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The Physiology, Signaling, and Pharmacology of Dopamine Receptors

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Abstract——G protein-coupled dopamine receptors (D1, D2, D3, D4, and D5) mediate all of the physiological functions of the catecholaminergic neurotransmitter dopamine, ranging from voluntary movement and reward to hormonal regulation and hypertension. Pharmacological agents targeting dopaminergic neurotransmission have been clinically used in the management of several neurological and psychiatric disorders, including Parkinson's disease, schizophrenia, bipolar disorder, Huntington's disease, attention deficit hyperactivity disorder (ADHD[1]), and Tourette's syndrome. Numerous advances have occurred in understanding the general structural, biochemical, and functional properties of dopamine receptors that have led to the development of multiple pharmacologically active compounds that directly target dopamine receptors, such as antiparkinson drugs and antipsychotics. Recent progress in understanding the complex biology of dopamine receptor-related signal transduction mechanisms has revealed that, in addition to their primary action on cAMP-mediated signaling, dopamine receptors can act through diverse signaling mechanisms that involve alternative G protein coupling or through G protein-independent mechanisms via interactions with ion channels or proteins that are characteristically implicated in receptor desensitization, such as β-arrestins. One of the future directions in managing dopamine-related pathologic conditions may involve a transition from the approaches that directly affect receptor function to a precise targeting of postreceptor intracellular signaling modalities either directly or through ligand-biased signaling pharmacology. In this comprehensive review, we discuss dopamine receptor classification, their basic structural and genetic organization, their distribution and functions in the brain and the periphery, and their regulation and signal transduction mechanisms. In addition, we discuss the abnormalities of dopamine receptor expression, function, and signaling that are documented in human disorders and the current pharmacology and emerging trends in the development of novel therapeutic agents that act at dopamine receptors and/or on related signaling events.

I. Introduction

Since the discovery of the physiological functions of 3-hydroxytyramine (dopamine), a metabolite of the amino acid tyrosine, more than 50 years ago (Carlsson et al.,

[1] Abbreviations: AC, adenylate cyclase; ACR16, huntexil; ADHD, attention deficit hyperactivity disorder; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BAC, bacterial artificial chromosome; BDNF, brain-derived neurotrophic factor; CDK5, cyclin-dependent kinase 5; CK, casein kinase; CREB, cAMP response element-binding protein; D2L, D2-long; D2S, D2-short; DAG, diacylglycerol; DARPP-32, 32-kDa dopamine and cAMP-regulated phosphoprotein; DAT, dopamine transporter; Epac, exchange proteins directly activated by cAMP; ERK, extracellular-signal regulated kinase 1 and 2; GIRK, G protein-coupled inwardly rectifying potassium channel; GPCR, G protein-coupled receptor; GRK, G protein-coupled receptor kinase; GSK-3, glycogen synthase kinase 3; HEK, human embryonic kidney; IP$_3$, inositol trisphosphate; KO, knockout; LTD, long-term depression; MAP, mitogen-activated protein; MEK, MAP/ERK kinase; MK-801, dizocilpine maleate; MSN, medium spiny neuron; NCS-1, neuronal calcium sensor-1; NMDA, N-methyl-D-aspartate; OSU6162, (3S)-3-[3-(methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride; Par-4, prostate apoptosis response-4; PD, Parkinson's disease; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; PP2B, protein phosphatase 2B; PSD-95, postsynaptic density-95; RGS, regulators of G protein signaling; SCH23390, 7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol; SL327, α-[amino [(4-aminophenyl)thio]methylene]-2-(trifluoromethyl)benzeneacetonitrile; STEP, striatal-enriched tyrosine phosphatase; WT, wild type.

1957), this catecholaminergic neurotransmitter has attracted an enormous amount of attention. In a similar manner to other monoamine neurotransmitters, dopamine generally exerts its actions on neuronal circuitry via a relatively slow modulation of the fast neurotransmission that is mediated by glutamate and GABA. Dopaminergic innervations are the most prominent in the brain. Four major dopaminergic pathways have been identified in the mammalian brain; the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular systems that originate from the A9 (nigrostriatal), A10 (mesolimbic and mesocortical, often collectively termed the mesocorticolimbic pathway), and A8 (tuberoinfundibular) groups of dopamine-containing cells (Anden et al., 1964; Dahlstroem and Fuxe, 1964), respectively. These neurons are critically involved in various vital central nervous system functions, including voluntary movement, feeding, affect, reward, sleep, attention, working memory, and learning. In the periphery, dopamine plays important physiological roles in the regulation of olfaction, retinal processes, hormonal regulation, cardiovascular functions, sympathetic regulation, immune system, and renal functions, among others (Snyder et al., 1970; Missale et al., 1998; Sibley, 1999; Carlsson, 2001; Iversen and Iversen, 2007).

Because dopamine is involved in a variety of critical functions, it is not surprising that multiple human dis-

orders have been related to dopaminergic dysfunctions. The most recognized dopamine-related disorder is Parkinson's disease (PD), which originates from a loss of striatal dopaminergic innervations in the brain (Ehringer and Hornykiewicz, 1960). Less straightforward evidence, such as the psychotomimetic effect of dopaminergic drugs and the fact that almost all of the clinically effective antipsychotics block D2 dopamine receptors, has provided a basis for the dopaminergic hypothesis of schizophrenia (Snyder et al., 1970; Creese et al., 1976; Seeman et al., 1976; Carlsson et al., 2001). Dopamine dysregulation is expected to occur in ADHD and Tourette's syndrome (Mink, 2006; Swanson et al., 2007; Gizer et al., 2009). In Huntington's disease, the selective vulnerability of neurons in the striatum, where the highest concentration of dopaminergic innervations exists, suggests an important role of dopamine in the pathogenesis of this disorder (Jakel and Maragos, 2000; Cyr et al., 2006). The abnormal plasticity of reward mechanisms that has been shown to be associated with drug abuse and addiction strongly suggests that dopamine plays an important role in this pathological condition (Hyman et al., 2006; Di Chiara and Bassareo, 2007; Koob and Volkow, 2010). A role for abnormal dopaminergic signaling has also been suggested for a host of other brain disorders, such as bipolar disorder, major depression, dyskinesias, and various somatic disorders, including hypertension and kidney dysfunction (Missale et al., 1998; Aperia, 2000; Carlsson, 2001; Iversen and Iversen, 2007).

Once released from presynaptic terminals, dopamine activates members of a family of G protein-coupled dopamine receptors named D1 to D5. Targeting these receptors using specific agonists and antagonists has provided an opportunity to significantly influence dopaminergic transmission and dopamine-dependent functions by enhancing or blocking the actions of dopamine. Hundreds of pharmacologically active compounds that interfere with dopamine receptor functions at the level of ligand binding have been developed, and many of these compounds have been used for clinical applications in the treatment of various disorders.

In addition to significant progress in understanding the structural, genetic and pharmacological properties of dopamine receptors, more recent studies have begun to uncover the complexity, intricacy, and plasticity of intracellular signaling mechanisms that are involved in dopamine receptor functions. This knowledge has led to the development of new paradigms to understand the role of dopamine receptors at a system level. Such frameworks can provide an opportunity to comprehend multilevel interactions between dopamine and other extracellular messengers, such as glutamate, serotonin, or neurotrophins, in the control of mechanisms through which dopamine affects gene expression or long-term synaptic plasticity. Furthermore, this approach can de-

fine the contribution of aberrant processes or genetic defects that are not obviously associated with dopaminergic neurotransmission to the pathogenesis of dopamine-related disorders and point to the specific intracellular processes that should be targeted by future pharmacological approaches.

A search for the terms "dopamine receptor" in the PubMed database results in more than 45,000 entries, and the number of articles that address dopamine receptor physiology is growing on a daily basis. Clearly, we could not cover every finding on dopamine receptor biology that has been reported. In this review, we elected to focus on only the most critical observations that highlight the major directions of progress in the field. Because of the large body of literature on dopamine receptor gene organization, structure, and expression profiles that has been reviewed extensively in several excellent review articles (Niznik and Van Tol, 1992; Sibley and Monsma, 1992; Sokoloff et al., 1992a; Civelli et al., 1993; Missale et al., 1998; Vallone et al., 2000; Seeman, 2006; Rankin et al., 2010), we cover these topics only briefly in section II. Instead, we focus on the recent progress toward understanding the molecular mechanisms that are involved in dopamine receptor regulation and signaling that could provide novel targets and approaches for pharmacological intervention in dopamine-related disorders.

II. Dopamine Receptors: Classification, Genes, Structure, Expression, and Functions

A. Basic Genetic and Structural Properties of Dopamine Receptors

The physiological actions of dopamine are mediated by five distinct but closely related G protein-coupled receptors (GPCRs) that are divided into two major groups: the D1 and D2 classes of dopamine receptors (Andersen et al., 1990; Niznik and Van Tol, 1992; Sibley and Monsma, 1992; Sokoloff et al., 1992a; Civelli et al., 1993; Vallone et al., 2000). This classification is generally based on the original biochemical observations showing that dopamine is able to modulate adenylyl cyclase (AC) activity. In a pioneering report, it was shown that dopamine receptors could exist in two distinct populations and that only one subgroup was positively coupled to AC (Spano et al., 1978). This finding subsequently led to the separation of the D1 and D2 subtypes of dopamine receptors, which was based mostly on their ability to modulate cAMP production and the differences in their pharmacological properties (Kebabian and Calne, 1979). A later characterization of the dopamine receptor families using genetic cloning approaches revealed that multiple receptor subtypes can be activated by dopamine (Bunzow et al., 1988; Dearry et al., 1990; Monsma et al., 1990; Sokoloff et al., 1990; Zhou et al., 1990; Sunahara et al., 1991; Tiberi et al., 1991; Van Tol et al., 1991). On the basis of their structural, pharmacological, and biochemical properties, these receptors were classified as either

D1-class dopamine receptors [D1 and D5 (originally identified as D1B) (Tiberi et al., 1991)] or D2-class dopamine receptors (D2, D3, and D4) (Andersen et al., 1990; Niznik and Van Tol, 1992; Sibley and Monsma, 1992; Sokoloff et al., 1992a; Civelli et al., 1993; Vallone et al., 2000). In addition to these functional receptors, two pseudogenes have been described for the human D5 dopamine receptor that encodes truncated nonfunctional receptor forms (Grandy et al., 1991).

The individual members of the subfamilies of the D1- and D2-class receptors share a high level of homology of their transmembrane domains and have distinct pharmacological properties. It is commonly accepted that the D1-class dopamine receptors (D1 and D5) activate the $G\alpha_{s/olf}$ family of G proteins to stimulate cAMP production by AC and are found exclusively postsynaptically on dopamine-receptive cells, such as GABA-ergic medium spiny neurons (MSNs) in the striatum. The D2-class dopamine receptors (D2, D3, and D4) couple to the $G\alpha_{i/o}$ family of G proteins and thus induce inhibition of AC. In contrast to the D1-class dopamine receptors, D2 and D3 dopamine receptors are expressed both postsynaptically on dopamine target cells and presynaptically on dopaminergic neurons (Sokoloff et al., 2006; Rankin et al., 2010; Rondou et al., 2010).

The D1- and D2-class dopamine receptors are also different at the level of genetic structure, primarily in the presence of introns in their coding sequences. The D1 and D5 dopamine receptor genes do not contain introns in their coding regions, but the genes that encode the D2-class receptors have several introns, with six introns found in the gene that encodes the D2 dopamine receptor, five in the gene for the D3 dopamine receptor, and three in the gene for the D4 dopamine receptor (Gingrich and Caron, 1993). Therefore, the genetic organization of the D2-class receptors provides the basis for the generation of receptor splice variants. For example, the alternative splicing of an 87-base-pair exon between introns 4 and 5 of the D2 dopamine receptor leads to the generation of two major D2 dopamine receptor variants that have been termed D2S (D2-short) and D2L (D2-long) (Giros et al., 1989; Monsma et al., 1989). These two alternatively spliced isoforms differ in the presence of an additional 29 amino acids in the third intracellular loop. These variants of the D2 dopamine receptor have distinct anatomical, physiological, signaling, and pharmacological properties. D2S has been shown to be mostly expressed presynaptically and to be mostly involved in autoreceptor functions, whereas D2L seems to be predominantly a postsynaptic isoform (Usiello et al., 2000; De Mei et al., 2009). Splice variants of the D3 dopamine receptor have also been described, and some of the encoding proteins have been shown to be essentially nonfunctional (Giros et al., 1991). For D4 dopamine receptor, several polymorphic variants with a 48-base-pair repeat sequence in the third cytoplasmic loop were described, and various numbers of repeats were observed up to 11 repeats (Van Tol et al., 1992). Some of these polymorphic variants might have a slightly altered affinity for the antipsychotic clozapine; however, no evidence has been reported that indicates an increased incidence of schizophrenia in the subjects with these variants (Wong and Van Tol, 2003).

