ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/328997886

Dopamine: Functions, Signaling, and Association with Neurological Diseases

Article *in* Cellular and Molecular Neurobiology · January 2019

DOI: 10.1007/s10571-018-0632-3

CITATIONS
651

READS
36,070

6 authors, including:

Marianne Orlandini Klein
University of São Paulo
21 PUBLICATIONS **911** CITATIONS

SEE PROFILE

Daniella Sabino Battagello
Universidade Federal do ABC (UFABC)
22 PUBLICATIONS **920** CITATIONS

SEE PROFILE

Ariel Cardoso
University of São Paulo
7 PUBLICATIONS **915** CITATIONS

SEE PROFILE

David N Hauser
34 PUBLICATIONS **2,772** CITATIONS

SEE PROFILE

All content following this page was uploaded by Ariel Cardoso on 23 November 2018.

The user has requested enhancement of the downloaded file.

Cellular and Molecular Neurobiology
https://doi.org/10.1007/s10571-018-0632-3

REVIEW PAPER

Dopamine: Functions, Signaling, and Association with Neurological Diseases

Marianne O. Klein[1] · Daniella S. Battagello[1] · Ariel R. Cardoso[1] · David N. Hauser[2] · Jackson C. Bittencourt[1,3] · Ricardo G. Correa[2]

Received: 21 August 2018 / Accepted: 2 November 2018
© Springer Science+Business Media, LLC, part of Springer Nature 2018

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 neurotropic 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-*O*-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

Marianne O. Klein and Daniella S. Battagello have contributed equally to the work.

✉ Jackson C. Bittencourt
jcbitten@icb.usp.br

✉ Ricardo G. Correa
rcorrea@sbpdiscovery.org

[1] Laboratory of Chemical Neuroanatomy, Department of Anatomy, Institute of Biomedical Sciences, University of São Paulo (USP), São Paulo 05508-000, Brazil

[2] Center for Translational Neuroscience, Sanford Burnham Prebys (SBP) Medical Discovery Institute, 10901 North Torrey Pines Rd., La Jolla, CA 92037, USA

[3] Center for Neuroscience and Behavior, Institute of Psychology, USP, São Paulo, Brazil

Published online: 16 November 2018

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 *N*-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
VTA	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 (Andretic 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 (O_2), and iron (Fe^{2+}) 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 O_2, 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*

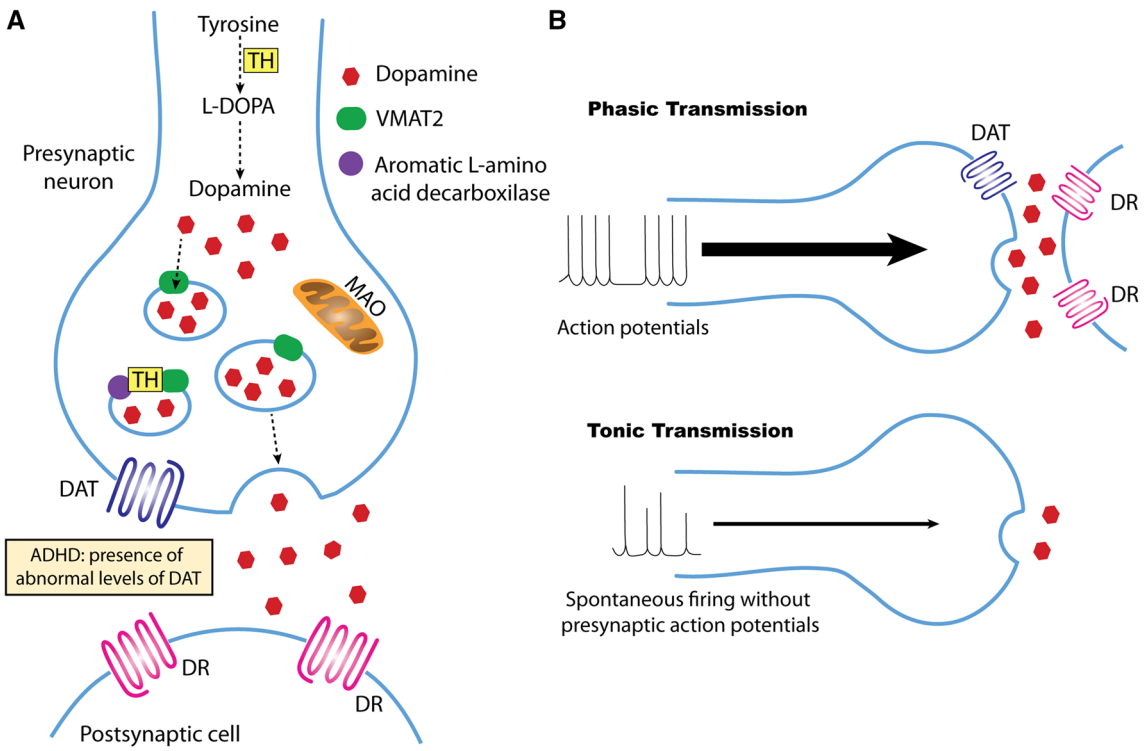

Fig. 1 Dopamine synthesis and phasic/tonic transmissions. **a** Primary metabolic route involving a two-step synthesis. First tyrosine hydroxylase (TH) converts tyrosine to L-DOPA which can then be converted to dopamine. Dopamine is transported from the cytosol by a vesicular monoamine transporter (VMAT2) 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 alpha2 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).

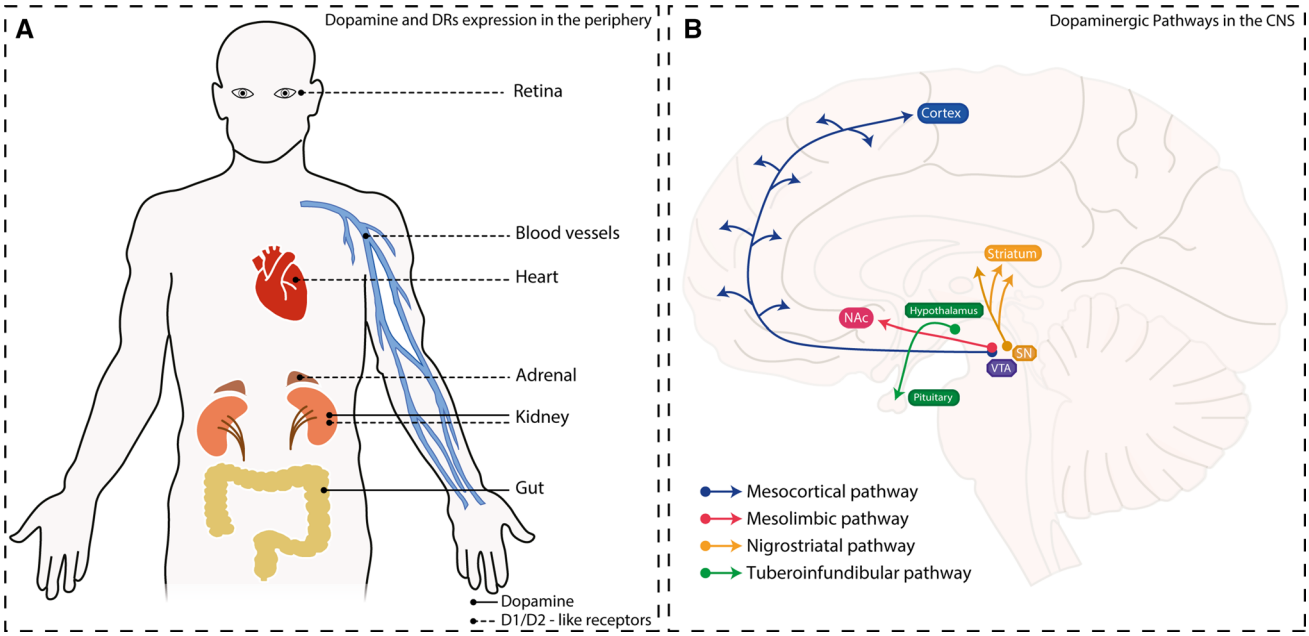

Fig. 2 Distribution of dopamine, dopamine receptors, and dopaminergic pathways in central and peripheral systems. **a** Expression of dopamine and dopamine receptors (D1/D2-like receptors) in the periphery. Dopamine (continuous black arrow) is produced in kidney and gut while dopamine receptors (dashed 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 βγ complex. Both the α/GTP-subunit and the βγ 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

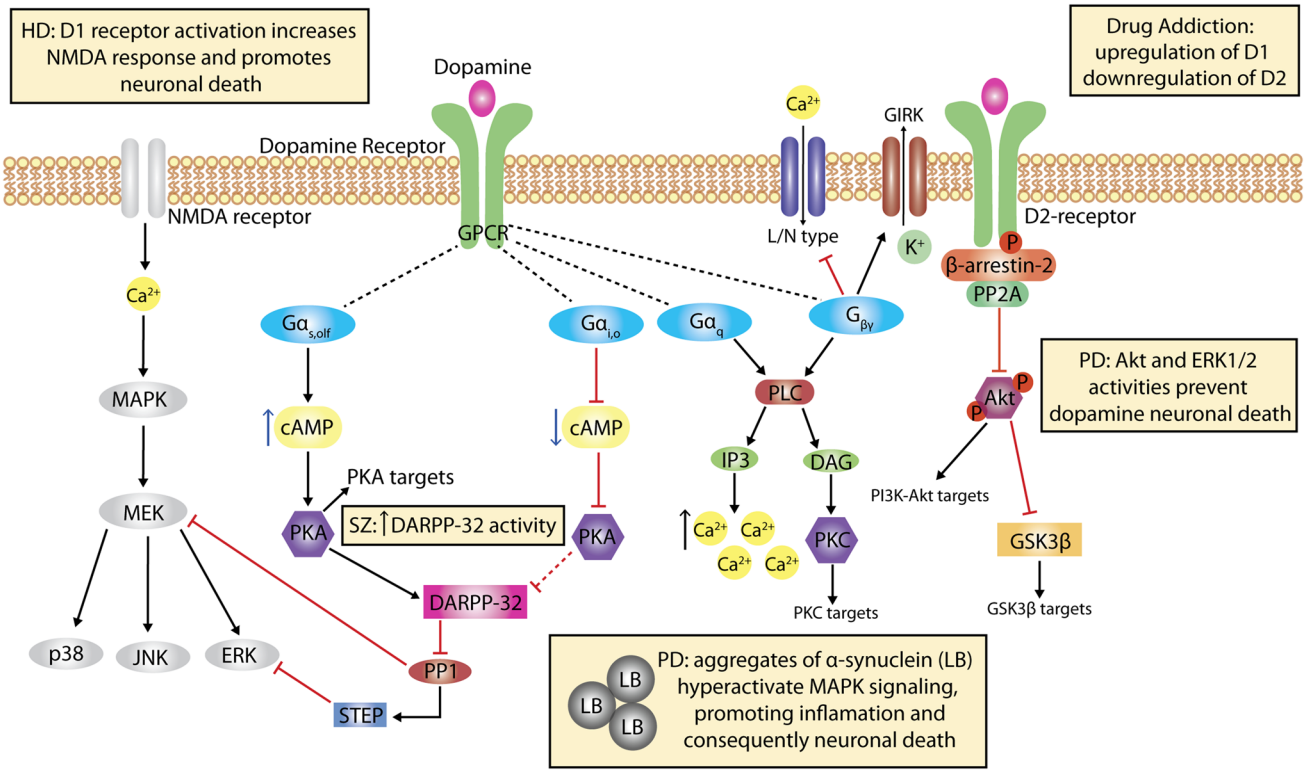

Fig. 3 Dopamine receptor signaling pathways and associated diseases. The main aspects of dopamine signaling and involved disorders discussed in this review are summarized. Dopamine receptors are in the super family of GPCRs associated with different types of G proteins. D1-like (D1 and D5) receptors 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 $G\alpha_q$, $G\beta\gamma$, 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 DARRP-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 DARRP-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 DARRP-32 at Thr34 can be impacted by other phosphosites in DARRP-32. Casein kinase 1 (CK1) phosphorylates DARRP-32 Ser137 which reduces Thr34 phosphorylation by PKA (Desdouits 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 $G\alpha_q$ 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 $G\alpha_q$ 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 $G\alpha_q$ protein (Sahu et al. 2009, So et al. 2009); D1-D2 receptors heterodimers, which also elicits $G\alpha_q$ protein (Lee et al. 2004; Rashid et al. 2007); and Gβγ 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 Gβγ 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 Gα-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; Celver 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 GSK3α and GSK3β, 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 D_1, D_2, and D_3 (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 D_2 agonists can depress the monosynaptic reflex amplitude, dependent on D_3 receptors, since this effect was absent in D_3 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 (Schrag 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 associate 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 (Baracskay 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 (Noaín 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'Evaluation 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.

