), CAPES, and the Comité Français d'Évaluation de la Coopération Universitaire avec le Brésil (French Committee for the Evaluation of Academic and Scientific Cooperation with Brazil; CAPES-COFECUB Grant #848/15). RGC was partially supported by a Special Visiting

Researcher (PVE) grant from the “Science without Borders” Program (CAPES).

Author Contributions In this review, all authors had full access to the data and take all responsibility for its integrity and accuracy. MOK, DSB, and ARC drafted the manuscript, under supervision of JCB and RGC. MOK and DSB conceptualized and designed the figures. DNH, JCB, and RGC made critical revisions of the manuscript for their relevant intellectual content. JCB and RGC obtained the funding. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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