D1-class dopamine receptors have several distinct characteristics in their genetic and structural properties. The D1 and D5 dopamine receptors are 80% homologous in their transmembrane domains, whereas the D3 and D4 dopamine receptors are 75 and 53% homologous, respectively, with the D2 receptor. Whereas the NH_2-terminal domain has a similar number of amino acids in all of the dopamine receptors, the COOH-terminal for the D1-class receptors is seven times longer than that for the D2-class receptors (Gingrich and Caron, 1993; Missale et al., 1998).

Dopamine activates D1 to D5 dopamine receptors with various affinity ranging from nanomolar to micromolar range. In general, different subtypes of dopamine receptors vary significantly in their sensitivity to dopamine agonists and antagonists (Missale et al., 1998; Sokoloff et al., 2006; Rankin et al., 2010; Rondou et al., 2010); for a detailed comparison of pharmacological properties of dopamine receptors, see the National Institute of Mental Health Psychoactive Drug Screening Program database (http://pdsp.med.unc.edu) or the International Union of Basic and Clinical Pharmacology database (http://www.iuphar-db.org). Over the past several decades, a number of selective compounds were developed for the D2, D3, and D4 dopamine receptor subtypes. Although ligands that are generally selective for the D1 class (compared with their affinity for the D2 class) have been developed, the development of specific D5 dopamine receptor ligands has proven to be difficult. The maximal degree of selectivity has been achieved for the D4-selective antagonists, which show a selectivity of more than a 1000-fold compared with their affinity for the other subtypes, whereas compounds antagonizing the D3 dopamine receptor show a maximal selectivity of approximately 100-fold compared with their affinity for D2 dopamine receptors (Missale et al., 1998; Vallone et al., 2000; Seeman, 2006; Sokoloff et al., 2006; Rankin et al., 2010; Rondou et al., 2010). The basic genetic and structural features of human dopamine receptors and a short list of their selective ligands are presented in Table 1.

B. Dopamine Receptor Expression

Dopamine receptors have broad expression patterns in the brain and in the periphery. In the brain, D1 dopamine receptors are expressed at a high level of density in the nigrostriatal, mesolimbic, and mesocortical areas, such as the caudate-putamen (striatum), nucleus accumbens, substantia nigra, olfactory bulb, amygdala, and frontal cortex, as well as at lower levels in the hippocampus, cerebellum, thalamic areas, and

TABLE 1
Basic genetic, structural and pharmacological properties of dopamine receptor subtypes

The table was compiled from information presented in review articles (Niznik and Van Tol, 1992; Sibley and Monsma, 1992; Sokoloff et al., 1992a; Civelli et al., 1993; Missale et al., 1998; Vallone et al., 2000; Seeman, 2006; Rankin et al., 2010) and from the references cited therein.

Dopamine Receptor Subtype	D1	D2	D3	D4	D5
Gene symbol	*DRD1*	*DRD2*	*DRD3*	*DRD4*	*DRD5*
Chromosomal gene map locus	5q35.1	11q23.1	3q13.3	11p15.5	4p16.1
Number of introns in the coding region	None	6	5	3	None
Pseudogenes	None	None	None	None	*DRD5P1, DRD5P2*
Presence of splice variants	None	Yes D2S, D2L	Yes	Yes	None
Number of amino acids	446	D2S, 414; D2L, 443	400	387	477
Molecular weight	49,300	D2S, 47,347; D2L, 50,619	44,225	41,487	52,951
G protein coupling	Gα_s, Gα_{olf}	Gα_i, Gα_o	Gα_i, Gα_o	Gα_i, Gα_o	Gα_s, Gα_q
Selective agonists	Fenoldopam, SKF-38393, SKF-81297	Bromocriptine, pergolide, cabergoline, ropinirole	7-OH-DPAT, pramipexole, rotigotine, (+)-PD-128907	A-412997, ABT-670, PD-168,077	None
Selective antagonists	SCH-23390, SCH-39166, SKF-83566	Haloperidol, spiperone, raclopride, sulpiride, risperidone	Nafadotride, GR 103,691, GR 218,231, SB-277011A	A-381393, FAUC 213, L-745,870, L-750,667	None

7-OH-DPAT, hydroxy-2-dipropylaminotetralin; A-381393, 2-[4-(3,4-dimethylphenyl)piperazin-1-ylmethyl[-1*H* benzimidazole; A-412997, *N*-(3-methylphenyl)-2-(4-pyridin-2-ylpiperidin-1-yl)acetamide; ABT-670, 3-methyl-*N*-(1-oxy-3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′-bipyridine]-1′-ylmethyl)benzamide; FAUC 213, 2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]pyrazolo[1,5-*a*]pyridine; GR 218,231, (+)-(2*R*)-1,2,3,4-tetrahydro-6-[[(4-methoxyphenyl)sulfonyl[methyl]-*N*,*N*-dipropyl-2-naphthalenamine; GR 103,691, 4′-acetyl-*N*-[4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl]-[1,1′-biphenyl]-4-carboxamide; L-745,870, 3-(4-[4-chlorophenyl]piperazin-1-yl)-methyl-1*H*-pyrrolo[2,3-*b*]pyridine; L-750,667, 3-[4-(4-iodophenyl)piperazin-1-yl]methyl-1*H*-pyrrolo[2,3-*b*]pyridine; PD-128907, (4*aR*,10*bR*)-3,3*a*,4,10*b*-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano-[4,3-*b*]-1,4-oxazin-9-ol; PD-168,077, *N*-{[4-(2-cyanophenyl)piperazin-1-yl]methyl}-3-methylbenzamide-(2*Z*)-but-2-enedioic acid; ; SB-277011A, *N*-{*trans*-4-[2-(6-cyano-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl]cyclohexyl}quinoline-4-carboxamide; SCH-39166, (−)-*trans*-6,7,7*a*,8,9,13*b*-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5*H*-benzo[*d*]naphtho[2,1-*b*]azepine; SKF-38393, 2,3,4,5-tetrahydroxy-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine; SKF-81297, (±)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide; SKF-83566, 8-bromo-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol.

hypothalamic areas. D5 dopamine receptors are expressed at low levels in multiple brain regions, including pyramidal neurons of the prefrontal cortex, the premotor cortex, the cingulated cortex, the entorhinal cortex, substantia nigra, hypothalamus, the hippocampus, and the dentate gyrus. A very low level of expression has also been observed in the MSNs of the caudate nucleus and nucleus accumbens (Missale et al., 1998; Gerfen, 2000; Sokoloff et al., 2006; Rankin et al., 2010).

The highest levels of D2 dopamine receptors are found in the striatum, the nucleus accumbens, and the olfactory tubercle. D2 receptors are also expressed at significant levels in the substantia nigra, ventral tegmental area, hypothalamus, cortical areas, septum, amygdala, and hippocampus (Missale et al., 1998; Gerfen, 2000; Vallone et al., 2000; Seeman, 2006). Bacterial artificial chromosome (BAC) transgenic mice that express specific gene reporters have been recently developed, such as those that express enhanced green fluorescent protein and/or the red fluorescent protein tdTomato under the control of specific promoters. The development of these mice allowed researchers to identify the level of segregation of the D1- and D2-dopamine receptor-containing MSNs in the striatum and the nucleus accumbens (Shuen et al., 2008; Valjent et al., 2009). These studies have convincingly demonstrated that the MSNs can be clearly separated into two principal subgroups that are defined by their projection sites and by the proteins that they express. In particular, the MSNs that project to the medial globus pallidus and the substantia nigra pars reticulata comprise a direct striatonigral pathway that

selectively expresses the D1 dopamine receptor. Another group of MSNs that project to the lateral globus pallidus and selectively express D2 dopamine receptors forms the indirect striatopallidal pathway. This pathway indirectly reaches the substantia nigra pars reticulata through synaptic relays in the lateral globus pallidus and the subthalamic nucleus. In addition to these main subgroups, there is a population of MSNs that express both D1 and D2 dopamine receptors, but their percentage was determined to be relatively low, ranging from 5 to 15% in the dorsal striatum (Valjent et al., 2009). Likewise, coexpression of D1 and D2 dopamine receptors was also observed in 20 to 25% of the pyramidal neurons in the prefrontal cortex of BAC transgenic mice (Zhang et al., 2010).

The D3 dopamine receptor has a more limited pattern of distribution, the highest level of expression being observed in the limbic areas, such as in the shell of the nucleus accumbens, the olfactory tubercle, and the islands of Calleja (Sokoloff et al., 1992b, 2006; Missale et al., 1998). At significantly lower levels, the D3 dopamine receptor is also detectable in the striatum, the substantia nigra pars compacta, the ventral tegmental area, the hippocampus, the septal area, and in various cortical areas. The D4 dopamine receptor has the lowest level of expression in the brain, with documented expression in the frontal cortex, amygdala, hippocampus, hypothalamus, globus pallidus, substantia nigra pars reticulata, and thalamus (Missale et al., 1998; Rondou et al., 2010).

D1, D2, and D4 dopamine receptors have also been observed in the retina, and prominent levels of expres-

sion of D2 dopamine receptors have been detected in the pituitary gland. In the periphery, all subtypes of dopamine receptors have been observed in varying proportions in the kidney, adrenal glands, sympathetic ganglia, gastrointestinal tract, blood vessels, and heart (Missale et al., 1998; Aperia, 2000; Carlsson, 2001; Witkovsky, 2004; Li et al., 2006; Iversen and Iversen, 2007; Villar et al., 2009).

C. Dopamine Receptor Functions

Because dopamine is critically involved in a number of physiological processes, the functional roles of the different dopamine receptor subtypes have been extensively characterized. The most studied role involves the effects of dopamine on locomotor activity. Multiple lines of evidence indicate that locomotor activity is primarily controlled by D1, D2, and D3 dopamine receptors (Missale et al., 1998; Sibley, 1999). The activation of D1 dopamine receptors that are exclusively expressed on the postsynaptic neurons has a moderate stimulatory effect on locomotor activity. The roles of the D2 and D3 dopamine receptors are much more complex than D1 dopamine receptors because they result from both presynaptic and postsynaptic expression of these subtypes of receptors (Missale et al., 1998; Sibley, 1999).

Presynaptically localized autoreceptors generally provide an important negative feedback mechanism that adjusts neuronal firing rate, synthesis, and release of the neurotransmitter in response to changes in extracellular neurotransmitter levels (Wolf and Roth, 1990; Missale et al., 1998; Sibley, 1999). Activation of presynaptic D2-class autoreceptors generally causes a decrease in dopamine release that results in decreased locomotor activity, whereas activation of postsynaptic receptors stimulates locomotion. Because D2-class autoreceptors are generally activated by a lower concentration of dopamine agonists than necessary to activate postsynaptic receptors, the same dopamine agonist can induce a biphasic effect, leading to decreased activity at low doses and behavioral activation at high doses. D2 dopamine receptors seem to be the predominant type of autoreceptors that are involved in the presynaptic regulation of the firing rate, synthesis of dopamine and release of dopamine. It should be noted that the splice variants of the D2 dopamine receptor, D2L and D2S, seem to have different neuronal distributions, D2S being predominantly presynaptic and D2L being postsynaptic. Therefore, the varying roles of the postsynaptic and presynaptic D2 dopamine receptors are probably determined by the different contributions of these isoforms (Usiello et al., 2000; De Mei et al., 2009). A significant body of evidence from pharmacological (Gainetdinov et al., 1996; Zapata and Shippenberg, 2002) and genetic studies in D3 dopamine receptor knockout mice (Sibley, 1999; Joseph et al., 2002) suggests that D3 autoreceptors may also contribute to the presynaptic regulation of tonically released dopamine, thereby complementing the D2S autoreceptor's role in regulating the neuronal firing rate, synthesis of dopamine, and phasic release of dopamine (De Mei et al., 2009).