References

Agnati LF, Zoli M, Strömberg I, Fuxe K (1995) Intercellular communication in the brain: wiring versus volume transmission. Neuroscience 69:711–726

Aguayo LG, Grossie J (1994) Dopamine inhibits a sustained calcium current through activation of alpha adrenergic receptors and a GTP-binding protein in adult rat sympathetic neurons. J Pharmacol Exp Ther 269:503–508

Aguirre P, Urrutia P, Tapia V et al (2012) The dopamine metabolite aminochrome inhibits mitochondrial complex I and modifies the expression of iron transporters DMT1 and FPN1. Biometals 25:795–803

Altar CA, Hunt RA, Jurata LW et al (2008) Insulin, IGF-1, and muscarinic agonists modulate schizophrenia-associated genes in human neuroblastoma cells. Biol Psychiatry 64:1077–1087. https://doi.org/10.1016/j.biopsych.2008.08.031

Andén N-E, Corrodi H, Dahlström A et al (1966) Effects of tyrosine hydroxylase inhibition on the amine levels of central monoamine neurons. Life Sci 5:561–568

Andretic R, van Swinderen B, Greenspan RJ (2005) Dopaminergic modulation of arousal in Drosophila. Curr Biol 15:1165–1175

Andrews ZB, Kokay IC, Grattan DR (2001) Dissociation of prolactin secretion from tuberoinfundibular dopamine activity in late pregnant rats. Endocrinology 142:2719–2724. https://doi.org/10.1210/endo.142.6.8196

Angers S, Salahpour A, Bouvier M (2002) Dimerization: an emerging concept for G protein-coupled receptor ontogeny and function. Annu Rev Pharmacol Toxicol 42:409–435. https://doi.org/10.1146/annurev.pharmtox.42.091701.082314

Anlauf M, Schäfer MKH, Eiden L, Weihe E (2003) Chemical coding of the human gastrointestinal nervous system: Cholinergic, VIPergic, and catecholaminergic phenotypes. J Comp Neurol 459:90–111. https://doi.org/10.1002/cne.10599

Aosaki T, Kiuchi K, Kawaguchi Y (1998) Dopamine D1-like receptor activation excites rat striatal large aspiny neurons in vitro. J Neurosci 18:5180–5190

Aperia AC (2000) Intrarenal dopamine: a key signal in the interactive regulation of sodium metabolism. Annu Rev Physiol 62:621–647

Arbogast LA, Voogt JL (1996) The responsiveness of tuberoinfundibular dopaminergic neurons to prolactin feedback is diminished between early lactation and midlactation in the rat. Endocrinology 137:47–54. https://doi.org/10.1210/endo.137.1.8536641

Arnsten AF, Dudley AG (2005) Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: relevance to therapeutic effects

in Attention Deficit Hyperactivity Disorder. Behav brain Funct 1:2. https://doi.org/10.1186/1744-9081-1-2
Arnt J, Scheel-Krüger J (1979) GABA in the ventral tegmental area: differential regional effects on locomotion, aggression and food intake after microinjection of GABA agonists and antagonists. Life Sci 25:1351–1360
Arriagada C, Paris I, de las Matas MJS et al (2004) On the neurotoxicity mechanism of leukoaminochrome o-semiquinone radical derived from dopamine oxidation: mitochondria damage, necrosis, and hydroxyl radical formation. Neurobiol Dis 16:468–477
Arriza JL, Dawson TM, Simerly RB et al (1992) The G-protein-coupled receptor kinases beta ARK1 and beta ARK2 are widely distributed at synapses in rat brain. J Neurosci 12:4045–4055
Asif-Malik A, Hoener MC, Canales JJ (2017) Interaction between the trace amine-associated receptor 1 and the dopamine D2 receptor controls cocaine's neurochemical actions. Sci Rep 7:13901
Aston-Jones G (2005) Brain structures and receptors involved in alertness. Sleep Med 6:S3–S7
Attwell D, Barbour B, Szatkowski M (1993) Nonvesicular release of neurotransmitter. Neuron 11:401–407
Baik J-H (2013a) Dopamine Signaling in reward-related behaviors. Front Neural Circuits 7:1–16. https://doi.org/10.3389/fncir.2013.00152
Baik J-H (2013b) Dopamine signaling in food addiction: role of dopamine D2 receptors. BMB Rep 46:519
Baracskay KL, Haroutunian V, Meador-Woodruff JH (2006) Dopamine receptor signaling molecules are altered in elderly schizophrenic cortex. Synapse 60:271–279
Bara-Jimenez W, Aksu M, Graham B et al (2000) Periodic limb movements in sleep state-dependent excitability of the spinal flexor reflex. Neurology 54:1609–1616
Bardo MT, Donohew RL, Harrington NG (1996) Psychobiology of novelty seeking and drug seeking behavior. Behav Brain Res 77:23–43
Barker RA, Parmar M, Studer L, Takahashi J (2017) Human trials of stem cell-derived dopamine neurons for Parkinson's disease: dawn of a new era. Cell Stem Cell 21:569–573. https://doi.org/10.1016/j.stem.2017.09.014
Barraud Q, Obeid I, Aubert I et al (2010) Neuroanatomical study of the A11 diencephalospinal pathway in the non-human primate. PLoS ONE 5:e13306
Bartfai T, Iverfeldt K, Fisone G, Serfozo P (1988) Regulation of the release of coexisting neurotransmitters. Annu Rev Pharmacol Toxicol 28:285–310
Basu S, Dasgupta PS (2000) Dopamine, a neurotransmitter, influences the immune system. J Neuroimmunol 102:113–124
Bateup HS, Svenningsson P, Kuroiwa M et al (2008) Cell type-specific regulation of DARPP-32 phosphorylation by psychostimulant and antipsychotic drugs. Nat Neurosci 11:932–939. https://doi.org/10.1038/nn.2153
Beaulieu J-M (2011) Beyond cAMP: the regulation of Akt and GSK3 by dopamine receptors. Front Mol Neurosci 4:1–13. https://doi.org/10.3389/fnmol.2011.00038
Beaulieu J-M, Gainetdinov RR (2011) The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev 63:182–217
Beaulieu J-M, Sotnikova TD, Yao W-D et al (2004) Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade. Proc Natl Acad Sci 101:5099–5104. https://doi.org/10.1073/pnas.0307921101
Beaulieu JM, Sotnikova TD, Marion S et al (2005) An Akt/β-arrestin 2/PP2A signaling complex mediates dopaminergic neurotransmission and behavior. Cell 122:261–273. https://doi.org/10.1016/j.cell.2005.05.012
Beaulieu J-M, Tirotta E, Sotnikova TD et al (2007) Regulation of Akt signaling by D2 and D3 dopamine receptors in vivo. J Neurosci 27:881–885. https://doi.org/10.1523/JNEUROSCI.5074-06.2007
Beaulieu J-M, Gainetdinov RR, Caron MG (2009) Akt/GSK3 signaling in the action of psychotropic drugs. Annu Rev Pharmacol Toxicol 49:327–347. https://doi.org/10.1146/annurev.pharmtox.011008.145634
Beaulieu JM, Espinoza S, Gainetdinov RR (2015) Dopamine receptors—IUPHAR review 13. Br J Pharmacol 172:1–23. https://doi.org/10.1111/bph.12906
Beilina A, Cookson MR (2016) Genes associated with Parkinson's disease: regulation of autophagy and beyond. J Neurochem 139 Suppl:91–107. https://doi.org/10.1111/jnc.13266
Ben-Jonathan N, Hnasko R (2001) Dopamine as a prolactin (PRL) inhibitor. Endocr Rev 22:724–763. https://doi.org/10.1210/edrv.22.6.0451
Beom S, Cheong D, Torres G et al (2004) Comparative studies of molecular mechanisms of dopamine D2 and D3 receptors for the activation of extracellular signal-regulated kinase. J Biol Chem 279:28304–28314. https://doi.org/10.1074/jbc.M403899200
Berman DM, Gilman AG (1998) Mammalian RGS proteins: barbarians at the gate. J Biol Chem 273:1269–1272. https://doi.org/10.1074/jbc.273.3.1269
Berridge MJ (2009) Inositol trisphosphate and calcium signalling mechanisms. Biochim Biophys Acta 1793:933–940. https://doi.org/10.1016/j.bbamcr.2008.10.005
Berridge MJ (2016) The inositol trisphosphate/calcium signaling pathway in health and disease. Physiol Rev 96:1261–1296. https://doi.org/10.1152/physrev.00006.2016
Berridge KC, Kringelbach ML (2008) Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology 199:457–480
Bertorello AM, Hopfield JF, Aperia A, Greengard P (1990) Inhibition by dopamine of (Na(+) + K+)ATPase activity in neostriatal neurons through D1 and D2 dopamine receptor synergism. Nature 347:386–388. https://doi.org/10.1038/347386a0
Bibb JA, Snyder GL, Nishi A et al (1999) Phosphorylation of DARPP-32 by Cdk5 modulates dopamine signalling in neurons. Nature 402:669–671. https://doi.org/10.1038/45251
Biederman J (2005) Attention-deficit/hyperactivity disorder: a selective overview. Biol Psychiatry 57:1215–1220
Bilder RM, Volavka J, Lachman HM, Grace AA (2004) The catechol-*O*-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology 29:1943–1961. https://doi.org/10.1038/sj.npp.1300542
Bjo A, Lindvall O, Nobin A et al (1975) Evidence of an incerto-hypothalamic dopamine neurone system in the rat. Brain Res 89:29–42
Borowsky B, Adham N, Jones KA et al (2001) Trace amines: identification of a family of mammalian G protein-coupled receptors. Proc Natl Acad Sci 98:8966–8971
Bozzi Y, Borrelli E (2006) Dopamine in neurotoxicity and neuroprotection: what do D2 receptors have to do with it? Trends Neurosci 29:167–174
Bromek E, Haduch A, Gołembiowska K, Daniel WA (2011) Cytochrome P450 mediates dopamine formation in the brain in vivo. J Neurochem 118:806–815
Brown GM, Krigstein E, Dankova J, Hornykiewicz O (1972) Relationship between hypothalamic and median eminence catecholamines and thyroid function. Neuroendocrinology 10:207–217
Buckholtz JW, Treadway MT, Cowan RL et al (2010) Dopaminergic network differences in human impulsivity. Science 329:532
Burchett S (2000) Regulators of G protein signaling: a bestiary of modular protein binding domains [In Process Citation]. J Neurochem 75:1335–1351

Burt DR, Enna SJ, Creese I, Snyder SH (1975) Dopamine receptor binding in the corpus striatum of mammalian brain. Proc Natl Acad Sci U S A 72:4655–4659. https://doi.org/10.1073/pnas.72.11.4655

Bychkov E, Zurkovsky L, Garret MB et al (2012) Distinct cellular and subcellular distributions of G protein-coupled receptor kinase and arrestin isoforms in the striatum. PLoS ONE 7:e48912. https://doi.org/10.1371/journal.pone.0048912

Cachope R, Cheer JF (2014) Local control of striatal dopamine release. Front Behav Neurosci 8:188

Cahill E, Salery M, Vanhoutte P, Caboche J (2014) Convergence of dopamine and glutamate signaling onto striatal ERK activation in response to drugs of abuse. Front Pharmacol 4 JAN:1–13. https://doi.org/10.3389/fphar.2013.00172

Calabresi P, Centonze D, Bernardi G (2000) Electrophysiology of dopamine in normal and denervated striatal neurons. Trends Neurosci 23:S57–S63

Calabresi P, Picconi B, Tozzi A et al (2014) Direct and indirect pathways of basal ganglia: a critical reappraisal. Nat Neurosci 17:1022

Carboni E, Silvagni A (2004) Dopamine reuptake by norepinephrine neurons: exception or rule? Crit Rev Neurobiol 16

Carboni E, Silvagni A, Vacca C, Di Chiara G (2006) Cumulative effect of norepinephrine and dopamine carrier blockade on extracellular dopamine increase in the nucleus accumbens shell, bed nucleus of stria terminalis and prefrontal cortex. J Neurochem 96:473–481

Cardinal RN, Pennicott DR, Lakmali C et al (2001) Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science 292:2499–2501