D3 dopamine receptors seem to exert a moderate inhibitory action on locomotion either by acting as autoreceptors or through the involvement of postsynaptic receptor populations (Sibley, 1999; Joseph et al., 2002). The roles of D4 and D5 dopamine receptors, which have a limited expression pattern in the primary motor regions of the brain, seem to be minimal in the control of movement (Missale et al., 1998; Sibley, 1999; Rondou et al., 2010). At the same time, it is clear that the activation of both the postsynaptic D1- and D2-class dopamine receptors is necessary for the full manifestation of locomotor activity (White et al., 1988).

Many other vital functions depend on the activation of brain dopamine receptors. D1, D2, and, to a lesser degree, D3 dopamine receptors are critically involved in reward and reinforcement mechanisms. Multiple studies have shown that pharmacological and genetic approaches that alter dopamine receptor function result in a significant modulation of the responses to natural rewards and addictive drugs. Thus, dopamine receptors remain an important topic of interest in drug addiction research (Missale et al., 1998; Hyman et al., 2006; Sokoloff et al., 2006; Di Chiara and Bassareo, 2007; De Mei et al., 2009; Koob and Volkow, 2010). Both D1 and D2 dopamine receptors seem to be critical for learning and memory mechanisms, such as working memory, that are mediated primarily by the prefrontal cortex (Goldman-Rakic et al., 2004; Xu et al., 2009). At the same time, D3, D4, and, potentially, D5 dopamine receptors seem to have a minor modulatory influence on some specific aspects of cognitive functions that are mediated by hippocampal areas (Missale et al., 1998; Sibley, 1999; Sokoloff et al., 2006; Rondou et al., 2010). The fact that essentially all clinically effective antipsychotics possess the ability to block D2 dopamine receptors indicates that D2 dopamine receptors are likely to play a critical role in the psychotic reactions observed in schizophrenia and bipolar disorder (Snyder et al., 1970; Roth et al., 2004). Other functions are mediated in part by various dopamine receptor subtypes in the brain, such as affect, attention, impulse control, decision making, motor learning, sleep, reproductive behaviors, and the regulation of food intake (Missale et al., 1998; Di Chiara and Bassareo, 2007; Iversen and Iversen, 2007; Koob and Volkow, 2010; Rondou et al., 2010). In general, the specific physiological roles played by D3, D4, and D5 dopamine receptors in the brain remain largely unknown. Whereas evidence is accumulating that D3 dopamine receptors exert some relatively minor modulatory influences on many of the functions generally attributed to D2 dopamine receptors (Sibley, 1999; Joseph et al., 2002; Sokoloff et al., 2006; Beaulieu et al., 2007b; De Mei et al., 2009), the functions of D4 and D5 dopamine receptors, as revealed by pharmacological and

genetic knockout studies, seem to be quite limited (Missale et al., 1998; Sibley, 1999; Rondou et al., 2010).

Other functions mediated by dopamine receptors that are localized outside the central nervous system include olfaction, vision, and hormonal regulation, such as the pituitary D2 dopamine receptor-mediated regulation of prolactin secretion; kidney D1 dopamine receptor-mediated renin secretion; adrenal gland D2 dopamine receptor-mediated regulation of aldosterone secretion; the regulation of sympathetic tone; D1, D2, and D4 receptor-mediated regulation of renal function; blood pressure regulation; vasodilation; and gastrointestinal motility (Missale et al., 1998; Aperia, 2000; Carlsson, 2001; Witkovsky, 2004; Li et al., 2006; Iversen and Iversen, 2007; Villar et al., 2009).

III. General Principles of Dopamine Receptor Signal Transduction and Regulation

A. Mechanisms of G Protein-Mediated Signaling

All dopamine receptors belong to a large superfamily of GPCRs. Dopamine receptors show a high degree of similarity in their primary amino acid sequences, have a common structure of seven transmembrane-spanning domains and are capable of activating heterotrimeric G proteins to induce intracellular signaling mechanisms (Gingrich and Caron, 1993; Missale et al., 1998; Neve et al., 2004). The commonly accepted mechanism for the activation of dopamine receptors involves G proteins, which led to the classification of these receptors as GPCRs. However, accumulating evidence suggests that these receptors do not signal exclusively through heterotrimeric G proteins and may also engage in G protein-independent signaling events (Luttrell et al., 1999; Luttrell and Lefkowitz, 2002). Thus, G protein-coupled receptors are also termed seven transmembrane-spanning receptors because of the overall structural motif shared by all of these receptors (Shenoy and Lefkowitz, 2005).

All G protein-related actions of GPCRs are mediated by a subset of the 16 heterotrimeric G protein subtypes, which are functionally classified into four broad classes: $G\alpha_s$, $G\alpha_i$, $G\alpha_q$, and $G\alpha_{12}$. In general, G proteins consist of three associated protein subunits: α, β, and γ. The classification of G proteins is based on the nature of the α-subunit sequence and the functional characteristics (Pierce et al., 2002). Without a ligand agonist, the α-subunit, which contains the guanine nucleotide binding site, is bound to GDP and to a tightly associated $\beta\gamma$-complex to form an inactive trimeric protein complex. Upon agonist binding, a sequence of events results in GDP release, GTP binding to the α-subunit, and the dissociation of the α-subunit from the $\beta\gamma$-complex. Both the α-subunit and the $\beta\gamma$-complex can then transduce the signal to activate a relatively small number of effector systems. For example, the activation of $G\alpha_s$ proteins stimulates AC, whereas the activation of $G\alpha_i$ inhibits cAMP production (Fig. 1). It is noteworthy that the freed $\beta\gamma$-subunit complex can engage in its own sinaling activities. When GTP hydrolysis occurs, the GDP-bound α-subunit and the $\beta\gamma$-subunit complex reassociate into the heterotrimeric inactive G protein complex (Pierce et al., 2002). The G protein coupling of the specific subtypes of dopamine receptors is presented in Table 1.

B. Inactivation of G Proteins

Additional mechanisms for the regulation of G protein-mediated signal transduction involve the specific GTPase-activating proteins of the regulators of G protein signaling (RGS) family (Dohlman and Thorner, 1997; Arshavsky and Pugh, 1998; Berman and Gilman, 1998; Chasse and Dohlman, 2003). This family of proteins includes at least 37 members that are characterized by the presence of the same 125-amino acid sequence, the so-called RGS box or RH homology domain, which binds the GTP-bound G protein α-subunits and dramatically accelerates the rate of GTP hydrolysis (Dohlman and Thorner, 1997; Dohlman, 2009). Thus, RGS proteins act as GTPase-accelerating proteins by facilitating the return of the G protein α-subunits to the inactive GTP-bound state. By reducing the lifetimes of the $G\alpha$–GTP and the $\beta\gamma$-subunit complexes, the RGS proteins act as negative modulators of G protein signaling and can affect both the potency and the efficacy of the agonist action and downstream signaling (Fig. 1). It is noteworthy that the RGS proteins accelerate GTP hydrolysis through the $G_{i/o}$ and G_q but not the G_s class of α-subunits, which rapidly hydrolyze GTP (Dohlman and Thorner, 1997; Berman and Gilman, 1998). A detailed description of the roles of the RGS proteins in the regulation of dopamine receptor functions in vivo can be found in section IV.C.1.

C. Involvement of β-Arrestins/G Protein-Coupled Receptor Kinases in Receptor Regulation

GPCRs undergo dynamic regulation upon activation, and receptor sensitivity changes depending on the intensity of the signal (Ferguson, 2001; Pierce et al., 2002). Thus, these receptors can undergo desensitization in response to extensive exposure to agonists and can undergo resensitization when an agonist does not activate them for an extended period of time. An important mechanism of GPCR regulation is the homologous desensitization that involves the phosphorylation of an activated receptor by G protein-coupled receptor kinases (GRKs) and the recruitment of the multifunctional adaptor proteins, termed arrestins (Lohse et al., 1990; Pitcher et al., 1998; Pierce et al., 2002; Gainetdinov et al., 2004; Premont, 2005). After activation of the receptors by an agonist ligand, GRKs phosphorylate the receptors at specific sites on their intracellular loops and COOH terminals (Fig. 1). The phosphorylated receptors then become targets for the recruitment and binding of arrestins in a process that prevents further G protein
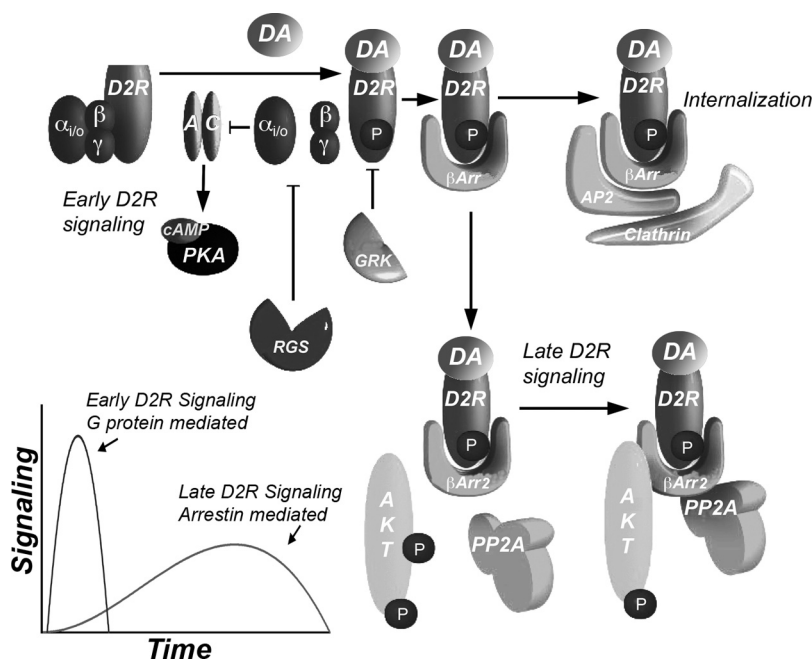
FIG. 1. Early and late D2 dopamine receptor signaling during slow synaptic transmission. In the early phase of signaling, G protein-mediated signaling induces a rapid and transient change in the phosphorylation of direct or indirect PKA targets such as DARPP-32 and CREB. This early phase of D2 dopamine receptor signaling is rapidly antagonized after the inactivation of G proteins by RGSs. In addition, receptor phosphorylation by GRKs results in G protein uncoupling, recruitment of β-arrestins, and clathrin-dependent receptor internalization, effectively shutting down G protein-mediated signaling. In the late phase of signaling, the D2 dopamine receptors stimulate the formation of a protein complex composed of β-arrestin 2, PP2A, and Akt. Formation of this complex results in the deactivation of Akt by PP2A and the subsequent stimulation of GSK-3-mediated signaling. This second wave of signaling mediated by the Akt/β-arrestin 2PP2A complex results in a more progressive and longer lasting response (see inset graph). AP2, adaptor protein complex; DA, dopamine; D2R, D2 dopamine receptor. For a detailed description, see sections III.A, III.B, III.C, IV.E, and IV.F.

activation, despite the continued activation of the receptor by the agonist. In addition to the cessation of G protein signaling, the GRK-arrestin regulatory mechanism also promotes receptor internalization from the cellular membrane through the binding of arrestins to the clathrin adaptor protein β-adaptin and to clathrin itself (Laporte et al., 2002). This process triggers clathrin-mediated endocytosis of the receptors (Fig. 1) and either subsequent recycling of the resensitized receptors to the cell surface or degradation of the receptors through an endosomal-lysosomal system (Ferguson et al., 1996; Ferguson, 2001; Claing et al., 2002; Claing and Laporte, 2005). In addition to the mechanisms that regulate receptor endocytosis and recycling, it should be noted that the trafficking of newly synthesized GPCRs also seems to be tightly regulated. For example, the endoplasmic reticulum chaperone protein calnexin interacts with D1 and D2 dopamine receptors and seems to critically regulate receptor trafficking and receptor expression at the cell surface, at least in transfected HEK293T cells (Free et al., 2007).

The human genome encodes seven different GRKs that are organized into three classes based on kinase sequences and functional similarities: GRK1-like, GRK2-like, or GRK4-like. The GRK1-like kinases, GRK1 (rhodopsin kinase) and GRK7 (iodopsin kinase), are expressed exclusively in the visual system and primarily regulate the light receptors, known as the opsins. Members of the GRK2-like

(GRK2 and GRK3) and the GRK4-like (GRK4, GRK5, and GRK6) classes are widely expressed all over the body and may be involved in the regulation of all of the GPCRs (Pitcher et al., 1998; Premont, 2005; Premont and Gainetdinov, 2007). Like GRKs, arrestin proteins have primarily visual-specific isoforms, termed arrestin-1 (rod arrestin) and arrestin-4 (cone arrestin). The other two arrestins, β-arrestin 1 (arrestin 2) and β-arrestin 2 (arrestin 3), are highly expressed in essentially every tissue and could be involved in the regulation of the vast majority of GPCRs (Luttrell and Lefkowitz, 2002; Gainetdinov et al., 2004; Gurevich and Gurevich, 2004).

GRKs and arrestins can serve also as signaling switches, promoting a new wave of signaling events that are G protein-independent (Hall et al., 1999; Luttrell et al., 1999). For example, arrestins can serve as adaptors that induce the scaffolding of a wide variety of signaling proteins, such as mitogen-activated protein kinases (MAP kinases), c-Src, Mdm2, N-ethylmaleimide-sensitive factor, Akt, and others (Luttrell and Lefkowitz, 2002; Shenoy and Lefkowitz, 2003, 2005; Beaulieu et al., 2009; Luttrell and Gesty-Palmer, 2010). Thus, the regulation of a specific GPCR by the GRK/arrestin system can have various outcomes ranging from the suppression of G protein signaling to the promotion of G protein-independent signaling. The role of the GRK/arrestin system in dopamine receptor regulation and signaling is discussed in detail in sections IV.E and IV.F.

D. Heterologous Desensitization

An additional mechanism of desensitization may involve receptor activation-independent regulation of GPCRs, known as heterologous desensitization. This process occurs when the activation of one GPCR, or another type of receptor, causes the desensitization of other GPCRs in the same cell. Heterologous desensitization often involves feedback regulation of receptors or various signaling components by activated downstream second messenger-regulated kinases and probably occurs in neurons that are exposed to multiple hormones or neurotransmitters simultaneously (Hamm and Gilchrist, 1996; Ferguson, 2001; Namkung and Sibley, 2004). For $G\alpha_{s/olf}$-coupled receptors, such regulation might be carried out by protein kinase A (PKA), protein kinase C (PKC), MAP kinases, or several other kinases (Hamm and Gilchrist, 1996).

For dopamine receptors, it has been demonstrated that PKC can mediate the phosphorylation, desensitization, and internalization of D2 dopamine receptors (Namkung and Sibley, 2004) and D3 dopamine receptors (Cho et al., 2007). Alternately spliced variants, the D2S and D2L dopamine receptors, display different levels of sensitivity to desensitization by PKC depending on the relative location of their phosphorylation and pseudosubstrate sites (Liu et al., 1992; Morris et al., 2007). Dopamine D1 receptors can also be phosphorylated and regulated by PKCγ and PKCδ as well as their interacting proteins, RanBP9 and RanBP10, in an ethanol-dependent manner, indicating a new mechanism for the potentiation of dopaminergic neurotransmission by ethanol (Rex et al., 2008; Rex et al., 2010).

IV. Dopamine Receptor Signaling

A. cAMP, Protein Kinase A, DARPP-32, and Associated Proteins

Dopamine receptor functions have typically been associated with the regulation of cAMP and PKA via G protein-mediated signaling. The D1-class receptors, D1 and D5, are generally coupled to $G\alpha_{s/olf}$ and stimulate the production of the second messenger cAMP and the activity of PKA. In contrast, D2-class dopamine receptors (D2, D3, and D4) are coupled to $G\alpha_{i/o}$ and negatively regulate the production of cAMP, resulting in a decrease in PKA activity (Kebabian and Greengard, 1971; Kebabian and Calne, 1979; Enjalbert and Bockaert, 1983; Missale et al., 1998).

1. Amplification of Protein Kinase A Signaling by DARPP-32. Several substrates of PKA, such as CREB, ionotropic glutamate receptors (AMPA and NMDA), and certain ion channels, have been shown to be affected by dopamine receptor stimulation (Greengard, 2001). Among the PKA substrates, the 32-kDa dopamine and cAMP-regulated phosphoprotein (DARPP-32) is one of the most extensively studied molecules involved in dopamine receptor signaling. DARPP-32 is a multifunctional phosphoprotein that is predominantly expressed in MSNs. In these cells, DARPP-32 acts as an integrator involved in the modulation of cell signaling in response to multiple neurotransmitters, including dopamine (Svenningsson et al., 2004). Phosphorylation of this molecule at threonine 34 by PKA or protein kinase G activates the protein phosphatase 1 (PP1) inhibitory function of DARPP-32 (Hemmings et al., 1984a,b). The direct regulation of DARPP-32 phosphorylation at threonine 34 by dopamine receptors has recently been demonstrated in vivo using BAC transgenic mice that overexpressed immunoprecipatable-tagged DARPP-32 proteins specifically in D1 or D2 dopamine receptor positive MSNs (Bateup et al., 2008). The results from studies conducted using these mice have shown that enhanced dopamine receptor stimulation results in an increased phosphorylation of DARPP-32 in response to PKA activation in D1 dopamine receptor-expressing neurons, whereas stimulation of D2 dopamine receptors reduces the phosphorylation of DARPP-32 at threonine 34, presumably as a consequence of a reduction in PKA activation (Bateup et al., 2008) and/or the dephosphorylation of threonine 34 by the calmodulin-dependent protein phosphatase 2B (PP2B; also known as calcineurin) that is activated by increased intracellular Ca^{2+} after activation of D2 dopamine receptors (Nishi et al., 1997).

In contrast to PKA, cyclin-dependent kinase 5 (CDK5) has been shown to phosphorylate DARPP-32 at threonine 75, preventing the inhibition of PP1 by DARPP-32 and converting DARPP-32 to an inhibitor of PKA (Bibb et al., 1999). Furthermore, DARPP-32 is also phosphorylated at serine 137 by casein kinase 1 (CK1) (Desdouits et al., 1995) and at serine 97/102 by casein kinase 2 (CK2) (Girault et al., 1989a). The phosphorylation of DARPP-32 by CK1 reduces threonine 34 phosphorylation, whereas CK2 enhances the phosphorylation of DARPP-32 by PKA. Furthermore, the dephosphorylation of serine 97/102 by protein phosphatase 2A (PP2A) also results in an accumulation of DARPP-32 in the nucleus, where it prevents the dephosphorylation of histone H3 by PP1 and leads to enhanced gene expression in response to D1 dopamine receptor stimulation (Stipanovich et al., 2008).

Studies of DARPP-32 function in vivo and in striatal slice preparations have shown that this regulator acts as an amplification mechanism for PKA signaling. In MSNs, the phosphorylation state of multiple PKA targets, such as ionotropic glutamate and GABA receptors, is the result of an equilibrium between PKA and PP1 activity (Greengard et al., 1999; Greengard, 2001), and similar mechanisms can have important effects on the regulation of synaptic plasticity by dopamine receptors in other brain areas, such as frontal cortex (Xu et al., 2009). By inhibiting PP1, DARPP-32 tips this equilibrium toward the phosphorylated state and enhances the efficacy of PKA-mediated signaling. Because the kinases that regulate DARRP-32 can be activated in response to multiple hormones, neuropeptides, and neurotransmit-

ters, it is not surprising that DARPP-32 has been shown to coordinate different signaling modalities (Greengard, 2001). In agreement with this finding, modulation of the inhibition of PP1 by DARPP-32 in response to nondopaminergic drugs, such as cannabinoids (Andersson et al., 2005) and caffeine (Lindskog et al., 2002), can affect PKA signaling responses after the activation of dopamine receptors and can modulate dopamine-associated behaviors.

Mice lacking DARPP-32 display deficits in their responses to dopaminergic drugs, such as cocaine (Fienberg et al., 1998), which elevates the extracellular concentration of dopamine by blocking the dopamine transporter (DAT). Similar results were obtained using knockin mice that expressed a mutant DARPP-32 lacking threonine 34 (Svenningsson et al., 2003; Zhang et al., 2006). Taken together, these findings confirm the role of phospho-threonine 34 DARPP-32 in the development of dopamine-dependent behaviors. However, a thorough ethological characterization of DARPP-32 knockout mice showed that several dopamine-associated behaviors, including basal locomotion, are not overtly disrupted in these mice (Nally et al., 2003, 2004; Waddington et al., 2005). By comparison, observations made in dopamine-depleted animals have shown that basal locomotion is essentially abolished in the absence of the stimulation of dopamine receptors (Zhou and Palmiter, 1995; Sotnikova et al., 2005). Moreover, behavioral responses to drugs that change dopamine levels, such as apomorphine and cocaine, are only partially affected in DARPP-32 knockout mice (Fienberg et al., 1998; Nally et al., 2004). For example, DARPP-32 knockout mice have been shown to exhibit a deficiency in their acute locomotor response only to intermediate doses (i.e.,10 mg/kg) of cocaine, whereas their responses to higher drug doses (i.e., 20 mg/kg) were essentially intact (Fienberg et al., 1998). Recent characterization of dopamine-mediated behaviors in mice lacking DARRP-32 in D1 dopamine receptor-expressing neurons revealed a slight reduction in spontaneous locomotion and cocaine-induced hyperactivity (Bateup et al., 2010). In contrast, the specific ablation of DARPP-32 in neurons that express D2 dopamine receptors resulted in enhanced locomotor responses to cocaine and an enhanced level of basal locomotor activity (Bateup et al., 2010). This latter observation is interesting because mice lacking D2 dopamine receptors or the predominantly postsynaptic D2L variant have been shown to display an overall reduction in basal locomotor activity and in their responsiveness to cocaine (Baik et al., 1995; Vargas-Pérez et al., 2004; Doi et al., 2006; Welter et al., 2007). These findings suggest that a reduction in phospho-threonine 34 DARPP-32 in response to D2 dopamine receptor stimulation may contribute to some of the pro-locomotor effects that are associated with D2 dopamine receptor activation. In general, the persistence of dopamine behaviors in DARPP-32 knockout mice suggests that

although DARPP-32 functions as an important modulator of dopamine receptor signaling, it is not the only modulator/effector of dopamine-related actions, and its activity may be compensated for by other signaling mechanisms.

The behavioral and physiological impacts of the phosphorylation of DARPP-32 by CDK5 have also been studied. Repeated exposure to cocaine in normal rats and the persistent elevation of extracellular dopamine levels in mice that lack the dopamine transporter (DAT-KO mice) enhance the expression of CDK5 and its coactivator p35 in the striatum (Bibb et al., 2001; Cyr et al., 2003). Moreover, transgenic mice that overexpress the transcription factor ΔFosB, which is accumulated after long-term over-stimulation of D1 dopamine receptors in DAT-KO or cocaine-treated animals, also displayed increased CDK5 expression, providing a mechanism for the regulation of the *CDK5* gene expression by dopamine (Bibb et al., 2001; Cyr et al., 2003). Enhanced CDK5 expression has been shown to antagonize the development of cocaine sensitization (Bibb et al., 2001); however, whether this effect is due to a postsynaptic inhibition of PKA via phospho-threonine 75 DARPP-32 or to a presynaptic function of CDK5 in the regulation of dopamine release remains controversial (Chergui et al., 2004).

2. Metabotropic Neurotoxicity of cAMP-Mediated Dopamine Receptor Signaling. Increased CDK5 expression in response to D1 dopamine receptor stimulation may also be associated with the degeneration of MSNs in response to excessive dopamine receptor stimulation. A subpopulation (30%) of hyperdopaminergic DAT-KO mice have been shown to sporadically develop progressive locomotor dysfunctions characterized by a loss of the locomotor hyperactivity that is typical of DAT-KO mice and by the development of dyskinesia, paralysis, and death (Cyr et al., 2003). This motor disorder resembles a phenotype that has been observed in the lines of transgenic mice that express the variants of huntingtin that are associated with Huntington's disease (Levine et al., 2004), suggesting that MSNs were affected in the DAT-KO mice that developed these symptoms (symptomatic DAT-KO). An examination of the nigrostriatal system of the symptomatic mice revealed a specific loss of ∼30% of the MSNs, a phenomenon that was not observed in the DAT-KO mice that did not develop locomotor dysfunctions (Cyr et al., 2003). Furthermore, terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL)-positive MSNs containing detectable levels of activated caspase 3 were also observed, indicating an activation of the apoptotic processes in these cells. The symptomatic mice displayed an enhanced level of CDK5 and p35 expression compared with their nonsymptomatic littermates. This up-regulation of CDK5 was accompanied by the accumulation of a hyperphosphorylated form of the microtubule-associated τ protein (Cyr et al., 2003). Hyperphosphorylation of τ on residues

that are phosphorylated by CDK5 has been shown to be associated with Alzheimer's disease (Patrick et al., 1999; Dhavan and Tsai, 2001) and other neurodegenerative disorders, including amyotrophic lateral sclerosis and Huntington's disease (Jellinger, 1998; Nguyen et al., 2001; Beaulieu and Julien, 2003).