Carlezon WA Jr, Thomas MJ (2009) Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis. Neuropharmacology 56:122–132

Carli M, Evenden JL, Robbins TW (1985) Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not sensory attention. Nature 313:679

Carlsson M, Carlsson A (1990) Interactions between glutamatergic and monoaminergic systems within the basal ganglia-implications for schizophrenia and Parkinson's disease. Trends Neurosci 13:272–276

Carlsson A, Lindqvist M, Magnusson TOR (1957) 3, 4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature 180:1200

Carman CV, Benovic JL (1998) G-protein-coupled receptors: turn-ons and turn-offs. Curr Opin Neurobiol 8:335–344. https://doi.org/10.1016/S0959-4388(98)80058-5

Carrick WT, Burks B, Cairns MJ, Kocerha J (2016) Noncoding RNA regulation of dopamine signaling in diseases of the central nervous system. Front Mol Biosci 3:1–8. https://doi.org/10.3389/fmolb.2016.00069

Castellanos FX, Tannock R (2002) Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 3:617. https://doi.org/10.1038/nrn896

Castle DJ, Murray RM (1991) The neurodevelopmental basis of sex differences in schizophrenia. Psychol Med 21:565–575

Celver J, Sharma M, Kovoor A (2010) RGS9-2 mediates specific inhibition of agonist-induced internalization of D2-dopamine receptors. J Neurochem 114:739–749. https://doi.org/10.1111/j.1471-4159.2010.06805.x

Cenci MA (2007) Dopamine dysregulation of movement control in L-DOPA-induced dyskinesia. Trends Neurosci 30:236–243

Cepeda C, Murphy KPS, Parent M, Levine MS (2014) The role of dopamine in Huntington's disease. Prog Brain Res 211:235–254

Champagne F, Chretien P, Stevenson C et al (2004) Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. J Neurosci 24:4113–4123. https://doi.org/10.1523/JNEUROSCI.5322-03.2004

Chang L, Karin M (2001) Mammalian MAP kinase signalling cascades. Nature 410:37–40. https://doi.org/10.1038/35065000

Chang D, Nalls MA, Hallgrimsdottir IB et al (2017) A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. Nat Genet 49:1511–1516. https://doi.org/10.1038/ng.3955

Chasse SA, Dohlman HG (2003) RGS proteins: G protein-coupled receptors meet their match. Assay Drug Dev Technol 1:357–364. https://doi.org/10.1089/154065803764958649

Chen J, Rusnak M, Luedtke RR, Sidhu A (2004) D1 dopamine receptor mediates dopamine-induced cytotoxicity via the ERK signal cascade. J Biol Chem 279:39317–39330. https://doi.org/10.1074/jbc.M403891200

Chen J, Song J, Yuan P et al (2011) Orientation and cellular distribution of membrane-bound catechol-*O*-methyltransferase in cortical neurons: implications for drug development. J Biol Chem 286:34752–34760

Cheng H, Ulane Christina M, Burke Robert E (2010) Clinical progression in Parkinson disease and the neurobiology of axons. Ann Neurol 67:715–725. https://doi.org/10.1002/ana.21995

Chio CL, Lajiness ME, Huff RM (1994) Activation of heterologously expressed D3 dopamine receptors: comparison with D2 dopamine receptors. Mol Pharmacol 45:51–60

Choi EY, Jeong D, Park KW, Baik JH (1999) G protein-mediated mitogen-activated protein kinase activation by two dopamine D2 receptors. Biochem Biophys Res Commun 256:33–40

Christenson JG, Dairman W, Udenfriend S (1970) Preparation and properties of a homogeneous aromatic L-amino acid decarboxylase from hog kidney. Arch Biochem Biophys 141:356–367

Chrousos GP (2009) Stress and disorders of the stress system. Nat Rev Endocrinol 5:374

Citrome L (2013) A review of the pharmacology, efficacy and tolerability of recently approved and upcoming oral antipsychotics: an evidence-based medicine approach. CNS Drugs 27:879–911. https://doi.org/10.1007/s40263-013-0105-7

Citrome L (2015) Brexpiprazole: a new dopamine D2 receptor partial agonist for the treatment of schizophrenia and major depressive disorder. Drugs Today 51:397–414. https://doi.org/10.1358/dot.2015.51.7.2358605

Clemens S, Hochman S (2004) Conversion of the modulatory actions of dopamine on spinal reflexes from depression to facilitation in D3 receptor knock-out mice. J Neurosci 24:11337–11345

Clemens S, Rye D, Hochman S (2006) Restless legs syndrome Revisiting the dopamine hypothesis from the spinal cord perspective. Neurology 67:125–130

Cohen I, Todd RD, Harmon S, O'Malley KL (1992) Photoreceptors of mouse retinas possess D4 receptors coupled to adenylate cyclase. Proc Natl Acad Sci USA 89:12093–12097. https://doi.org/10.1073/pnas.89.24.12093

Colbran RJ, Brown AM (2004) Calcium/calmodulin-dependent protein kinase II and synaptic plasticity. Curr Opin Neurobiol 14:318–327. https://doi.org/10.1016/j.conb.2004.05.008

Contreras F, Fouillioux C, Bol\'\ivar A et al (2002) Dopamine, hypertension and obesity. J Hum Hypertens 16:S13

Cornil CA, Balthazart J, Motte P et al (2002) Dopamine activates noradrenergic receptors in the preoptic area. J Neurosci 22:9320–9330

Cornil CA, Castelino CB, Ball GF (2008) Dopamine binds to alpha2-adrenergic receptors in the song control system of zebra finches (Taeniopygia guttata). J Chem Neuroanat 35:202–215

Cross D, Alessi DR, Cohen P et al (1995) Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature 378:785–789. https://doi.org/10.1038/378785a0

Crowley WR (2015) Neuroendocrine regulation of lactation and milk production. Compr Physiol 5:255–291. https://doi.org/10.1002/cphy.c140029

Cunha-Filho JS, Gross JL, Lemos NA et al (2002) Prolactin and growth hormone secretion after thyrotrophin-releasing hormone infusion and dopaminergic (DA2) blockade in infertile patients with minimal/mild endometriosis. Hum Reprod 17:960–965

Cyr M, Sotnikova TD, Gainetdinov RR, Caron MG (2006) Dopamine enhances motor and neuropathological consequences of polyglutamine expanded huntingtin. FASEB J 20:2541–2543

Dahlström A, Fuxe K (1964) A method for the demonstration of monoamine-containing nerve fibres in the central nervous system. Acta Physiol 60:293–294

Dal Toso R, Sommer B, Ewert M et al (1989) The dopamine D2 receptor: two molecular forms generated by alternative splicing. Embo J 8:4025–4034

Dale H (1935) Pharmacology and nerve-endings: Walter Ernest Dixon Memorial Lecture. Proc R Soc Med 28:319–332

Dale H (1937) Transmission of nervous effects by acetylcholine: Harvey Lecture, May 20, 1937. Bull N Y Acad Med 13:379

Damier P, Kastner A, Agid Y, Hirsch EC (1996) Does monoamine oxidase type B play a role in dopaminergic nerve cell death in Parkinson's disease? Neurology 46:1262

Damsma G, Pfaus JG, Wenkstern D et al (1992) Sexual behavior increases dopamine transmission in the nucleus accumbens and striatum of male rats: comparison with novelty and locomotion. Behav Neurosci 106:181

Dauer W, Przedborski S (2003) Parkinson's disease: mechanisms and models. Neuron 39:889–909

De Deurwaerdère P (2016) Cariprazine: new dopamine biased agonist for neuropsychiatry disorders. Drugs of Today 52:97–110. https://doi.org/10.1358/dot.2016.52.2.2461868

De Mei C, Ramos M, Iitaka C, Borrelli E (2009) Getting specialized: presynaptic and postsynaptic dopamine D2 receptors. Curr Opin Pharmacol 9:53–58. https://doi.org/10.1016/j.coph.2008.12.002

Demarest KT, McKay DW, Riegle GD, Moore KE (1983) Biochemical indices of tuberoinfundibular dopaminergic neuronal activity during lactation: a lack of response to prolactin. Neuroendocrinology 36:130–137

Demarest KT, Riegle GD, Moore KE (1984) Prolactin-induced activation of tuberoinfundibular dopaminergic neurons: evidence for both a rapid 'tonic' and a delayed 'delayed' component. Neuroendocrinology 38:467–475

Deming JD, Shin JA, Lim K et al (2015) Dopamine receptor D4 internalization requires a beta-arrestin and a visual arrestin. Cell Signal 27:2002–2013. https://doi.org/10.1016/j.cellsig.2015.06.008

Depue RA, Collins PF (1999) Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behav Brain Sci 22:491–517

Desdouits F, Siciliano JC, Greengard P, Girault JA (1995) Dopamine- and cAMP-regulated phosphoprotein DARPP-32: phosphorylation of Ser-137 by casein kinase I inhibits dephosphorylation of Thr-34 by calcineurin. Proc Natl Acad Sci 92:2682–2685. https://doi.org/10.1073/pnas.92.7.2682

Devoto P, Flore G (2006) On the origin of cortical dopamine: is it a co-transmitter in noradrenergic neurons? Curr Neuropharmacol 4:115–125

Devoto P, Flore G, Saba P et al (2015) Selective inhibition of dopamine-beta-hydroxylase enhances dopamine release from noradrenergic terminals in the medial prefrontal cortex. Brain Behav 5:e00393

DeWire SM, Ahn S, Lefkowitz RJ, Shenoy SK (2007) Beta-arrestins and cell signaling. Annu Rev Physiol 69:483–510. https://doi.org/10.1146/annurev.ph.69.013107.100021

Dexter DT, Jenner P (2013) Parkinson disease: from pathology to molecular disease mechanisms. Free Radic Biol Med 62:132–144

Di GC, Tanda GL, Frau R, Carboni E (1992) Heterologous monoamine reuptake: lack of transmitter specificity of neuron-specific carriers. Neurochem Int 20:231S–235S

Dickey AS, La Spada AR (2017) Therapy development in Huntington disease: from current strategies to emerging opportunities. Am J Med Genet Part A 176:842–861

Dingledine R, Borges K, Bowie D, Traynelis SF (1999) The glutamate receptor ion channels. Pharmacol Rev 51:7–62

Doi M, Yujnovsky I, Hirayama J et al (2006) Impaired light masking in dopamine D2 receptor-null mice. Nat Neurosci 9:732–734. https://doi.org/10.1038/nn1711

Dolmetsch RE, Pajvani U, Fife K et al (2001) Signaling to the nucleus by an L-type calcium channel- calmodulin complex through the MAP kinase pathway. Science 294:333–339. https://doi.org/10.1126/science.1063395

Ebaugh FG (1923) Neuropsychiatric sequelae of acute epidemic encephalitis in children. Am J Dis Child 25:89–97

Eiden LE, Weihe E (2011) VMAT2: a dynamic regulator of brain monoaminergic neuronal function interacting with drugs of abuse. Ann N Y Acad Sci 1216:86–98. https://doi.org/10.1111/j.1749-6632.2010.05906.x

Eiden LE, Schäfer MKH, Weihe E, Schütz B (2004) The vesicular amine transporter family (SLC18): Amine/proton antiporters required for vesicular accumulation and regulated exocytotic secretion of monoamines and acetylcholine. Pflugers Arch Eur J Physiol 447:636–640. https://doi.org/10.1007/s00424-003-1100-5

Eisenhofer G, Kopin IJ, Goldstein DS (2004) Catecholamine metabolism: a contemporary view with implications for physiology and medicine. Pharmacol Rev 56:331

Elliott TR (1905) The action of adrenalin. J Physiol 32:401–467

Erdtmann-Vourliotis M, Mayer P, Ammon S et al (2001) Distribution of G-protein-coupled receptor kinase (GRK) isoforms 2, 3, 5 and 6 mRNA in the rat brain. Brain Res Mol Brain Res 95:129–137. https://doi.org/10.1016/S0006-8993(01)03046-3

Espinoza S, Salahpour A, Masri B et al (2011) Functional interaction between trace amine-associated receptor 1 and dopamine D2 receptor. Mol Pharmacol 80:416–425

Fallon JH, Moore RY (1978) Catecholamine innervation of the basal forebrain III. Olfactory bulb, anterior olfactory nuclei, olfactory tubercle and piriform cortex. J Comp Neurol 180:533–544

Fambrough DM, Drachman DB, Satyamurti S (1973) Neuromuscular junction in myasthenia gravis: decreased acetylcholine receptors. Science 182:293–295

Faraone SV, Sergeant J, Gillberg C, Biederman J (2003) The worldwide prevalence of ADHD: is it an American condition? World Psychiatry 2:104

Faraone SV, Perlis RH, Doyle AE et al (2005) Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1313–1323

Fearnley JM, Lees AJ (1991) Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114 (Pt 5:2283–2301

Felder CC, Jose PA, Axelrod J (1989) The dopamine-1 agonist, SKF 82526, stimulates phospholipase-C activity independent of adenylate cyclase. J Pharmacol Exp Ther 248:171–175

Felicio AC, Shih MC, Godeiro-Junior C et al (2009) Molecular imaging studies in Parkinson disease: reducing diagnostic uncertainty. Neurologist 15:6–16

Ferguson SS (2001) Evolving concepts in G protein-coupled receptor endocytosis: the role in receptor desensitization and signaling. Pharmacol Rev 53:1–24

Ferguson CS, Tyndale RF (2011) Cytochrome P450 enzymes in the brain: emerging evidence of biological significance. Trends Pharmacol Sci 32:708–714

Fernstrom JD, Fernstrom MH (2007) Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain. J Nutr 137:1539S–1547S

Fienberg AA, Hiroi N, Mermelstein PG et al (1998) DARPP-32: regulator of the efficacy of dopaminergic neurotransmission. Science 281:838–842

Fleming AS, Suh EJ, Korsmit M, Rusak B (1994) Activation of Fos-like immunoreactivity in the medial preoptic area and limbic structures of maternal and social interactions in rats. Behav Neurosci 108:724

Flores-Barrera E, Thomases DR, Heng LJ et al (2014) Late adolescent expression of GluN2B transmission in the prefrontal cortex is input-specific and requires postsynaptic protein kinase A and D1 dopamine receptor signaling. Biol Psychiatry 75:508–516. https://doi.org/10.1016/j.biopsych.2013.07.033

Floresco SB, Maric TT (2007) Dopaminergic regulation of inhibitory and excitatory transmission in the basolateral amygdala–prefrontal cortical pathway. J Neurosci 27:2045–2057

Floresco SB, West AR, Ash B et al (2003) Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat Neurosci 6:968

Foster DJ, Conn PJ (2017) Allosteric modulation of GPCRs: new insights and potential utility for treatment of schizophrenia and other CNS disorders. Neuron 94:431–446. https://doi.org/10.1016/j.neuron.2017.03.016

Frankel JS, Schwartz TL (2017) Brexpiprazole and cariprazine: distinguishing two new atypical antipsychotics from the original dopamine stabilizer aripiprazole. Ther Adv Psychopharmacol 7:29–41. https://doi.org/10.1177/2045125316672136

Frankle WG, Laruelle M (2002) Neuroreceptor imaging in psychiatric disorders. Ann Nucl Med 16:437

Freedman R (2003) Schizophrenia. N Engl J Med 349:1738–1749. https://doi.org/10.1056/NEJMra035458

Freyberg Z, Ferrando SJ, Javitch JA (2010) Roles of the Akt/GSK-3 and Wnt signaling pathways in schizophrenia and antipsychotic drug action. Am J Psychiatry 167:388–396. https://doi.org/10.1176/appi.ajp.2009.08121873

Gainetdinov RR, Wetsel WC, Jones SR et al (1999) Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. Science 283:397–401

Gainetdinov RR, Bohn LM, Sotnikova TD et al (2003) Dopaminergic supersensitivity in G protein-coupled receptor kinase 6-deficient mice. Neuron 38:291–303. https://doi.org/10.1016/S0896-6273(03)00192-2

Gandhi S, Wood NW (2005) Molecular pathogenesis of Parkinson's disease. Hum Mol Genet 14:2749–2755

Gao Y, Peterson S, Masri B et al (2015) Cariprazine exerts antimanic properties and interferes with dopamine D2receptor β-arrestin interactions. Pharmacol Res Perspect 3:1–10. https://doi.org/10.1002/prp2.73

Gardner EL (2011) Addiction and brain reward and antireward pathways. Adv Psychosom Med 30:22–60

Gardner B, Hall DA, Strange PG (1996) Pharmacological analysis of dopamine stimulation of [35S]-GTP gamma binding via human D2short and D2long dopamine receptors expressed in recombinant cells. Br J Pharmacol 118:1544–1550

Gardner BR, Hall DA, Strange PG (1997) Agonist action at D2 (short) dopamine receptors determined in ligand binding and functional assays. J Neurochem 69:2589–2598

Garris PA, Ciolkowski EL, Pastore P, Wightman RM (1994) Efflux of dopamine from the synaptic cleft in the nucleus accumbens of the rat brain. J Neurosci 14:6084–6093

Gasbarri A, Sulli A, Packard MG (1997) The dopaminergic mesencephalic projections to the hippocampal formation in the rat. Prog Neuro-Psychopharmacol Biol Psychiatry 21:1–22

Gerfen CR, Surmeier DJ (2011) Modulation of striatal projection systems by dopamine. Annu Rev Neurosci 34:441–466

Gibb WR, Lees AJ (1988) The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 51:745–752

Gingrich JA, Caron MG (1993) Recent advances in the molecular biology of dopamine receptors. Annu Rev Neurosci 16:299–321

Giordano AL, Johnson AE, Rosenblatt JS (1990) Haloperidol-induced disruption of retrieval behavior and reversal with apomorphine in lactating rats. Physiol Behav 48:211–214

Girault JA, Hemmings HCJ, Williams KR et al (1989) Phosphorylation of DARPP-32, a dopamine- and cAMP-regulated phosphoprotein, by casein kinase II. J Biol Chem 264:21748–21759

Giros B, Sokoloff P, Martres MP et al (1989) Alternative splicing directs the expression of two D2 dopamine receptor isoforms. Nature 342:923–926. https://doi.org/10.1038/342923a0

Giros B, Martres MP, Pilon C et al (1991) Shorter variants of the D3dopamine receptor produced through various patterns of alternative splicing. Biochem Biophys Res Commun 176:1584–1592. https://doi.org/10.1016/0006-291X(91)90469-N

Giros B, Jaber M, Jones SR et al (1996) Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature 379:606–612

Gizer IR, Ficks C, Waldman ID (2009) Candidate gene studies of ADHD: a meta-analytic review. Hum Genet 126:51–90

Gold JM, Waltz JA, Matveeva TM et al (2012) Negative symptoms and the failure to represent the expected reward value of actions: behavioral and computational modeling evidence. Arch Gen Psychiatry 69:129–138

Goldberg LI, Volkman PH, Kohli JD (1978) A comparison of the vascular dopamine receptor with other dopamine receptors. Annu Rev Pharmacol Toxicol 18:57–79

Gomez-Sintes R, Bortolozzi A, Artigas F, Lucas JJ (2014) Reduced striatal dopamine DA D2 receptor function in dominant-negative GSK-3 transgenic mice. Eur Neuropsychopharmacol 24:1524–1533. https://doi.org/10.1016/j.euroneuro.2014.07.004

Goto Y, Otani S, Grace AA (2007) The Yin and Yang of dopamine release: a new perspective. Neuropharmacology 53:583–587. https://doi.org/10.1016/j.neuropharm.2007.07.007

Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 41:1–24

Grace AA, Floresco SB, Goto Y, Lodge DJ (2007) Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci 30:220–227. https://doi.org/10.1016/j.tins.2007.03.003

Grattan DR, Averill RLW (1995) Absence of short-loop autoregulation of prolactin during late pregnancy in the rat. Brain Res Bull 36:413–416. https://doi.org/10.1016/0361-9230(94)00216-N

Graybiel AM (1997) The basal ganglia and cognitive pattern generators. Schizophr Bull 23:459

Graybiel AM (2000) The basal ganglia. Curr Biol 10:R509–R511

Greengard P (2001) The neurobiology of slow synaptic transmission. Science 294:1024–1030. https://doi.org/10.1126/science.294.5544.1024

Gregerson KA, Chuknyiska R, Golesorkhi N (1994) Stimulation of prolactin release by dopamine withdrawal: role of calcium influx. Am J Physiol 267:E789–E794

Gresch PJ, Sved AF, Zigmond MJ, Finlay JM (1995) Local influence of endogenous norepinephrine on extracellular dopamine in rat medial prefrontal cortex. J Neurochem 65:111–116

Grossman GH, Mistlberger RE, Antle MC et al (2000) Sleep deprivation stimulates serotonin release in the suprachiasmatic nucleus. Neuroreport 11:1929–1932

Gu H (2013) Stem cell-derived neurons for the treatment of neurodegenerative diseases. Clin Pharmacol Biopharm 2:1000111/1–1000111/4. https://doi.org/10.4172/2167-065X.1000111

Gudelsky GA (1981) Tuberoinfundibular dopamine neurons and the regulation of prolactin secretion. Psychoneuroendocrinology 6:3–16

Gudelsky G, Porter J (1980) Release of dopamine from tuberoinfundibular neurons into pituitary stalk blood after prolactin or haloperidol administration. Endocrinology 106:526–529

Guillot TS, Miller GW (2009) Protective actions of the vesicular monoamine transporter 2 (VMAT2) in monoaminergic neurons. Mol Neurobiol 39:149–170. https://doi.org/10.1007/s12035-009-8059-y

Gurevich VV, Gurevich EV (2006) The structural basis of arrestin-mediated regulation of G-protein-coupled receptors. Pharmacol Ther 110:465–502. https://doi.org/10.1016/j.pharmthera.2005.09.008

Gurevich VV, Gurevich EV (2014) Overview of different mechanisms of arrestin-mediated signaling. Curr Protoc Pharmacol 67:1–9. https://doi.org/10.1002/0471141755.ph0210s67

Gurevich EV, Benovic JL, Gurevich VV (2002) Arrestin2 and arrestin3 are differentially expressed in the rat brain during postnatal development. Neuroscience 109:421–436. https://doi.org/10.1016/S0306-4522(01)00511-5

Gurevich EV, Gainetdinov RR, Gurevich VV (2016) G protein-coupled receptor kinases as regulators of dopamine receptor functions. Pharmacol Res 111:1–16. https://doi.org/10.1016/j.phrs.2016.05.010

Ha AD, Fung VSC (2012) Huntington's disease. Curr Opin Neurol 25:491–498

Ha AD, Jankovic J (2011) Exploring the correlates of intermediate CAG repeats in Huntington disease. Postgrad Med 123:116–121

Haber SN (2003) The primate basal ganglia: parallel and integrative networks. J Chem Neuroanat 26:317–330

Halpain S, Girault J-A, Greengard P (1990) Activation of NMDA receptors induces dephosphorylation of DARPP-32 in rat striatal slices. Nature 343:369–372. https://doi.org/10.1038/343369a0

Hampson EC, Vaney DI, Weiler R (1992) Dopaminergic modulation of gap junction permeability between amacrine cells in mammalian retina. J Neurosci 12:4911–4922

Hansen S (1994) Maternal behavior of female rats with 6-OHDA lesions in the ventral striatum: characterization of the pup retrieval deficit. Physiol Behav 55:615–620

Hansen S, Harthon C, Wallin E et al (1991) The effects of 6-OHDA-induced dopamine depletions in the ventral or dorsal striatum on maternal and sexual behavior in the female rat. Pharmacol Biochem Behav 39:71–77

Harrington KA, Augood SJ, Kingsbury AE et al (1996) Dopamine transporter (Dat) and synaptic vesicle amine transporter (VMAT2) gene expression in the substantia nigra of control and Parkinson's disease. Mol brain Res 36:157–162

Hasue RH, Shammah-Lagnado SJ (2002) Origin of the dopaminergic innervation of the central extended amygdala and accumbens shell: a combined retrograde tracing and immunohistochemical study in the rat. J Comp Neurol 454:15–33

Hauser DN, Hastings TG (2013) Mitochondrial dysfunction and oxidative stress in Parkinson's disease and monogenic parkinsonism. Neurobiol Dis 51:35–42. https://doi.org/10.1016/j.nbd.2012.10.011

Hemmings HC, Greengard P, Tung HYL, Cohen P (1984a) DARPP-32, a dopamine-regulated neuronal phosphoprotein, is a potent inhibitor of protein phosphatase-1. Nature 310:503–505. https://doi.org/10.1038/310503a0

Hemmings HC, Nairn AC, Greengard P (1984b) DARPP-32, a dopamine- and adenosine 3′:5′-monophosphate-regulated neuronal phosphoprotein. II. Comparison of the kinetics of phosphorylation of DARPP-32 and phosphatase inhibitor 1. J Biol Chem 259:14491–14497