An increase in the level of dopamine neurotransmission has been shown to enhance the motor and neuropathological phenotypes in a knockin mouse model expressing a mutant form of huntingtin that contains 92 CAG repeats (Cyr et al., 2006). In addition, activation of the D1 dopamine receptor accelerates the formation of mutant huntingtin nuclear aggregates in SK-N-MC neuroblastoma cells (Robinson et al., 2008). Overstimulation of ionotropic neurotransmitter receptors, in particular glutamate receptors, is well known to exert adverse excitotoxic effects (Choi, 1987). Taken together, these observations concerning the neurotoxicity that is caused by the overstimulation of D1 dopamine receptors suggest that the overstimulation of metabotropic receptors might have "metabotoxic" effects that render neurons more susceptible to other insults, such as those caused by the expression of mutant huntingtin.

3. Coincidence Detection by Mitogen-Activated Protein Kinases. The complexity of the signaling network that is regulated by cAMP downstream from dopamine receptors also provides mechanisms for a context-dependent regulation of cellular responses to dopamine. For example, it is possible that many of the consequences of dopamine receptor stimulation occur only under specific conditions that require the coactivation of other types of receptors. These types of cellular responses that are dependent on the co-occurrence of different forms of stimulation are designated coincidence detectors and are known to play a central role in the regulation of synaptic plasticity. MAP kinases have been shown to act as important coincidence detectors that integrate the actions of dopamine with those of other neurotransmitter systems.

Many MAP kinases have been shown to be signaling intermediates that are involved in the regulation of dopamine-associated behaviors (Berhow et al., 1996). Results obtained from heterologous cell culture systems suggest that both D1- and D2-class dopamine receptors can regulate the MAP kinases extracellular-signal regulated kinases 1 and 2 (ERK1 and ERK2) (Beom et al., 2004; Chen et al., 2004b; Wang et al., 2005; Kim et al., 2006). In vivo, the administration of amphetamine (Beaulieu et al., 2006; Valjent et al., 2006b), cocaine (Berhow et al., 1996; Valjent et al., 2000), or the D2-class dopamine receptor antagonist haloperidol (Pozzi et al., 2003) has been shown to enhance striatal ERK1 and ERK2 phosphorylation. Moreover, ERK2 phosphorylation has also been shown to increase in response to elevated dopamine levels in the striatum of DAT-KO mice (Beaulieu et al., 2006). Pharmacological and genetic characterizations of the dopamine receptor types

that are involved in the activation of striatal ERK have revealed that D1 dopamine receptors are essential for the activation of these kinases in MSNs (Valjent et al., 2000, 2005; Zhang et al., 2004; Liu et al., 2006a). In contrast, D2-class dopamine receptors, in particular D3 dopamine receptors, have been shown to mediate the inhibition of ERK-mediated signaling in the striatum (Zhang et al., 2004).

The activation of ERK by D1 dopamine receptors in response to cocaine administration has been shown to be dependent upon the stimulation of ionotropic glutamate receptors and to be preventable by the NMDA receptor antagonist known as MK-801 (Valjent et al., 2005). The regulation of ERK phosphorylation by D1 dopamine receptors and NMDA receptors may result from the convergence of several signaling modalities that are regulated by these two types of receptors. NMDA receptor stimulation results in the activation of the ERK kinase MEK. In the absence of D1 dopamine receptor stimulation, the action of MEK on ERK activity is counteracted by the activity of striatal-enriched tyrosine phosphatase (STEP), resulting in a zero-sum equilibrium in which the overall activity of ERK remains unchanged. The activity of STEP depends on its dephosphorylation by PP1. Activation of the D1 dopamine receptor/PKA/DARRP-32 signaling cascade leads to the inactivation of PP1 and the consequent inactivation of STEP (Valjent et al., 2000, 2005). This modification of the equilibrium of STEP and MEK activity after D1 dopamine receptor stimulation allows for the activation of ERK by MEK (Fig. 2A). The coregulation of ERK by D1 dopamine receptors and NMDA receptors has indicated that ERK might act as a signal integrator for dopamine and glutamate neurotransmission during the development of the behavioral responses to drugs of abuse.

An inhibition of brain ERK activity has been shown to affect short- and long-term responses to psychostimulants. At high doses, the administration of the blood-brain barrier-permeant MEK inhibitor α-[amino[(4-aminophenyl)thio]methylene]-2-(trifluoromethyl)benzeneacetonitrile (SL327) results in a massive reduction in ERK phosphorylation and antagonizes the locomotor actions of cocaine and amphetamine (Valjent et al., 2000, 2006b; Beaulieu et al., 2006). At low doses, this drug does not affect short-term locomotor responses, but it does interfere with the development of long-term changes in behavioral and synaptic plasticity that are associated with neuronal adaptation and addiction to drugs of abuse (Valjent et al., 2000, 2006b). The mechanism underlying these long-lasting behavioral outcomes is not fully understood. Multiple groups have reported that ERK-mediated signaling is essential for the activation of the transcription factors CREB, Zif268, and c-Fos and for the phosphorylation of histone H3 in response to cocaine (Valjent et al., 2000, 2006a; Brami-Cherrier et al., 2005; Miller and Marshall, 2005). Activation of this cascade is believed to be associated with the development of long-lasting changes in gene

D1-class responding neurons

FIG. 2. Signaling networks regulated by dopamine in D1-class dopamine receptor responding neurons. A, regulation of $G\alpha_s$/cAMP/PKA signaling by D1-class dopamine receptors. B, regulation of $G\alpha_q$/PLC signaling by D1-class dopamine receptors or D1:D2 dopamine receptor heterodimers. The action of other neurotransmitters, growth factors, and neurotrophins has been included to illustrate the role of these intermediates as signal integrators. Blue arrows indicate activation, red T-arrows indicate inhibition, and green arrows indicate the amplification of an already activated function. Black arrows indicate actions that can either be activatory or inhibitory on the function of specific substrates. D1R, D1 dopamine receptor; D2R, D2 dopamine receptor; D5R, D5 dopamine rceptor. For a detailed description of these different signaling pathways, see sections IV.A and IV.B.

expression and in the development of behavioral adaptations. The epigenetic regulation of gene expression by ERK may result in part from the activation of the mitogen- and stress-activated protein kinase 1 in the dorsal striatum and the nucleus accumbens (Brami-Cherrier et al., 2005). Although experiments involving the local administration of MEK inhibitors have shown that ERK signaling in the nucleus accumbens is important for the development of long-lasting adaptations to cocaine (Miller and Marshall, 2005), ERK signaling in other brain regions, such as the amygdala (Lu et al., 2005; Radwanska et al., 2005), also seems to play a role in these phenomena.

In addition, long-lasting regulation of epigenetic mechanisms might contribute to the development of unwanted side effects in response to treatment with L-DOPA (Santini et al., 2007, 2009a). In 6-hydroxydopamine-lesioned/L-DOPA-treated mice, DARPP-32-dependent ERK activation is associated with the development of dyskinesia, whereas inhibition of ERK signaling during long-term L-DOPA treatment counteracts the induction of dyskinesia (Santini et al., 2007). It is noteworthy that ERK activation in dyskinetic mice was accompanied with changes in mitogen- and stress-activated protein kinase 1 activation and histone H3 phosphorylation that are reminiscent of responses to D1 dopamine receptor-mediated ERK activation after repeated cocaine administration (Santini et al., 2007, 2009a). However, in addition to ERK signaling, other types of cell-signaling mechanisms that regulate gene expression and synaptic plasticity, such as D1 dopamine receptor-mediated activation of the mTOR complex 1, also

seem to be involved in dyskinesia (Santini et al., 2009b). Understanding these mechanisms and their role in dyskinesia and addiction may be important for controlling the unwanted side effects of drugs that act on dopamine neurotransmission.

Modulation of ERK signaling has also been implicated in the regulation of hyperactivity resulting from psychostimulants in DAT-KO mice (Beaulieu et al., 2006). In normal animals, psychostimulants such as amphetamine and methylphenidate increase extracellular levels of dopamine, leading to the development of locomotor hyperactivity and to an augmented activation of ERK. Increased extracellular dopamine levels also result in an elevation in the level of ERK activity and in the development of a hyperactive phenotype in DAT-KO mice (Giros et al., 1996; Gainetdinov et al., 1999b; Beaulieu et al., 2004). However, the administration of psychostimulants in these mice results in a reduction of locomotor activity that is reminiscent of the action of psychostimulants in ADHD (Gainetdinov et al., 1999b; Beaulieu et al., 2006). This paradoxical effect of psychostimulants in the DAT-KO mice can also be mimicked by drugs that enhance serotonergic neurotransmission, suggesting that psychostimulants act through a serotonergic mechanism in DAT-KO mice (Gainetdinov et al., 1999b). A characterization of the signaling mechanisms that are affected by amphetamine and methylphenidate revealed that, in contrast to their effects in normal control mice, psychostimulants inhibit ERK in the striatum of DAT-KO mice (Beaulieu et al., 2006). It is noteworthy

that the administration of the serotonergic drugs fluoxetine and nonselective serotonin agonist 5-carboxamido-tryptamine has also been shown to result in an inhibition of striatal ERK in DAT-KO mice. Furthermore, administration of ERK inhibitor SL327 recapitulated the actions of psychostimulants in DAT-KO animals, whereas it had no effect on locomotion in wild-type (WT) mice that were treated with the NMDA receptor antagonist dizocilpine maleate (MK-801) (Beaulieu et al., 2006). These data suggest that ERK can integrate the actions of dopamine and serotonin at the level of striatal MSNs. Moreover, these observations raise the possibility that the inhibitory action of psychostimulants on dopamine-dependent hyperactivity results from an altered regulation of striatal ERK phosphorylation. However, further studies will be needed to clarify whether this paradoxical action of psychostimulants on ERK-mediated signaling can provide a mechanism of action of these drugs for the management of ADHD.

4. Interaction with Epac Proteins. In addition to their effects on PKA, dopamine receptors may also exert physiological actions by acting on other cAMP-regulated molecules. Exchange proteins that are directly activated by cAMP (Epac1 and Epac2) are cAMP-regulated signaling proteins that are highly enriched in the striatum (Gloerich and Bos, 2010). Recent evidence suggests that Epac2 is involved in D1 dopamine receptor-mediated synapse remodeling and depression in cultured rat cortical neurons (Woolfrey et al., 2009). In addition to this finding, there are also reports of cAMP-dependent effects of dopamine receptor signaling that seems to be independent of PKA and Epac (exchange protein directly activated by cAMP) activity (Podda et al., 2010), suggesting that other cAMP-responsive molecules are effectors of dopamine receptor signaling.

B. Alternative G Protein Mechanisms

1. Receptor Signaling through $G\alpha_q$. There is evidence that, in addition to their effects on cAMP-regulated signaling, dopamine receptors can also couple to $G\alpha_q$ to regulate phospholipase C (PLC) (Fig. 2B). Activation of PLC leads to the production of inositol trisphosphate (IP_3) and diacylglycerol (DAG). This activation results in the activation of PKC by DAG and an increased mobilization of intracellular calcium in response to IP_3. Although several lines of evidence indicate that dopamine can regulate PKC activity or intracellular calcium signaling (Felder et al., 1989; Friedman et al., 1997; Lee et al., 2004; Sahu et al., 2009), the exact mechanisms involved in this effect are still controversial. As early as 1989, Felder et al. reported that the D1 dopamine receptor agonist SKF 82526 stimulates PLC activity independently of cAMP in renal tubular membranes. It is noteworthy that this result of D1-class receptor activation has been observed in D1-KO mice (Friedman et al., 1997) but not in mice lacking the D5 dopamine receptor (Sahu et al., 2009). Furthermore, the

expression of D1 dopamine receptors in transfected HEK293 cells did not affect intracellular calcium signaling, whereas the expression of D5 dopamine receptors in the same cells induced extensive calcium mobilization after stimulation (So et al., 2009). Although these observations do not make it possible to exclude completely the contribution of D1 dopamine receptors in $G\alpha_q$-mediated signaling, they suggest either that the D5 dopamine receptor is the main regulator of this signaling in vivo or that the D1 dopamine receptor needs to interact with other proteins to couple to $G\alpha_q$.