Henry DJ, Hu X-T, White FJ (1998) Adaptations in the mesoaccumbens dopamine system resulting from repeated administration of dopamine D1 and D2 receptor-selective agonists: relevance to cocaine sensitization. Psychopharmacology 140:233–242

Hernandez DG, Reed X, Singleton AB (2016) Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. J Neurochem 139 Suppl:59–74. https://doi.org/10.1111/jnc.13593

Hernandez-Lopez S, Tkatch T, Perez-Garci E et al (2000) D2 dopamine receptors in striatal medium spiny neurons reduce L-type Ca2 + currents and excitability via a novel PLC[beta]1-IP3-calcineurin-signaling cascade. J Neurosci 20:8987–8995 doi: 20/24/8987 [pii]

Herrera-Soto A, Diaz-Veliz G, Mora S et al (2017) On the role of DT-diaphorase inhibition in aminochrome-induced neurotoxicity in vivo. Neurotox Res 32:134–140

Heximer SP, Blumer KJ (2007) RGS proteins: swiss army knives in seven-transmembrane domain receptor signaling networks. Sci STKE 2007:. https://doi.org/10.1126/stke.3702007pe2

Hikosaka O, Nakamura K, Sakai K, Nakahara H (2002) Central mechanisms of motor skill learning. Curr Opin Neurobiol 12:217–222

Hnasko TS, Edwards RH (2012) Neurotransmitter corelease: mechanism and physiological role. Annu Rev Physiol 74:225–243

Hohman LB (1922) Post-encephalitic behavior disorders in children. Johns Hopkins Hospt Bull 33:372–375

Hollinger S, Hepler JR (2002) Cellular regulation of RGS proteins: modulators and integrators of G protein signaling. Pharmacol Rev 54:527–559. https://doi.org/10.1124/pr.54.3.527

Holstege JC, Van Dijken H, Buijs RM et al (1996) Distribution of dopamine immunoreactivity in the rat, cat, and monkey spinal cord. J Comp Neurol 376:631–652

Horvitz JC (2000) Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96:651–656

Howes OD, McCutcheon R, Owen MJ, Murray RM (2017) The role of genes, stress, and dopamine in the development of schizophrenia. Biol Psychiatry 81:9–20. https://doi.org/10.1016/j.biopsych.2016.07.014

Hu X-T, Dong Y, Zhang X-F, White FJ (2005) Dopamine D2 receptor-activated Ca2 + signaling modulates voltage-sensitive sodium currents in rat nucleus accumbens neurons. J Neurophysiol 93:1406–1417. https://doi.org/10.1152/jn.00771.2004

Hu W, MacDonald ML, Elswick DE, Sweet RA (2015) The glutamate hypothesis of schizophrenia: evidence from human brain tissue studies. Ann N Y Acad Sci 1338:38–57

Huenchuguala S, Muñoz P, Graumann R et al (2016) DT-diaphorase protects astrocytes from aminochrome-induced toxicity. Neurotoxicology 55:10–12

Huenchuguala S, Muñoz P, Segura-Aguilar J (2017) The importance of mitophagy in maintaining mitochondrial function in U373MG Cells. Bafilomycin A1 restores aminochrome-induced mitochondrial damage. ACS Chem Neurosci 8:2247–2253

Ikemoto S (2007) Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens–olfactory tubercle complex. Brain Res Rev 56:27–78

Ikemoto S, Panksepp J (1999) The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res Rev 31:6–41

Iversen LL (1971) Role of transmitter uptake mechanisms in synaptic neurotransmission. Br J Pharmacol 41:571–591

Iversen SD, Iversen LL (2007) Dopamine: 50 years in perspective. Trends Neurosci 30:188–193

Jakel RJ, Maragos WF (2000) Neuronal cell death in Huntington's disease: a potential role for dopamine. Trends Neurosci 23:239–245

Jones CK, Byun N, Bubser M (2012) Muscarinic and nicotinic acetylcholine receptor agonists and allosteric modulators for the treatment of schizophrenia. Neuropsychopharmacology 37:16

Jose PA, Yu PY, Yamaguchi I et al (1995) Dopamine D1 receptor regulation of phospholipase C. Hypertens Res 18(Suppl 1):S39–S42

Jose PA, Eisner GM, Felder RA (2002) Role of dopamine receptors in the kidney in the regulation of blood pressure. Curr Opin

Nephrol Hypertens 11:87–92. https://doi.org/10.1097/00041552-200201000-00013
Joyce EM, Roiser JP (2007) Cognitive heterogeneity in schizophrenia. Curr Opin Psychiatry 20:268
Kahn RS, Sommer IE, Murray RM et al (2015) Schizophrenia. Nat Rev Dis Prim 1:15067. https://doi.org/10.1038/nrdp.2015.67
Kaidanovich-Beilin O, Woodgett JR (2011) GSK-3: functional insights from cell biology and animal models. Front Mol Neurosci 4:40. https://doi.org/10.3389/fnmol.2011.00040
Kalia LV, Lang AE (2015) Parkinson's disease. Lancet 386:896–912. https://doi.org/10.1016/S0140-6736(14)61393-3
Kambeitz J, Abi-Dargham A, Kapur S, Howes OD (2014) Alterations in cortical and extrastriatal subcortical dopamine function in schizophrenia: systematic review and meta-analysis of imaging studies. Br J Psychiatry 204:420–429
Kandel E, Jessell TM, Schwartz JH et al (2013) Principles of neural science. McGraw-Hill Education, New York
Kanner BI, Schuldiner S (1987) Mechanism of transport and storage of neurotransmitter. Crit Rev Biochem 22:1–38
Kebabian JW (1978) Multiple classes of dopamine receptors in mammalian central nervous system: the involvement of dopamine-sensitive adenylyl cyclase. Life Sci 23:479–483. https://doi.org/10.1016/0024-3205(78)90157-1
Kebabian JW, Calne DB (1979) Multiple receptors for dopamine. Nature 277:93–96. https://doi.org/10.1038/277093a0
Kebabian JW, Greengard P (1971) Dopamine-sensitive adenyl cyclase: possible role in synaptic transmission. Science 174:1346–1349. https://doi.org/10.1126/science.174.4016.1346
Kebabian JW, Petzold GL, Greengard P (1972) Dopamine-sensitive adenylate cyclase in caudate nucleus of rat brain, and its similarity to the "dopamine receptor". Proc Natl Acad Sci USA 69:2145–2149. https://doi.org/10.1073/PNAS.69.8.2145
Kelley AE, Berridge KC (2002) The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci 22:3306–3311
Kenny PJ (2011) Common cellular and molecular mechanisms in obesity and drug addiction. Nat Rev Neurosci 12:638
Kim EK, Choi E-J (2010) Pathological roles of MAPK signaling pathways in human diseases. Biochim Biophys Acta (BBA) 1802:396–405
Kim SD, Fung VSC (2014) An update on Huntington's disease: from the gene to the clinic. Curr Opin Neurol 27:477–483
Kim KM, Valenzano KJ, Robinson SR et al (2001) Differential regulation of the dopamine D2 and D3 receptors by G protein-coupled receptor kinases and beta-arrestins. J Biol Chem 276:37409–37414. https://doi.org/10.1074/jbc.M106728200
Kim SJ, Kim MY, Lee EJ et al (2004) Distinct regulation of internalization and mitogen-activated protein kinase activation by two isoforms of the dopamine D2 receptor. Mol Endocrinol 18:640–652. https://doi.org/10.1210/me.2003-0066
King MM, Huang CY, Chock PB et al (1984) Mammalian brain phosphoproteins as substrates for calcineurin. J Biol Chem 259:8080–8083
Kiss B, Horvath A, Nemethy Z et al (2010) Cariprazine (RGH-188), a dopamine D3 receptor-preferring, D3/D2 dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. J Pharmacol Exp Ther 333:328–340. https://doi.org/10.1124/jpet.109.160432
Komolov KE, Benovic JL (2018) G protein-coupled receptor kinases: past, present and future. Cell Signal 41:17–24. https://doi.org/10.1016/j.cellsig.2017.07.004
Koob GF, Le Moal M (1997) Drug abuse: hedonic homeostatic dysregulation. Science 278:52–58
Koob GF, Sanna PP, Bloom FE (1998) Neuroscience of addiction. Neuron 21:467–476
Kortekaas R, Leenders KL, van Oostrom JCH et al (2005) Blood-brain barrier dysfunction in parkinsonian midbrain in vivo. Ann Neurol 57:176–179
Kovoor A, Seyffarth P, Ebert J et al (2005) D2 dopamine receptors colocalize regulator of G-protein signaling 9-2 (RGS9-2) via the RGS9 DEP domain, and RGS9 knock-out mice develop dyskinesias associated with dopamine pathways. J Neurosci 25:2157–2165. https://doi.org/10.1523/JNEUROSCI.2840-04.2005
Kravitz AV, Freeze BS, Parker PRL et al (2010) Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature 466:622
Krüger THC, Hartmann U, Schedlowski M (2005) Prolactinergic and dopaminergic mechanisms underlying sexual arousal and orgasm in humans. World J Urol 23:130–138
Kuzhikandathil EV, Yu W, Oxford GS (1998) Human dopamine D3 and D2L receptors couple to inward rectifier potassium channels in mammalian cell lines. Mol Cell Neurosci 12:390–402. https://doi.org/10.1006/mcne.1998.0722
Lange KW, Reichl S, Lange KM et al (2010) The history of attention deficit hyperactivity disorder. ADHD Atten Deficit Hyperact Disord 2:241–255
Laporte SA, Miller WE, Kim K-M, Caron MG (2002) Beta-Arrestin/AP-2 interaction in G protein-coupled receptor internalization: identification of a beta-arrestin binging site in beta 2-adaptin. J Biol Chem 277:9247–9254. https://doi.org/10.1074/jbc.M108490200
Ledonne A, Berretta N, Davoli A et al (2011) Electrophysiological effects of trace amines on mesencephalic dopaminergic neurons. Front Syst Neurosci 5:56
Lee M, O'Regan S, Moreau JL et al (2000) Regulation of the PcI7-Pho85 cyclin-cdk complex by Pho81. Mol Microbiol 38:411–422. https://doi.org/10.1046/j.1365-2958.2000.02140.x
Lee SP, So CH, Rashid AJ et al (2004) Dopamine D1 and D2 receptor co-activation generates a novel phospholipase C-mediated calcium signal. J Biol Chem 279:35671–35678. https://doi.org/10.1074/jbc.M401923200
Lee S, Hjerling-Leffler J, Zagha E et al (2010) The largest group of superficial neocortical GABAergic interneurons expresses ionotropic serotonin receptors. J Neurosci 30:16796–16808
Lee S-M, Yang Y, Mailman RB (2014) Dopamine D1 receptor signaling: does GαQ-phospholipase C actually play a role? J Pharmacol Exp Ther 351:9–17. https://doi.org/10.1124/jpet.114.214411
Leggio GM, Bucolo C, Platania CBM et al (2016) Current drug treatments targeting dopamine D3 receptor. Pharmacol Ther 165:164–177. https://doi.org/10.1016/j.pharmthera.2016.06.007
Levesque D, Diaz J, Pilon C et al (1992) Identification, characterization, and localization of the dopamine D3 receptor in rat brain using 7-[3H] hydroxy-N, N-di-n-propyl-2-aminotetralin. Proc Natl Acad Sci 89:8155–8159
Li C, Chen P, Smith MS (1999) Neuropeptide Y and tuberoinfundibular dopamine activities are altered during lactation: role of prolactin. Endocrinology 140:118–123
Li D, Sham PC, Owen MJ, He L (2006) Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). Hum Mol Genet 15:2276–2284
Li Y-C, Xi D, Roman J et al (2009) Activation of glycogen synthase kinase-3 is required for hyperdopamine and D2 receptor-mediated inhibition of synaptic NMDA receptor function in the rat prefrontal cortex. J Neurosci 29:15551–15563. https://doi.org/10.1523/JNEUROSCI.3336-09.2009
Li L, Homan KT, Vishnivetskiy SA et al (2015) G protein-coupled receptor kinases of the GRK4 protein subfamily phosphorylate inactive G protein-coupled receptors (GPCRs). J Biol Chem 290:10775–10790. https://doi.org/10.1074/jbc.M115.644773

Liang C-L, Nelson O, Yazdani U et al (2004) Inverse relationship between the contents of neuromelanin pigment and the vesicular monoamine transporter-2: human midbrain dopamine neurons. J Comp Neurol 473:97–106

Lieberman JA, Kane JM, Alvir J (1987) Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology 91:415–433

Lindemann L, Meyer CA, Jeanneau K et al (2008) Trace amine-associated receptor 1 modulates dopaminergic activity. J Pharmacol Exp Ther 324:948–956

Lindvall OL, Björklund AB, Skagerberg G (1983) Dopamine-containing neurons in the spinal cord: anatomy and some functional aspects. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc 14:255–260

Liu F, Wan Q, Pristupa ZB et al (2000) Direct protein-protein coupling enables cross-talk between dopamine D5 and gamma-aminobutyric acid A receptors. Nature 403:274–280. https://doi.org/10.1038/35002014

Liu P, Cheng H, Roberts TM, Zhao JJ (2009) Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov 8:627–644. https://doi.org/10.1038/nrd2926

Liu C, Kershberg L, Wang J et al (2018) Dopamine secretion is mediated by sparse active zone-like release sites. Cell 172:706–718. e15. https://doi.org/10.1016/j.cell.2018.01.008

Loewi O (1921) Über humorale übertragbarkeit der Herznervenwirkung. Pflüger's Arch für die gesamte Physiol des Menschen der Tiere 189:239–242

Lohse MJ, Benovic JL, Codina J et al (1990) beta-Arrestin: a protein that regulates beta-adrenergic receptor function. Science 248:1547–1550. https://doi.org/10.1126/science.2163110

Loughlin SE, Fallon JH (1983) Dopaminergic and non-dopaminergic projections to amygdala from substantia nigra and ventral tegmental area. Brain Res 262:334–338

Lozano J, Munoz P, Nore BF et al (2010) Stable expression of short interfering RNA for DT-diaphorase induces neurotoxicity. Chem Res Toxicol 23:1492–1496

Luciana M, Collins PF, Depue RA (1998) Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions. Cereb Cortex 8:218–226

Luttrell LM, Lefkowitz RJ (2002) The role of beta-arrestins in the termination and transduction of G-protein-coupled receptor signals. J Cell Sci 115:455–465. https://doi.org/10.1074/jbc.274.3.1185

Lynch WJ, Peterson AB, Sanchez V et al (2013) Exercise as a novel treatment for drug addiction: a neurobiological and stage-dependent hypothesis. Neurosci Biobehav Rev 37:1622–1644

Ma J, Long LH, Hu ZL et al (2015) Activation of D1-like receptor-dependent phosphatidylinositol signal pathway by SKF83959 inhibits voltage-gated sodium channels in cultured striatal neurons. Brain Res 1615:71–79. https://doi.org/10.1016/j.brainres.2015.04.030

MacDermott AB, Role LW, Siegelbaum SA (1999) Presynaptic ionotropic receptors and the control of transmitter release. Annu Rev Neurosci 22:443–485

MacDonald ME, Ambrose CM, Duyao MP et al (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72:971–983

Madras BK, Miller GM, Fischman AJ (2005) The dopamine transporter and attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1397–1409

Maeda K, Sugino H, Akazawa H et al (2014) Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther 350:589–604. https://doi.org/10.1124/jpet.114.213793

Magnusson JE, Fisher K (2000) The involvement of dopamine in nociception: the role of D1 and D2 receptors in the dorsolateral striatum. Brain Res 855:260–266

Maia TV, Frank MJ (2017) An integrative perspective on the role of dopamine in schizophrenia. Biol Psychiatry 81:52–66

Manger PR, Fuxe K, Ridgway SH, Siegel JM (2004) The distribution and morphological characteristics of catecholaminergic cells in the diencephalon and midbrain of the bottlenose dolphin (Tursiops truncatus). Brain Behav Evol 64:42–60

Martelli AM, Chiarini F, Evangelisti C et al (2010) The phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin signaling network and the control of normal myelopoiesis. Histol Histopathol 25:669–680

Martinez G, Weiner RI, Martinez G (1992) Dissociation of dopamine from its receptor as a signal in the pleiotropic hypothalamic regulation of prolactin secretion. Endocr Rev 13:241–245. https://doi.org/10.1210/edrv-13-2-241

Martini M, De Santis MC, Braccini L et al (2014) PI3K/AKT signaling pathway and cancer: an updated review. Ann Med 46:372–383. https://doi.org/10.3109/07853890.2014.912836

Matthews M, Nigg JT, Fair DA (2014) Attention deficit hyperactivity disorder. Curr Top Behav Neurosci 16:235–266. https://doi.org/10.1007/7854_2013_249

Meyer N, MacCabe JH (2016) Schizophrenia. Medicine (Baltimore) 44:649–653. https://doi.org/10.1016/j.mpmed.2016.08.003

Michael-Titus A, Bousselmame R, Costentin J (1990) Stimulation of dopamine D2 receptors induces an analgesia involving an opiodergic but non enkephalinergic link. Eur J Pharmacol 187:201–207

Miller GW, Gainetdinov RR, Levey AI, Caron MG (1999) Dopamine transporters and neuronal injury. Trends Pharmacol Sci 20:424–429

Miller JS, Barr JL, Harper LJ et al (2014) The GSK3 signaling pathway is activated by cocaine and is critical for cocaine conditioned reward in mice. PLoS ONE 9:. https://doi.org/10.1371/journal.pone.0088026

Milligan G (2009) G protein-coupled receptor hetero-dimerization: contribution to pharmacology and function. Br J Pharmacol 158:5–14. https://doi.org/10.1111/j.1476-5381.2009.00169.x

Missale C, Nash SR, Robinson SW et al (1998) Dopamine receptors: from structure to function. Physiol Rev 78:189–225

Missale C, Fiorentini C, Collo G, Spano P (2010) The neurobiology of dopamine receptors: evolution from the dual concept to heterodimer complexes. J Recept Signal Transduct 30:347–354. https://doi.org/10.3109/10799893.2010.506192

Mitchell HA, Weinshenker D (2010) Good night and good luck: norepinephrine in sleep pharmacology. Biochem Pharmacol 79:801–809

Mogenson GJ, Nielsen M (1984) Neuropharmacological evidence to suggest that the nucleus accumbens and subpallidal region contribute to exploratory locomotion. Behav Neural Biol 42:52–60

Mogenson GJ, Wu M, Jones DL (1980) Locomotor activity elicited by injections of picrotoxin into the ventral tegmental area is attenuated by injections of GABA into the globus pallidus. Brain Res 191:569–571

Moore KE (1987) Interactions between prolactin and dopaminergic neurons. Biol Reprod 36:47–58. https://doi.org/10.1095/biolreprod36.1.47

Morelli M, Carboni E, Cozzolino A et al (1992) Combined microdialysis and fos immunohistochemistry for the estimation of dopamine neurotransmission in the rat caudate-putamen. J Neurochem 59:1158–1160

Morimoto S, Takao M, Hatsuta H et al (2017) Homovanillic acid and 5-hydroxyindole acetic acid as biomarkers for dementia with Lewy bodies and coincident Alzheimer's disease: An autopsy-confirmed study. PLoS ONE 12:e0171524

Morón JA, Brockington A, Wise RA et al (2002) Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knockout mouse lines. J Neurosci 22:389–395

Mougeot JLC, Hirsch MA, Stevens CB, Mougeot FKB (2016) Oral biomarkers in exercise-induced neuroplasticity in Parkinson's disease. Oral Dis 22:745–753. https://doi.org/10.1111/odi.12463

Murphy JA, Stein IS, Lau CG et al (2014) Phosphorylation of Ser1166 on GluN2B by PKA is critical to synaptic NMDA receptor function and Ca^{2+} signaling in spines. J Neurosci 34:869–879. https://doi.org/10.1523/JNEUROSCI.4538-13.2014

Mushegian A, Gurevich VV, Gurevich EV (2012) The origin and evolution of G protein-coupled receptor kinases. PLoS One 7:. https://doi.org/10.1371/journal.pone.0033806

Myers RH, Sax DS, Schoenfeld M et al (1985) Late onset of Huntington's disease. J Neurol Neurosurg Psychiatry 48:530–534

Nagatsu T, Levitt M, Udenfriend S (1964) Tyrosine hydroxylase the initial step in norepinephrine biosynthesis. J Biol Chem 239:2910–2917

Nakagawa M, Kuri M, Kambara N et al (2008) Dopamine D2 receptor Taq IA polymorphism is associated with postoperative nausea and vomiting. J Anesth 22:397–403

Newman-Tancredi A, Nicolas J-P, Audinot V et al (1998) Actions of alpha2 adrenoceptor ligands at alpha2A and 5-HT1A receptors: the antagonist, atipamezole, and the agonist, dexmedetomidine, are highly selective for alpha2A adrenoceptors. Naunyn Schmiedebergs Arch Pharmacol 358:197–206

Nigg JT (2013) Attention-deficit/hyperactivity disorder and adverse health outcomes. Clin Psychol Rev 33:215–228

Nikolaus S, Antke C, Müller H-W (2009) In vivo imaging of synaptic function in the central nervous system: I. Movement disorders and dementia. Behav Brain Res 204:1–31

Nishi A, Snyder GL, Greengard P (1997) Bidirectional regulation of DARPP-32 phosphorylation by dopamine. J Neurosci 17:8147–8155

Nishi A, Matamales M, Musante V et al (2017) Glutamate counteracts dopamine/pka signaling via dephosphorylation of DARPP-32 Ser-97 and alteration of its cytonuclear distribution. J Biol Chem 292:1462–1476. https://doi.org/10.1074/jbc.M116.752402

Noaín D, Avale ME, Wedemeyer C et al (2006) Identification of brain neurons expressing the dopamine D4 receptor gene using BAC transgenic mice. Eur J Neurosci 24:2429–2438

Numan M (2007) Motivational systems and the neural circuitry of maternal behavior in the rat. Dev Psychobiol 49:165–171. https://doi.org/10.1002/dev

Numan M, Sheehan TP (1997) Neuroanatomical circuitry for mammalian maternal behavior. Ann N Y Acad Sci 807:101–125

Numan M, Smith HG (1984) Maternal behavior in rats: evidence for the involvement of preoptic projections to the ventral tegmental area. Behav Neurosci 98:712–712. https://doi.org/10.1037/0735-7044.98.4.712

Numan M, Numan MJ, Pliakou N et al (2005) The effects of D1 or D2 dopamine receptor antagonism in the medial preoptic area, ventral pallidum, or nucleus accumbens on the maternal retrieval response and other aspects of maternal behavior in rats. Behav Neurosci 119:1588–1604. https://doi.org/10.1037/0735-7044.119.6.1588

Nutt DJ, Lingford-Hughes A, Erritzoe D, Stokes PRA (2015) The dopamine theory of addiction: 40 years of highs and lows. Nat Rev Neurosci 16:305

O'Brien WT, Huang J, Buccafusca R et al (2011) Glycogen synthase kinase-3 is essential for β-arrestin-2 complex formation and lithium-sensitive behaviors in mice. J Clin Invest 121:3756–3762. https://doi.org/10.1172/JCI45194

O'Donnell P (2013) Of mice and men: what physiological correlates of cognitive deficits in a mouse model of schizophrenia tell us about psychiatric disease. Neuron 80:265–266

Obeso Jose A, Marin C, Rodriguez-Oroz C et al (2009) The basal ganglia in Parkinson's disease: Current concepts and unexplained observations. Ann Neurol 64:S30–S46. https://doi.org/10.1002/ana.21481

Otmakhova N, Duzel E, Deutch AY, Lisman J (2013) The hippocampal-VTA loop: the role of novelty and motivation in controlling the entry of information into long-term memory. In: Baldassarre G, Mirolli M (eds) Intrinsically motivated learning in natural and artificial systems. Springer, Berlin, Heidelberg, pp 235–254

Owen MJ, Sawa A, Mortensen PB (2016) Schizophrenia Lancet 388:86–97. https://doi.org/10.1016/S0140-6736(15)01121-6

Pan WHT, Yang S-Y, Lin S-K (2004) Neurochemical interaction between dopaminergic and noradrenergic neurons in the medial prefrontal cortex. Synapse 53:44–52

Pan B, Chen J, Lian J et al (2015) Unique effects of acute aripiprazole treatment on the dopamine D2 receptor downstream cAMP-PKA and Akt-GSK3β signalling pathways in rats. PLoS ONE 10:. https://doi.org/10.1371/journal.pone.0132722

Paoletti P, Vila I, Rifé M et al (2008) Dopaminergic and glutamatergic signaling crosstalk in Huntington's disease neurodegeneration: the role of p25/cyclin-dependent kinase 5. J Neurosci 28:10090–10101