The molecular determinants that regulate the alternative coupling of D1-class receptors to $G\alpha_q$ are still not completely understood. Among the possible mechanisms, it has been postulated that proteins that interact with dopamine receptors may regulate the coupling of these receptors to different G proteins in vivo (Bergson et al., 2003) or that the activation of dopamine receptors may enhance the signaling of other GPCRs through the PLC/IP_3 pathway (Dai et al., 2008). Alternatively, it has also been shown that D1/D2 dopamine receptor heterodimers can regulate DAG and IP_3 signaling in transfected cells (Lee et al., 2004). The physiological relevance of this observation has remained controversial because studies conducted in BAC-transgenic mice that express fluorescent gene-reporter proteins have shown that D1 and D2 dopamine receptors are not coexpressed in most striatal neurons in mice (Heiman et al., 2008; Shuen et al., 2008; Valjent et al., 2009). However, the coexpression of D1 and D2 dopamine receptors has been reported after immunohistological detection in the nucleus accumbens of 8-month-old mice (Rashid et al., 2007) in addition to several other locations in the basal ganglia (Perreault et al., 2010). There is also evidence for the regulation of BDNF production through a calcium-dependent D1 dopamine receptor signaling mechanism in the nucleus accumbens of adult rats (Hasbi et al., 2009) and for a potential contribution of D1/D2 dopamine receptor heterodimers in the regulation of dopamine-responsive behaviors in adult rats (Perreault et al., 2010). Finally, a recent study of dopamine receptor expression in the prefrontal cortex of BAC transgenic mice that express fluorescent gene-reporter proteins in neurons with D1 and D2 dopamine receptors showed that most D1 dopamine receptor-positive pyramidal neurons in the prefrontal cortex also express low levels of D2 dopamine receptors (Zhang et al., 2010). Therefore, it is possible that D1/D2 dopamine receptor heterodimers occur in vivo and regulate calcium-dependent cell signaling in some neuronal populations (Fig. 2B).

2. Regulation of $G\beta\gamma$ Signaling and Ion Channels by D2 Dopamine Receptors. D2-class receptors also modulate intracellular calcium levels (Fig. 3, A and B) by acting on ion channels or by triggering the release of intracellular calcium stores (Nishi et al., 1997; Missale et al., 1998). Some of these actions of D2-class receptors on calcium signaling seem to be related to signaling
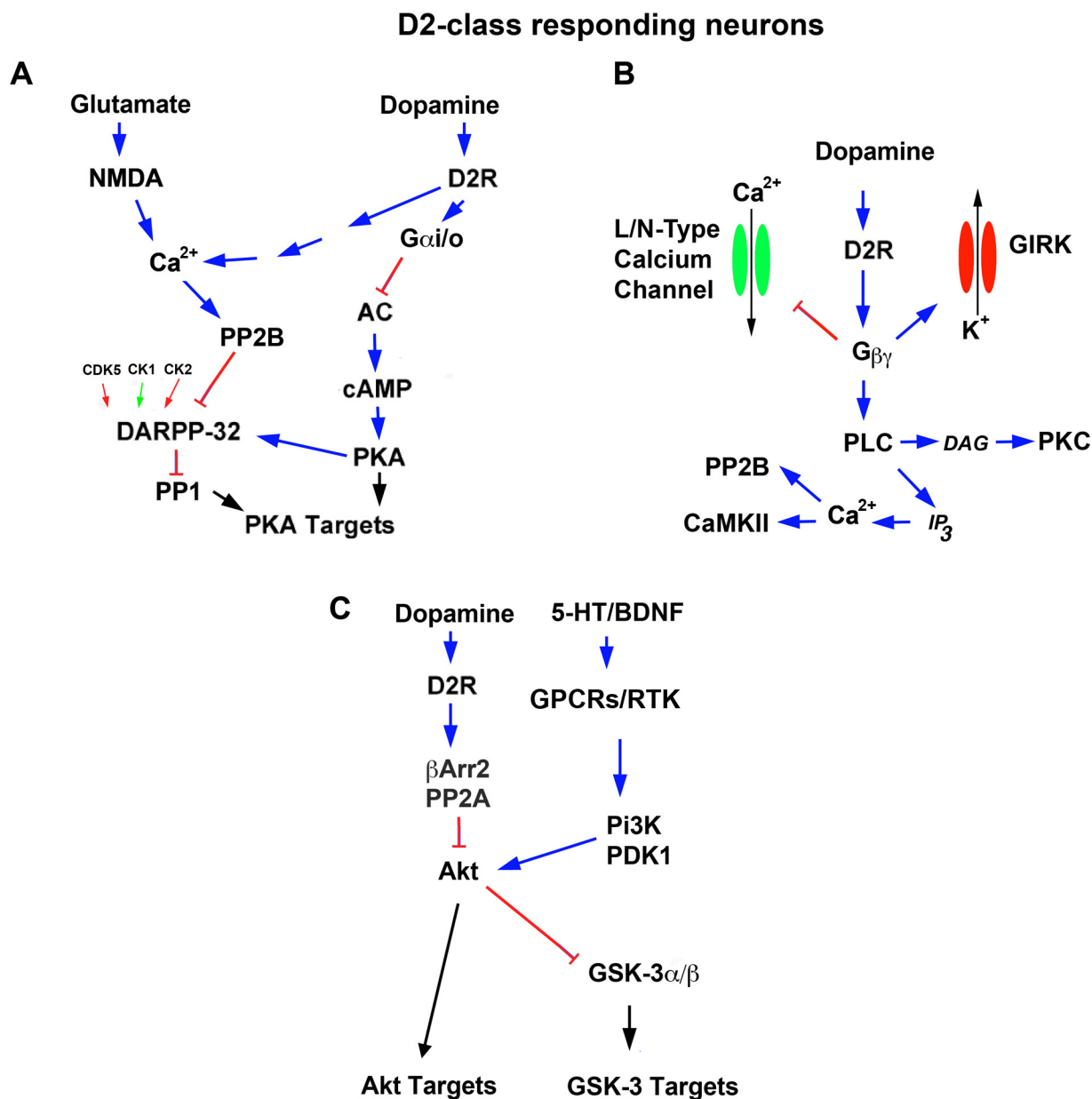
D2-class responding neurons

A

Glutamate

Dopamine

NMDA

D2R

Gαi/o

Ca²⁺

AC

PP2B

CDK5 CK1 CK2

cAMP

DARPP-32

PKA

PP1

PKA Targets

B

Dopamine

L/N-Type
Calcium
Channel

Ca²⁺

D2R

GIRK

K⁺

Gβγ

PLC → DAG → PKC

PP2B

CaMKII ← Ca²⁺ ← IP₃

C

Dopamine

5-HT/BDNF

D2R

GPCRs/RTK

βArr2
PP2A

Pi3K
PDK1

Akt

GSK-3α/β

Akt Targets

GSK-3 Targets

FIG. 3. Signaling networks regulated by dopamine in D2-class dopamine receptor responding neurons. A, regulation of Gα$_s$/cAMP/PKA signaling by D2-class receptors. B, regulation of Gβγ signaling by D2-class receptors. C, regulation of β-arrestin 2/Akt/GSK-3 signaling by D2 and D3 dopamine receptors. The action of other neurotransmitters, growth factors, and neurotrophin has been included to illustrate the role of many of these intermediates as signal integrators. Blue arrows indicate activation, red T-arrows indicate inhibition, and green arrows indicate the amplification of an already activated function. Black arrows indicate actions that can either be activatory or inhibitory on the function of specific substrates. PDK1, phosphatidylinositol-dependent kinase 1; Pi3K, phosphatidylinositol 3-kinase; RTK, receptor tyrosine kinase. For a detailed description of these different signaling pathways, see sections IV.A, IV.B, IV.D, and IV.F.

responses that are mediated by the Gβγ subunits of heterotrimeric G proteins, which are separated from Gα subunits after receptor activation. Gβγ subunits that are regulated by D2 dopamine receptors have been shown to activate PLC and to increase the cytoplasmic calcium concentration in MSNs (Hernandez-Lopez et al., 2000). It is noteworthy that this mechanism also reduces the level of activity of the L-type calcium channels in these cells, indicating that stimulation of D2 dopamine receptors has complex effects on calcium-mediated biological processes in these neurons (Fig. 3B). It is note-

worthy that D2 dopamine receptor-regulated Gβγ subunits are also involved in the regulation of N-type calcium channels in striatal interneurons (Yan et al., 1997). Finally, the role of the Gβγ subunits is not limited to calcium channels. These proteins are also involved in the association/regulation of the D2 dopamine receptor and G protein-coupled inwardly rectifying potassium channels (GIRKs) (Kuzhikandathil et al., 1998; Lavine et al., 2002). The activation of GIRKs after activation of the D2 dopamine receptor (Fig. 3B) and other GPCRs has an inhibitory effect in neurons and could potentially

mediate several functions of dopamine in vivo. For a recent review of the potential implications of the activation of GIRKs in human pathologic conditions, see Lüscher and Slesinger (2010).

C. Regulation of G Protein Activity

1. Evidence for the Involvement of Regulators of G Protein Signaling. The regulation of G protein-mediated dopamine receptor signaling by RGSs has been studied extensively both in vitro and in vivo. Compelling evidence exists that indicates that the RGS9-2 subtype, which is particularly enriched in the striatum, plays an important role in the regulation of D2 dopamine receptor signaling. This regulation was clearly demonstrated in direct biochemical and electrophysiological experiments in heterologous cellular systems and striatal neurons (Granneman et al., 1998; Cabrera-Vera et al., 2004; Kovoor et al., 2005; Seeman et al., 2007; Martemyanov and Arshavsky, 2009). Furthermore, the functional role of this regulation was observed in studies that showed an altered regulation of RGS9-2 protein levels after short-term or repeated exposure to psychostimulants and D2 dopamine receptor ligands in normal animals (Seeman et al., 2007). In addition, this finding was supported by the demonstration of the enhanced psychomotor and rewarding effects of psychostimulants in mice lacking RGS9-2 (Rahman et al., 2003; Traynor et al., 2009). In contrast, animals with an increased expression of RGS9-2 have been shown to exhibit a diminished response to psychostimulants, D2 (but not D1) dopamine receptor agonists and to undesirable dyskinetic effects of long-term L-DOPA treatment in experimental models of PD (Gold et al., 2007; Traynor et al., 2009). The results of a recent report have indicated that the function of striatal RGS9-2 is controlled by its association with an additional subunit, R7BP, and have demonstrated motor coordination deficits and locomotor supersensitivity to morphine, but not cocaine, in mice lacking R7BP. In addition, the sensitivity of locomotor stimulation to cocaine seemed to depend on RGS7 because its interaction with R7BP is dictated by RGS9-2 expression. Thus, a cooperative role in the regulation of dopamine signaling in the striatum has been proposed for two RGS proteins, RGS7 and RGS9-2, which are balanced by a common subunit R7BP (Anderson et al., 2010). Other members of the RGS family that are enriched in the primary dopaminergic areas of the brain, RGS2 and RGS4, may also contribute to the regulation of dopamine receptors; however, the evidence supporting this role has not yet been confirmed through direct testing in vivo (Burchett et al., 1999; Taymans et al., 2003, 2004; Schwendt et al., 2006; Anderson et al., 2010).

2. Evidence for Additional Regulatory Mechanisms. Other regulatory proteins have been identified as potential modulators of D2 dopamine receptor cAMP-mediated signaling, such as prostate apoptosis response-4 (Par-4), a leucine zipper-containing protein that plays a role in apoptosis (Park et al., 2005). The results of this study have shown that recombinant Par-4 directly interacts with D2 dopamine receptors via a calmodulin-binding motif that is situated in the third cytoplasmic loop of the receptor. A reduction in Par-4 expression in a heterologous cell system or in cultured neurons from knockin mice expressing a mutant Par-4 that lacked an interaction domain for the D2 dopamine receptor resulted in a reduction of D2 dopamine receptor signaling via cAMP. Last, knockin mice expressing a Par-4 mutant that does not interact with D2 dopamine receptors have been shown to display behavioral abnormalities in tests that model depression in rodents (Park et al., 2005). However, these behavioral paradigms have been traditionally associated with serotonergic or adrenergic, rather than dopaminergic, neurotransmission (Xu et al., 2000; Cervo et al., 2005; Crowley et al., 2005). In the absence of a characterization of the actions of dopaminergic drugs in Par-4 mutant mice, the role of this molecule in the regulation of dopamine signaling in vivo is not yet completely understood.