Parada M, King S, Li M, Fleming AS (2008) The roles of accumbal dopamine D1 and D2 receptors in maternal memory in rats. Behav Neurosci 122:368–376. https://doi.org/10.1037/0735-7044.122.2.368

Park SM, Chen M, Schmerberg CM et al (2016) Effects of β-arrestin-biased dopamine D2 receptor ligands on schizophrenia-like behavior in hypoglutamatergic mice. Neuropsychopharmacology 41:704–715. https://doi.org/10.1038/npp.2015.196

Parkinson JA, Olmstead MC, Burns LH et al (1999) Dissociation in effects of lesions of the nucleus accumbens core and shell on appetitive pavlovian approach behavior and the potentiation of conditioned reinforcement and locomotor activity byd-amphetamine. J Neurosci 19:2401–2411

Pascoli V, Besnard A, Herv D et al (2011) Cyclic adenosine monophosphateindependent tyrosine phosphorylation of NR2B mediates cocaine-induced extracellular signal-regulated kinase activation. Biol Psychiatry 69:218–227. https://doi.org/10.1016/j.biopsych.2010.08.031

Paul S, Nairn AC, Wang P, Lombroso PJ (2003) NMDA-mediated activation of the tyrosine phosphatase STEP regulates the duration of ERK signaling. Nat Neurosci 6:34–42. https://doi.org/10.1038/nn989

Paus T (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nat Rev Neurosci 2:417

Pedersen CA, Caldwell JD, Walker C et al (1994) Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. Behav Neurosci 108:1163

Peineau S, Taghibiglou C, Bradley C et al (2007) LTP Inhibits LTD in the Hippocampus via Regulation of GSK3β. Neuron 53:703–717. https://doi.org/10.1016/j.neuron.2007.01.029

Perez-Costas E, Melendez-Ferro M, Roberts RC (2010) Basal ganglia pathology in schizophrenia: dopamine connections and anomalies. J Neurochem 113:287–302

Perreault ML, Hasbi A, O'dowd BF, George SR (2014) Heteromeric dopamine receptor signaling complexes: Emerging neurobiology and disease relevance. Neuropsychopharmacology 39:156–168. https://doi.org/10.1038/npp.2013.148

Peterson SM, Pack TF, Wilkins AD et al (2015) Elucidation of G-protein and β-arrestin functional selectivity at the dopamine D2 receptor. Proc Natl Acad Sci 112:7097–7102. https://doi.org/10.1073/pnas.1502742112

Peyron C, Luppi P-H, Kitahama K et al (1995) Origin of the dopaminergic innervation of the rat dorsal raphe nucleus. Neuroreport 6:2527–2531

Pierce KL, Premont RT, Lefkowitz RJ (2002) Seven-transmembrane receptors. Nat Rev Mol Cell Biol 3:639–650. https://doi.org/10.1038/nrm908

Pijnenburg AJ, Van Rossum JM (1973) Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens. J Pharmacy Pharmacol 25:1003–1005

Pitcher JA, Freedman NJ, Lefkowitz RJ (1998) G protein-coupled receptor kinases. Annu Rev Biochem 67:653–692. https://doi.org/10.1146/annurev.biochem.67.1.653

Poewe W (2008) Non-motor symptoms in Parkinson's disease. Eur J Neurol 15:14–20

Polanczyk G, De Lima MS, Horta BL et al (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry

Popat RA, Van Den Eeden SK, Tanner CM et al (2005) Effect of reproductive factors and postmenopausal hormone use on the risk of Parkinson disease. Neurology 65:383–390

Postuma RB, Berg D, Stern M et al (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 30:1591–1601

Premont RT, Gainetdinov RR (2007) Physiological roles of G protein–coupled receptor kinases and arrestins. Annu Rev Physiol 69:511–534. https://doi.org/10.1146/annurev.physiol.69.022405.154731

Premont RT, Inglese J, Lefkowitz RJ (1995) Protein kinases that phosphorylate activated G protein-coupled receptors. FASEB J 9:175–182

Puig S, Noble F, Benturquia N (2012) Short-and long-lasting behavioral and neurochemical adaptations: relationship with patterns of cocaine administration and expectation of drug effects in rats. Transl Psychiatry 2:e175

Qu S, Ondo WG, Zhang X et al (2006) Projections of diencephalic dopamine neurons into the spinal cord in mice. Exp brain Res 168:152–156

Quan W, Kim JH, Albert PR et al (2008) Roles of G protein and β-arrestin in dopamine D2 receptor-mediated ERK activation. Biochem Biophys Res Commun 377:705–709. https://doi.org/10.1016/j.bbrc.2008.10.044

Rajagopal S, Shenoy SK (2018) GPCR desensitization: acute and prolonged phases. Cell Signal 41:9–16. https://doi.org/10.1016/j.cellsig.2017.01.024

Ralph RJ, Paulus MP, Fumagalli F et al (2001) Prepulse inhibition deficits and perseverative motor patterns in dopamine transporter knock-out mice: differential effects of D1 and D2 receptor antagonists. J Neurosci 21:305–313

Rashid AJ, So CH, Kong MMC et al (2007) D1-D2 dopamine receptor heterooligomers with unique pharmacology are coupled to rapid activation of Gq/11 in the striatum. Proc Natl Acad Sci 104:654–659. https://doi.org/10.1073/pnas.0604049104

Reitz C, Mayeux R (2014) Alzheimer disease: epidemiology, diagnostic criteria, rist factors and biomarkers. Biochem Pharmacol 88:640–651. https://doi.org/10.1016/j.bcp.2013.12.024.Alzheimer

Revel FG, Moreau J-L, Gainetdinov RR et al (2011) TAAR1 activation modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypoglutamatergic activity. Proc Natl Acad Sci 108:8485–8490

Rey E, Hernández-Diáz FJ, Abreu P et al (2001) Dopamine induces intracellular Ca^{2+} signals mediated by alpha1B-adrenoceptors in rat pineal cells. Eur J Pharmacol 430:9–17

Robbins TW, Everitt BJ (1996) Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol 6:228–236

Romano N, Yip SH, Hodson DJ et al (2013) Plasticity of hypothalamic dopamine neurons during lactation results in dissociation of electrical activity and release. J Neurosci 33:4424–4433. https://doi.org/10.1523/JNEUROSCI.4415-12.2013

Roos RAC (2010) Huntington's disease: a clinical review. Orphanet J Rare Dis 5:40

Ross CA, Margolis RL, Reading SAJ et al (2006) Neurobiology of schizophrenia. Neuron 52:139–153

Rossi M, Fasciani I, Marampon F et al (2017) The first negative allosteric modulator for dopamine D_2 and D_3 receptors, SB269652 may lead to a new generation of antipsychotic drugs. Mol Pharmacol 91:586–594. https://doi.org/10.1124/mol.116.107607

Sahin B, Hawasli AH, Greene RW et al (2008) Negative regulation of cyclin-dependent kinase 5 targets by protein kinase C. Eur J Pharmacol 581:270–275. https://doi.org/10.1016/j.ejphar.2007.11.061

Sahu A, Tyeryar KR, Vongtau HO et al (2009) D5 dopamine receptors are required for dopaminergic activation of phospholipase C. Mol Pharmacol 75:447–453

Salamone JD, Correa M (2012) The mysterious motivational functions of mesolimbic dopamine. Neuron 76:470–485

Sams-Dodd F (1998) Effects of dopamine agonists and antagonists on PCP-induced stereotyped behaviour and social isolation in the rat social interaction test. Psychopharmacology 135:182–193

Savasta M, Dubois A, Scatton B (1986) Autoradiographic localization of D1 dopamine receptors in the rat brain with [3H]SCH 23390. Brain Res 375:291–301

Scheid M, Woodgett J (2001) PKB/AKT: functional insights from genetic models. Nat Rev Mol Cell Biol 2:760–768. https://doi.org/10.1038/35096067

Schmidt MJ, Mirnics K (2015) Neurodevelopment, GABA system dysfunction, and schizophrenia. Neuropsychopharmacology 40:190

Schrag A, Ben-Shlomo Y, Quinn NP (2000) Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London. Bmj 321:21–22

Schultz W (1998) Predictive reward signal of dopamine neurons. J Neurophysiol 80:1–27

Sedaghat K, Nantel M-F, Ginsberg S et al (2006) Molecular characterization of dopamine D2 receptor isoforms tagged with green fluorescent protein. Mol Biotechnol 34:1–14. https://doi.org/10.1385/MB:34:1:1

Seeman P, Chau-Wong M, Tedesco J, Wong K (1975) Brain receptors for antipsychotic drugs and dopamine: direct binding assays. Proc Natl Acad Sci 72:4376–4380. https://doi.org/10.1073/pnas.72.11.4376

Seeman P, Weinshenker D, Quirion R et al (2005) Dopamine supersensitivity correlates with D2High states, implying many paths to psychosis. Proc Natl Acad Sci 102:3513–3518. https://doi.org/10.1073/pnas.0409766102

Seeman P, Ko F, Jack E et al (2007) Consistent with dopamine supersensitivity, RGS9 expression is diminished in the amphetamine-treated animal model of schizophrenia and in postmortem schizophrenia brain. Synapse 61:303–309. https://doi.org/10.1002/syn.20368

Segura-Aguilar J, Huenchuguala S (2018) Aminochrome induces irreversible mitochondrial dysfunction by inducing autophagy dysfunction in Parkinson's disease. Front Neurosci 12:106

Segura-Aguilar J, Paris I, Munoz P et al (2014) Protective and toxic roles of dopamine in Parkinson's disease. J Neurochem 129:898–915. https://doi.org/10.1111/jnc.12686

Shaywitz BA, Yager RD, Klopper JH (1976) Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction. Science 191:305–308

Shioda N (2017) Dopamine D2L receptor-interacting proteins regulate dopaminergic signaling. J Pharmacol Sci 135:51–54. https://doi.org/10.1016/j.jphs.2017.10.002

Silvano E, Millan MJ, Mannoury C et al (2010) The tetrahydroisoquinoline derivative SB269,652 Is an allosteric antagonist at