D. Direct Interactions with Ion Channels and Associated Proteins

In addition to the regulation of neuronal ion channels through G protein- mediated signaling, dopamine receptors have been shown to interact directly with several proteins including ion channels or ionotropic receptors in neurons.

1. Interactions with Calcium Channels. D1 dopamine receptors and N-type calcium channels are highly expressed and colocalized on apical dendrites in the prefrontal cortex. A recent study of the regulation of N-type calcium channels by D1 dopamine receptors showed that the second intracellular loop of D1 dopamine receptors can directly interact with the COOH terminal region of N-type calcium channel Cav2.2 subunits in vitro. Furthermore, these full-length molecules also interact in native tissue, and the activation of D1 dopamine receptors results in a protein interaction-dependent inhibition/internalization of N-type calcium channels in the prefrontal cortex (Kisilevsky et al., 2008). A similar interaction of N-type calcium channels with potentially similar effects on the regulation of N-type calcium channels has also been reported for transfected cells (Kisilevsky and Zamponi, 2008).

2. Direct Interactions with Ionotropic Receptors. Dopamine receptors can also interact directly with ionotropic glutamate and GABA receptors. The COOH terminal domain of the D1 dopamine receptor has been shown to interact with the NR1 and the NR2A subunit of the glutamatergic NMDA receptor in transfected cells and hippocampal cultured neurons (Lee et al., 2002; Fiorentini et al., 2003). The D2 dopamine receptor also interacts with the NR2B subunit of the NMDA receptor in response to cocaine in the postsynaptic density microdomain of excitatory synapses in striatal neurons (Liu et al., 2006b). Finally, the COOH terminal domain

of the D5 dopamine receptor has been shown to interact with the second intracellular loop of the GABA-A γ2-receptor subunit in the rat hippocampus (Liu et al., 2000). It is noteworthy that the interaction of dopamine receptors with GABA-A receptors seems to be specific to the D5 dopamine receptor, because this interaction does not occur for the D1 dopamine receptor.

The functional consequences of these interactions of dopamine and ionotropic receptor functions are diverse. The interaction of the D5 dopamine receptor with GABA-A reduces GABA-A receptor-mediated whole-cell currents (Liu et al., 2000). Likewise, the interaction of the D2 dopamine receptor with the NR2B NMDA receptor subunit disrupts the association of the NMDA receptor with CaMKII and inhibits the phosphorylation of this receptor and the resulting NMDA receptor-mediated currents (Liu et al., 2006b). Finally, the diverse interactions of the D1 dopamine receptor with the NMDA receptor have several functional consequences for NMDA receptor functions and appear to be important in regulating working memory in rats (Nai et al., 2010).

Initial observations indicate that the disruption of the D1/NR1 interaction after D1 dopamine receptor activation allows for the recruitment of calmodulin and phosphatidylinositol 3-kinases to NR1, resulting in the activation of cell survival mechanisms. In addition, the interaction of the D1 dopamine receptor with NR2A inhibits NMDA currents by reducing cell-surface expression (Lee et al., 2002). However, the functional interactions between the D1 receptor and the NMDA receptor are complex (Yao et al., 2008). In addition to these consequences of physical receptor interactions, activation of the D1 dopamine receptor has been shown to increase NMDA receptor activation or otherwise affect synaptic plasticity through mechanisms that involve protein kinases (Dunah and Standaert, 2001; Flores-Hernández et al., 2002; Chen et al., 2004a) or dopamine receptor interactions at a neural circuit level (Xu and Yao, 2010).

There is also evidence that the interaction with NMDA receptors affects D1 dopamine receptor cell surface expression and trafficking, resulting in increased plasma membrane insertion of D1 dopamine receptors (Fiorentini et al., 2003; Pei et al., 2004). However, this action of the NMDA receptor on the D1 dopamine receptor is probably restricted to specific neuronal populations in vivo because mice that exhibit a 95% reduction in the expression of the NR1 NMDA receptor subunit (Mohn et al., 1999) have normal striatal D1 dopamine receptor functioning (Ramsey et al., 2008).

The interaction of the D1 dopamine receptor and the NMDA receptor is also regulated by proteins that associate, either directly or indirectly, with both of these receptor types. For example, the synaptic scaffolding protein PSD-95 not only plays a role in stabilizing glutamate receptors in the postsynaptic density but is also down-regulated in several mouse models of psycho-stimulant or dopamine supersensitivity (Yao et al., 2004). It is noteworthy that PSD-95 directly interacts with the COOH terminal of D1 dopamine receptors to reduce its expression at the cell surface through enhanced dynamin-dependent endocytosis (Zhang et al., 2007). This increased internalization of D1 dopamine receptors in the presence of PSD-95 correlates with a reduced D1-NMDA receptor interaction (Zhang et al., 2009). This interplay between NMDA receptors, D1 dopamine receptors, and PSD-95 supports a model for the regulation of D1 dopamine receptor expression at the cell surface. Its interaction with NMDA receptors would anchor the D1 dopamine receptors at the cell surface and would interfere with their internalization after activation. In turn, competition between PSD-95 and NMDA receptors for interaction with the COOH terminal of D1 dopamine receptors might modulate internalization by dissociating D1 dopamine receptors from NMDA receptors, thereby liberating the D1 dopamine receptors and allowing for their internalization (Zhang et al., 2009). This type of interaction between receptors, ion channels, and their respective or shared associated proteins provides ample possibilities for the regulation of receptor functions in response to local conditions at the subcellular level.

E. β-Arrestins/G Protein-Coupled Receptor Kinases: from Dopamine Receptor Desensitization to Signaling

Given the complexity of the GRK/arrestin mechanisms of dopamine receptor regulation and signaling and the number of isoforms of the proteins that could be interacting with one another (five receptors, five nonvisual GRKs, and two nonvisual arrestins or β-arrestin), it is very important to delineate which GRK(s) and β-arrestin (s) regulate each dopamine receptor subtype. Multiple in vitro studies over the last 2 decades have revealed the ability of GRKs and β-arrestins to phosphorylate and desensitize dopamine receptors in artificial cellular model systems (Gainetdinov et al., 2004); however, an understanding of the functional specifity of this regulation remains quite limited. This knowledge is particularly important because there seems to be a continuum of GPCR regulation by GRKs and β-arrestins, with some receptors interacting exclusively with one particular GRK or arrestin and other receptors requiring the action of several GRKs or arrestins for their regulation (Premont and Gainetdinov, 2007). Furthermore, it is likely that the mechanisms of regulation of one GPCR are not the same in all tissues, depending on the expression pattern of the GRKs and β-arrestins. Therefore, to understand the functional specifity of the regulation of a receptor, it is critical to investigate the regulation of that receptor in its native conditions and context. Recent progress in the in vivo characterization of the roles of GRKs and arrestins in dopaminergic functions, particularly in studies involving mouse lines that bear deletions of each of the GRK and arrestin genes (Table 2), have provided some preliminary evidence

TABLE 2
GRKs and β-arrestins in dopamine receptor functions

GRK or β-Arrestin	Function Affected	References
GRK2	Minor locomotor supersensitivity to cocaine in GRK2 heterozygous mice	Gainetdinov et al., 2004
GRK3	Decreased locomotor responses to cocaine and apomorphine in GRK3 knockout mice	Gainetdinov et al., 2004
GRK4	Normal locomotor responses to cocaine	Gainetdinov et al., 2004
	Hypertension-associated polymorphic variants of GRK4 cause persistent D1 dopamine receptor desensitization and a loss of dopamine-dependent salt and fluid excretion	Felder et al., 2002
GRK5	Normal responses to dopaminergic drugs	Gainetdinov et al., 1999a
GRK6	Central D2 dopamine receptor supersensitivity and enhanced locomotor responses to cocaine, amphetamine, morphine and dopaminergic agonists in GRK6 deficient mice	Gainetdinov et al., 2003; Raehal et al., 2009
	Reduced L-DOPA-induced dyskinesia in rodent and primate models of Parkinson's disease after lentivirus-mediated overexpression of striatal GRK6	Ahmed et al., 2010
	Exacerbated L-DOPA-induced dyskinesia in animals with decreased striatal GRK6 levels	Ahmed et al., 2010
β-Arrestin1	Reduced locomotor responses to cocaine and apomorphine in β-arrestin 1 knockout mice	Gainetdinov et al., 2004
β-Arrestin2	Reduced locomotor responses to amphetamine, apomorphine, and morphine, but not cocaine, in β-arrestin 2 knockout mice	Bohn et al., 2003; Gainetdinov et al., 2004; Urs et al., 2011
	Lack of D2 dopamine receptor-mediated Akt/GSK-3 signaling in the striatum of β-arrestin 2 knockout mice	Beaulieu et al., 2005, 2007a

on the selectivity of the involvement of individual GRKs or β-arrestins in dopamine receptor regulation and signaling (Gainetdinov et al., 2004). It should be emphasized, however, that global manipulations of such critical and ubiquitous proteins likely to be involved in the regulation of multiple receptors simultaneously have limitations, and caution should be exercised in the interpretation of the behavioral data obtained using these models.

1. G Protein-Coupled Receptor Kinases. GRK2 is widely expressed in the brain, including primary dopaminergic areas (Arriza et al., 1992) and can phosphorylate and regulate D1, D2, and D3 dopamine receptors in in vitro cellular systems (Tiberi et al., 1996; Iwata et al., 1999; Kim et al., 2001; Kabbani et al., 2002; Sedaghat et al., 2006; Banday et al., 2007). Indirect evidence for the role of this kinase in the regulation of dopamine receptors was provided by the observation of alterations in the GRK2 expression levels in the striatum of animals with experimental parkinsonism (Bezard et al., 2005), rats treated with antipsychotics (Ahmed et al., 2008b), and rats receiving long-term cocaine treatment (Schroeder et al., 2009). Whereas a deletion of the *GRK2* gene in mice results in embryonic lethality, presumably as a result of cardiac hypoplasia (Jaber et al., 1996), mice heterozygous for this mutation are viable and were used to investigate the role of GRK2 in dopamine receptor functioning (Gainetdinov et al., 2004). Locomotor effects of the psychostimulant amphetamine, which interacts with the DAT to elevate extracellular dopamine and thus indirectly induces dopamine receptor stimulation (Jones et al., 1998), and the direct D1/D2 dopamine receptor agonist apomorphine were tested in GRK2 heterozygous (HET) mice. These treatments caused similar behavioral responses in the mutant and WT mice, suggesting that the impact of a partial loss of GRK2 on dopamine receptor-mediated responses is limited (Gainetdinov et al., 2004). However, cocaine treatment caused a minor enhancement in locomotor activity in the mutants at only one dosage, suggesting that some populations of dopamine receptors may be supersensitive. A more pronounced level of GRK2 deficiency might be necessary to demonstrate a potential involvement of this kinase in dopamine receptor regulation in physiological settings, and future studies with mouse lines bearing region- or cell-specific deletions of GRK2 in the brain would be particularly informative. Although it is unclear at present which dopamine receptor subtype(s) could be regulated by GRK2, recent evidence suggests that the fragile X mental retardation protein interacts with GRK2 to cause alterations in the regulation and function of the D1 dopamine receptor (Wang et al., 2008). Furthermore, the neuronal calcium sensor-1 (NCS-1) has been shown to directly interact with GRK2 to modulate the desensitization of D2 dopamine receptors, suggesting that the abnormalities in NCS-1 expression described in schizophrenia and bipolar disorder could cause changes in the NCS-1-dependent GRK2 regulation of the D2 dopamine receptor (Kabbani et al., 2002). In addition, the possibility of a constitutive regulation of D2 dopamine receptor expression and signaling by GRK2 that may be independent of receptor phosphorylation has been demonstrated (Namkung et al., 2009). Further detailed investigations are necessary to test these potential mechanisms in in vivo physiological settings.