dopamine D3 and D2 receptors. Mol Pharmacol 78:925–934. https://doi.org/10.1124/mol.110.065755
Simon V, Czobor P, Bálint S et al (2009) Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry 194:204–211
Skagerberg G, Björklund A, Lindvall O, Schmidt RH (1982) Origin and termination of the diencephalo-spinal dopamine system in the rat. Brain Res Bull 9:237–244
So CH, Varghese G, Curley KJ et al (2005) D1 and D2 dopamine receptors form heterooligomers and cointernalize after selective activation of either receptor. Mol Pharmacol 68:568–578. https://doi.org/10.1124/mol.105.012229.the
So CH, Verma V, Alijaniaram M et al (2009) Calcium signaling by dopamine D5 receptor and D5-D2 receptor hetero-oligomers occurs by a mechanism distinct from that for dopamine D1-D2 receptor hetero-oligomers. Mol Pharmacol 75:843–854. https://doi.org/10.1124/mol.108.051805
Sourkes TL (2009) The discovery of neurotransmitters, and applications to neurology. Handb Clin Neurol 95:869–883
Spector S, Sjoerdsma A, Udenfriend S (1965) Blockade of endogenous norepinephrine synthesis by $α$-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. J Pharmacol Exp Ther 147:86–95
Spillantini MG, Schmidt ML, Lee VM-Y et al (1997) α-Synuclein in Lewy bodies. Nature 388:839
Stahl SM (1985) Platelets as pharmacologic models for the receptors and biochemistry of monoaminergic neurons. In: The platelets: physiology and pharmacology. Academic Press, New York, pp 307–335
Starke K (2014) History of catecholamine research. Chem Immunol Allergy 100:288–301
Stefani A, Pierantozzi M, Olivola E et al (2017) Homovanillic acid in CSF of mild stage Parkinson's disease patients correlates with motor impairment. Neurochem Int 105:58–63
Steinhardt RA, Bi G, Alderton JM (1994) Cell membrane resealing by a vesicular mechanism similar to neurotransmitter release. Science 263:390–393
Stephan KE, Friston KJ, Frith CD (2009) Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 35:509–527
Stern JM, Taylor LA (1991) Haloperidol inhibits maternal retrieval and licking, but enhances nursing behavior and litter weight gains in lactating rats. J Neuroendocrinol 3:591–596
Stinus L, Herman JP, Le Moal M (1982) GABAergic mechanisms within the ventral tegmental area: involvement of dopaminergic (A 10) and non-dopaminergic neurones. Psychopharmacology 77:186–192
Stipanovich A, Valjent E, Matamales M et al (2008) A phosphatase cascade by which rewarding stimuli control nucleosomal response. Nature 453:879–884. https://doi.org/10.1038/nature06994
Stokes AH, Hastings TG, Vrana KE (1999) Cytotoxic and genotoxic potential of dopamine. J Neurosci Res 55:659–665
Stolzenberg DS, Zhang KY, Luskin K et al (2010) Dopamine D1 receptor activation of adenylyl cyclase, not phospholipase C, in the nucleus accumbens promotes maternal behavior onset in rats. Horm Behav 57:96–104. https://doi.org/10.1016/j.yhbeh.2009.09.014
Stryker S (1925) Encephalitis lethargica—the behavior residuals. Train Sch Bull (Vinel) 22:152–157
Surmeier DJ, Ding J, Day M et al (2007) D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. Trends Neurosci 30:228–235
Svenningsson P, Nishi A, Fisone G et al (2004) DARPP-32: an integrator of neurotransmission. Annu Rev Pharmacol Toxicol 44:269–296. https://doi.org/10.1146/annurev.pharmtox.44.101802.121415
Swift JL, Godin AG, Doré K et al (2011) Quantification of receptor tyrosine kinase transactivation through direct dimerization and surface density measurements in single cells. Proc Natl Acad Sci USA 108:7016–7021. https://doi.org/10.1073/pnas.1018280108
Takano H, Cancel G, Ikeuchi T et al (1998) Close associations between prevalences of dominantly inherited spinocerebellar ataxias with CAG-repeat expansions and frequencies of large normal CAG alleles in Japanese and Caucasian populations. Am J Hum Genet 63:1060–1066
Tan ML, Basu D, Kwiecien JM et al (2013) Preclinical pharmacokinetic and toxicological evaluation of MIF-1 peptidomimetic, PAOPA: Examining the pharmacology of a selective dopamine D2 receptor allosteric modulator for the treatment of schizophrenia. Peptides 42:89–96. https://doi.org/10.1016/j.peptides.2013.02.004
Tanda G, Frau R, Di Chiara G (1995) Local 5HT 3 receptors mediate fluoxetine but not desipramine-induced increase of extracellular dopamine in the prefrontal cortex. Psychopharmacology 119:15–19
Tang T-S, Chen X, Liu J, Bezprozvanny I (2007) Dopaminergic signaling and striatal neurodegeneration in Huntington's disease. J Neurosci 27:7899–7910
Thomas GM, Huganir RL (2004) MAPK cascade signalling and synaptic plasticity. Nat Rev Neurosci 5:173–183. https://doi.org/10.1038/nrn1346
Tiberi M, Nash SR, Bertrand L et al (1996) Differential regulation of dopamine D1A receptor responsiveness by various G protein-coupled receptor kinases. J Biol Chem 271:3771–3778. https://doi.org/10.1074/jbc.271.7.3771
Trincavelli ML, Daniele S, Orlandini E et al (2012) A new D_2 dopamine receptor agonist allosterically modulates A(2A) adenosine receptor signalling by interacting with the A(2A)/D_2 receptor heteromer. Cell Signal 24:951–960. https://doi.org/10.1016/j.cellsig.2011.12.018
Tritsch NX, Sabatini BL (2012) Dopaminergic modulation of synaptic transmission in cortex and striatum. Neuron 76:33–50. https://doi.org/10.1016/j.neuron.2012.09.023
Udenfriend S, Wyngaarden JB (1956) Precursors of adrenal epinephrine and norepinephrine in vivo. Biochim Biophys Acta 20:48–52
Ugi S, Imamura T, Maegawa H et al (2004) Protein phosphatase 2A negatively regulates insulin's metabolic signaling pathway by inhibiting Akt (protein kinase B) activity in 3T3-L1 adipocytes. Mol Cell Biol 24:8778–8789. https://doi.org/10.1128/MCB.24.19.8778-8789.2004
Undie AS, Weinstock J, Sarau HM, Friedman E (1994) Evidence for a distinct D1-like dopamine receptor that couples to activation of phosphoinositide metabolism in brain. J Neurochem 62:2045–2048. https://doi.org/10.1046/j.1471-4159.1994.62052045.x
Urs NM, Peterson SM, Caron MG (2017) New concepts in dopamine D2 receptor biased signaling and implications for schizophrenia therapy. Biol Psychiatry 81:78–85. https://doi.org/10.1016/j.biopsych.2016.10.011
Valentini V, Cacciapaglia F, Frau R, Di Chiara G (2006) Differential alpha2-mediated inhibition of dopamine and noradrenaline release in the parietal and occipital cortex following noradrenaline transporter blockade. J Neurochem 98:113–121
Valjent E, Corvol JC, Pages C et al (2000) Involvement of the extracellular signal-regulated kinase cascade for cocaine-rewarding properties. J Neurosci 20:8701–8709 doi: 20/23/8701 [pii]
Valjent E, Pascoli V, Svenningsson P et al (2005) Regulation of a protein phosphatase cascade allows convergent dopamine and glutamate signals to activate ERK in the striatum. Proc Natl Acad Sci 102:491–496. https://doi.org/10.1073/pnas.0408305102
Vallone D, Picetti R, Borrelli E (2000) Structure and function of dopamine receptors. Neurosci Biobehav Rev 24:125–132

Van Tol HH, Bunzow JR, Guan HC et al (1991) Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature 350:610–614. https://doi.org/10.1038/350610a0

Venton BJ, Zhang H, Garris PA et al (2003) Real-time decoding of dopamine concentration changes in the caudate–putamen during tonic and phasic firing. J Neurochem 87:1284–1295. https://doi.org/10.1046/j.1471-4159.2003.02109.x

Veselinović T, Paulzen M, Gründer G (2013) Cariprazine, a new, orally active dopamine D2/3 receptor partial agonist for the treatment of schizophrenia, bipolar mania and depression. Expert Rev Neurother 13:1141–1159. https://doi.org/10.1586/14737175.2013.853448

Viggiano D, Grammatikopoulos G, Sadile AG (2002) A morphometric evidence for a hyperfunctioning mesolimbic system in an animal model of ADHD. Behav Brain Res 130:181–189

Volkow ND, Fowler JS, Wang GJ et al (2009) Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56:3–8

von Euler U (1946) A Specific Sympathomimetic Ergone in Adrenergic Nerve Fibres (Sympathin) and its Relations to Adrenaline and Nor-Adrenaline. Acta Physiol Scand 12:73–97. https://doi.org/10.1111/j.1748-1716.1946.tb00368.x doi

Voogt JL, Lee Y, Yang S, Arbogast L (2001) Regulation of prolactin secretion during pregnancy and lactation. Prog Brain Res 133:173–185

Walaas SI, Aswad DW, Greengard P (1983) A dopamine-and cyclic AMP-regulated phosphoprotein enriched in dopamine-innervated brain regions. Nature 301:69

Walker FO (2007) Huntington's disease. Lancet 369:218–228

Wamsley JK, Gehlert DR, Filloux FM, Dawson TM (1989) Comparison of the distribution of D-1 and D-2 dopamine receptors in the rat brain. J Chem Neuroanat 2:119–137

Wang G-J, Volkow ND, Logan J et al (2001) Brain dopamine and obesity. Lancet 357:354–357

Wang H, Farhan M, Xu J et al (2017) The involvement of darpp-32 in the pathophysiology of schizophrenia. Oncotarget 8:53791

Watabe-Uchida M, Zhu L, Ogawa SK et al (2012) Whole-brain mapping of direct inputs to midbrain dopamine neurons. Neuron 74:858–873

Wauquier A, Rolls ET (1976) Brain-stimulation reward. North-Holland, Amsterdam

Weinshilboum RM, Thoa NB, Johnson DG et al (1971) Proportional release of norepinephrine and dopamine-$β$-hydroxylase from sympathetic nerves. Science 174:1349–1351

Welsh GI, Hall D, Warnes A et al (1998) Activation of microtubule-associated protein kinase (Erk) and p70 S6 kinase by D2 dopamine receptors. J Neurochem 70:2139–2146

Werhahn KJ, Kunesch E, Noachtar S et al (1999) Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J Physiol 517:591–597

Whitehouse PJ, Martino AM, Antuono PG et al (1986) Nicotinic acetylcholine binding sites in Alzheimer's disease. Brain Res 371:146–151

Willems JL, Buylaert WA, Lefebvre RA, Bogaert MG (1985) Neuronal dopamine receptors on autonomic ganglia and sympathetic nerves and dopamine receptors in the gastrointestinal system. Pharmacol Rev 37:165–216

Williams-Gray CH, Worth PF (2016) Parkinson's disease. Med (United Kingdom) 44:542–546. https://doi.org/10.1016/j.mpmed.2016.06.001

Winkelman JW (1999) The evoked heart rate response to periodic leg movements of sleep. Sleep 22:575–580

Wise RA (2009) Roles for nigrostriatal not just mesocorticolimbic dopamine in reward and addiction. Trends Neurosci 32:517–524

Woodard GE, Jardín I, Berna-Erro A et al (2015) Regulators of G-protein-signaling proteins: negative modulators of G-protein-coupled receptor signaling. Int Rev Cell Mol Biol 317:97–183. https://doi.org/10.1016/bs.ircmb.2015.02.001

Wright HH, Still CN, Abramson RK (1981) Huntington's disease in black kindreds in South Carolina. Arch Neurol 38:412–414

Wurtman RJ, Hefti F, Melamed E (1980) Precursor control of neurotransmitter synthesis. Pharmacol Rev 32:315–335

Xie Z, Miller GM (2007) Trace amine-associated receptor 1 is a modulator of the dopamine transporter. J Pharmacol Exp Ther 321:128–136

Xu K, Näveri L, Frerichs KU et al (1993) Extracellular catecholamine levels in rat hippocampus after a selective alpha-2 adrenoceptor antagonist or a selective dopamine uptake inhibitor: evidence for dopamine release from local dopaminergic nerve terminals. J Pharmacol Exp Ther 267:211–217

Xu W, Wang X, Tocker AM et al (2017) Functional Characterization of a Novel Series of Biased Signaling Dopamine D3 Receptor Agonists. ACS Chem Neurosci 8:486–500. https://doi.org/10.1021/acschemneuro.6b00221

Yan Z, Song WJ, Surmeier J (1997) D2 dopamine receptors reduce N-type Ca^{2+} currents in rat neostriatal cholinergic interneurons through a membrane-delimited, protein-kinase-C-insensitive pathway. J Neurophysiol 77:1003–1015. https://doi.org/10.1152/jn.1997.77.2.1003

Yang LI, Wang Y-F, Li JUN, Faraone SV (2004) Association of norepinephrine transporter gene with methylphenidate response. J Am Acad Child Adolesc Psychiatry 43:1154–1158

Yokoyama C, Okamura H, Nakajima T et al (1994) Autoradiographic distribution of [3H]YM-09151-2, a high-affinity and selective antagonist ligand for the dopamine D2 receptor group, in the rat brain and spinal cord. J Comp Neurol 344:121–136. https://doi.org/10.1002/cne.903440109

Yujnovsky I, Hirayama J, Doi M et al (2006) Signaling mediated by the dopamine D2 receptor potentiates circadian regulation by CLOCK:BMAL1. Proc Natl Acad Sci 103:6386–6391. https://doi.org/10.1073/pnas.0510691103

Zhang W, Klimek V, Farley JT et al (1999) alpha-2C adrenoceptors inhibit adenylyl cyclase in mouse striatum: potential activation by dopamine. J Pharmacol Exp Ther 289:1286–1292

Zhang W-P, Ouyang M, Thomas SA (2004) Potency of catecholamines and other L-tyrosine derivatives at the cloned mouse adrenergic receptors. Neuropharmacology 47:438–449

Zheng W, Zeng Z, Bhardwaj SK et al (2013) Lithium normalizes amphetamine-induced changes in striatal FoxO1 phosphorylation and behaviors in rats. Neuroreport 24:560–565

Zion IZB, Tessler R, Cohen L et al (2006) Polymorphisms in the dopamine D4 receptor gene (DRD4) contribute to individual differences in human sexual behavior: desire, arousal and sexual function. Mol Psychiatry 11:782

Zucchi R, Chiellini G, Scanlan TS, Grandy DK (2006) Trace amine-associated receptors and their ligands. Br J Pharmacol 149:967–978

View publication stats