Similar to GRK2, GRK3 has a ubiquitous pattern of expression in the brain, and in vitro studies using cell culture have indicated a potential role of GRK3 in the regulation of D1, D2, and D3 dopamine receptors (Tiberi et al., 1996; Kim et al., 2001; Kabbani et al., 2002; Sedaghat et al., 2006). Alterations in the GRK3 expression in several brain areas were observed after the long-term treatment of rats with the antipsychotics haloperidol and clozapine or in experimental animal models of PD (Ahmed et al., 2008a,b). In mice lacking GRK3, significantly reduced locomotor responses to cocaine and apomorphine were observed, indicating that this kinase is unlikely to be involved in the desensitization of locomotion-controlling dopamine receptors but rather is "positively" involved in dopamine receptor signaling. Al-

ternatively, GRK3 may be involved in the desensitization of D3 dopamine autoreceptors, thereby providing negative presynaptic control of dopamine release (Kim et al., 2005).

Given the limited expression of GRK4 in the brain, it is not surprising that no evidence for the role of this kinase in the regulation of neuronal dopamine receptors has been found (Gainetdinov et al., 2004). However, the role of GRK4 in D1 dopamine receptor regulation, which has important physiological consequences, has been convincingly demonstrated in the kidney. It has been observed that constitutive activity of polymorphic variants of the GRK4 protein that are observed in patients with hypertension can lead to perpetually phosphorylated, inactive D1 dopamine receptors (Felder et al., 2002). Likewise, in vitro cellular systems transfected with GRK4 variants display marked constitutive activity toward the D1 dopamine receptor (Rankin et al., 2006). These and other (Staessen et al., 2008) observations have demonstrated that the hypertension-associated polymorphic variants of GRK4 that are constitutively active lead to persistent D1 dopamine receptor desensitization in the kidney and a loss of dopamine-dependent salt and fluid excretion. Recent evidence also indicates that D3 dopamine receptors in the kidney are phosphorylated and regulated by GRK4 and that this regulation is critical for their signaling in human proximal tubule cells (Villar et al., 2009).

One widely expressed member of the GRK4 subfamily of GRKs, GRK5 (Premont et al., 1995, 1999), can regulate D1 and D2 dopamine receptors in cellular model systems (Tiberi et al., 1996; Iwata et al., 1999; Sedaghat et al., 2006). It has also been reported that long-term treatment with cocaine causes an up-regulation of GRK5 mRNA in the septum (Erdtmann-Vourliotis et al., 2001), and significant alterations in expression have been found in experimental PD animals (Ahmed et al., 2008a), suggesting a possible involvement of this kinase in the regulation of receptor responsiveness to dopaminergic drugs. However, a direct assessment of the potential role of GRK5 in the regulation of dopamine receptors in mice that lack GRK5 revealed that these animals exhibited normal responses to several dopaminergic drugs, indicating that the regulation of dopamine receptors is not affected by a deletion of GRK5. In contrast, significantly altered muscarinic receptor-mediated responses were observed in these mice, indicating a prominent role of this kinase in M2 muscarinic receptor regulation (Gainetdinov et al., 1999a).

GRK6 is highly expressed in many brain areas and in the periphery (Fehr et al., 1997). It is noteworthy that GRK6 seems to be the most prominent GRK in the striatum and in other dopaminergic brain areas (Erdtmann-Vourliotis et al., 2001). A particularly high level of expression of the GRK6 protein was found in the dopamine-receptive GABA-ergic MSNs and in the cholinergic interneurons in the striatum of mice (Gainetdinov

et al., 2003). A direct analysis of dopaminergic functioning in mice that lack GRK6 revealed a significantly enhanced responsiveness to primarily dopaminergic psychostimulant drugs and direct dopamine agonists (Gainetdinov et al., 2003; Raehal et al., 2009). Furthermore, an increased level of coupling of striatal D2 dopamine receptors to G proteins and an increased affinity of D2 dopamine receptors for these G proteins was observed in these mice compared with WT mice (Gainetdinov et al., 2003; Seeman et al., 2005). These observations have revealed that D2 dopamine receptors are physiological targets for GRK6-mediated regulation. In addition, these observations suggest that a strategy aimed at a modulation of GRK6 expression or activity could be beneficial in pathological conditions in which dopamine signaling is affected, such as PD. In fact, it has been reported that GRK6 expression was significantly altered in the striatum in animal models of PD and that this expression was sensitive to L-DOPA treatment (Bezard et al., 2005). Intriguingly, lentivirus-mediated overexpression of GRK6 in the striatum in rodent and primate models of Parkinson's disease can alleviate the dyskinesia in these animals that is caused by long-term L-DOPA treatment. At the same time, a reduction in the GRK6 concentration caused by the administration of microRNA with lentiviral vectors increased the level of dyskinesia in parkinsonian rats compared with untreated rats by enhancing the responsiveness of D1 and D2 dopamine receptors (Ahmed et al., 2010). These observations suggest promising new approaches for controlling dyskinesia and motor fluctuations in Parkinson's disease, thereby providing evidence for the potential effectiveness of a therapeutic strategy that aims to target receptor regulatory mechanisms.

2. β-Arrestins. The nonvisual arrestins, β-arrestins 1 and 2, are ubiquitously expressed in essentially all tissues (Arriza et al., 1992), although β-arrestin 1 is 10- to 20-fold more concentrated in brain compared with β-arrestin 2 (Gurevich et al., 2002). The majority of the evidence that supports the role of β-arrestin 1 in the regulation of D1 and D2 dopamine receptors has been reported in in vitro cellular studies (Kim et al., 2001; Oakley et al., 2001). Striatal β-arrestin 1 levels have been shown to be modulated by dopamine depletion and L-DOPA treatment (Bezard et al., 2005). Mice lacking this regulatory protein appear normal and do not show obvious abnormalities (Conner et al., 1997). However, the locomotor effects of cocaine and apomorphine have been found to be reduced in these mice compared with WT mice (Gainetdinov et al., 2004), suggesting that β-arrestin 1 may be involved in G protein-independent dopamine receptor signaling events rather than being directly involved in dopamine receptor desensitization. Further studies are necessary to investigate this possibility in detail.

Investigations performed in β-arrestin 2 knockout mice have directly demonstrated that the β-arrestin 2

isoform has signaling functions in vivo (Beaulieu et al., 2009). In heterologous cellular systems, β-arrestin 2 has been shown to regulate many GPCRs, including D1, D2, and D3 dopamine receptors (Kim et al., 2001; Oakley et al., 2001; Gainetdinov et al., 2004; Lan et al., 2009a,b). In an initial study, β-arrestin 2-deficient mice were found to exhibit enhanced morphine-induced analgesia compared with WT mice, which indicates that β-arrestin 2 plays an important role in μ-opioid receptor desensitization (Bohn et al., 1999, 2000, 2003, 2004). However, the effects of amphetamine and apomorphine (Gainetdinov et al., 2004; Beaulieu et al., 2005), but not cocaine (Bohn et al., 2003), were reduced in β-arrestin 2 knockout mice compared with WT mice. Furthermore, mice lacking both β-arrestin 2 and DAT have been shown to display a reduction in the typical novelty-induced locomotor hyperactivity phenotype that is characteristic of DAT-KO mice (Beaulieu et al., 2005). These findings indicated that β-arrestin 2 plays a positive role in dopamine receptor regulation. In fact, subsequent in vivo biochemical studies have directly demonstrated that β-arrestin 2 plays a critical role in D2 dopamine receptor signaling (Fig. 1) by regulating the Akt/glycogen synthase kinase 3 (GSK-3) pathway (Beaulieu et al., 2005; Beaulieu et al., 2007a) (see section IV.F for details).

Taken together, these studies have revealed a significant degree of specificity in the regulation of dopamine receptors by GRKs and β-arrestins in vivo (Table 2). However, although a significant amount of data have been collected on the regulatory mechanisms affecting D2 dopamine receptor function, relatively little information exists about the regulation of other receptor subtypes in vivo. It has become evident that the regulation of any receptor subtype is extremely complex, with multiple mechanisms of regulation that may occur simultaneously or consecutively. For example, a significant body of evidence, from in vitro and in vivo studies, indicates that the D2 dopamine receptor can be regulated via heterologous desensitization (Rogue et al., 1990; Namkung and Sibley, 2004), desensitized homologously in a GRK6-dependent manner (Gainetdinov et al., 2003), or involved in a G protein-independent, β-arrestin 2-mediated Akt/GSK-3 signaling cascade (Beaulieu et al., 2009). Furthermore, RGS9-2 mediates the regulation of D2 dopamine receptor-activated G protein signaling (Traynor et al., 2009). Understanding the logic and dynamics of this complexity will require detailed studies in native tissues with naturally expressed cellular complements of the desensitization/regulation machinery that involve in vivo analysis of relevant physiological output. Another important question relates to the fact that no evidence of an arresting role of β-arrestin 1 or β-arrestin 2 on dopaminergic signaling has been observed so far in in vivo functional studies. In addition, whereas an absolute deficiency of both β-arrestin 1 and β-arrestin 2 was found to be embryonic lethal in mice (Kohout et al., 2001), three-allele knockout [β-arrestin 1 KO/β-arrestin 2 HET, and β-arrestin 1 HET/β-arrestin 2 KO]

mice exhibited reduced responses to apomorphine compared with WT mice (Gainetdinov et al., 2004), suggesting predominant roles of both β-arrestins as signaling hubs in dopamine receptor signaling (Luttrell and Lefkowitz, 2002; Beaulieu et al., 2007a). Intriguingly, in addition to the established contribution of β-arrestin 2 to the regulation of Akt-mediated signaling responses by D2 dopamine receptor (Beaulieu et al., 2005), a recent investigation has suggested that β-arrestin 2 may also be involved in the regulation of ERK signaling by D1 dopamine receptors (Urs et al., 2011). Further delineation of the negative and positive roles of the β-arrestins in dopamine-mediated functions represents a major challenge for future research on dopamine receptor regulation and signaling.

F. β-Arrestin-Mediated Signaling and the Regulation of Akt by Dopamine

1. Role of the β-Arrestin 2/Akt/Glycogen Synthase Kinase 3 Pathway in D2 Dopamine Receptor-Mediated Functions. The reduced behavioral responsiveness to dopamine or to drugs that enhance dopamine neurotransmission in β-arrestin 2 knockout mice compared with their WT littermates points toward a role of β-arrestin-containing protein complexes in dopamine receptor signaling. Recent investigations have identified one of these mechanisms and have shown that β-arrestin 2 is a signaling intermediate that is implicated in the cAMP-independent regulation of Akt and GSK-3 by dopamine (Fig. 3C) (Beaulieu et al., 2004, 2005, 2006).

Akt, also termed protein kinase B, is a serine/threonine kinase that is regulated through phosphatidylinositol-mediated signaling. The activation of Akt involves the recruitment of this kinase to the plasma membrane by phosphorylated phosphatidylinositol, phosphorylation at a regulatory threonine residue (threonine 308) by the phosphatidylinositol-dependent kinase 1 and further phosphorylation at another regulatory residue (serine 473) by the rictor-mammalian target of rapamycin (mTOR) protein complexes (Jacinto et al., 2006). Regulation of Akt by phosphorylated phosphatidylinositol has been associated with the action of insulin, insulin-related peptides (e.g., insulin-like growth factor), and neurotrophins (e.g., nerve growth factor, BDNF, and neurotrophin-3) that exert their biological function by stimulating receptor tyrosine kinase (Scheid and Woodgett, 2001). GSK-3α and -3β are two closely related serine/threonine kinases that were originally associated with the regulation of glycogen synthesis in response to insulin (Embi et al., 1980; Frame and Cohen, 2001). These kinases can be inactivated through the phosphorylation of single serine residues, serine 21 (GSK-3α) and serine 9 (GSK-3β), in their regulatory NH$_2$-terminal domain (Frame and Cohen, 2001). Akt has been shown to inhibit GSK-3α and -3β in response to multiple hormones and growth factors including insulin, insulin-like

growth factor, and BDNF (Cross et al., 1995; Frame and Cohen, 2001; Chen and Russo-Neustadt, 2005).

Investigations of altered cell signaling in response to persistently elevated extracellular dopamine levels have identified a reduction in Akt phosphorylation/activity in the striatum of DAT-KO mice compared with WT mice (Beaulieu et al., 2004; Beaulieu et al., 2006). Inactivation of Akt in these mice resulted in concomitant activation of GSK-3α and -3β (Beaulieu et al., 2004). Further characterization of these signaling responses using dopamine depletion or dopamine receptor antagonists [7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzaz-epin-8-ol (SCH23390) and raclopride] in DAT-KO mice has revealed that Akt, GSK-3α, and GSK-3β are regulated by D2-class receptors in these mice (Beaulieu et al., 2004; Sotnikova et al., 2005). Furthermore, the D2 dopamine receptor antagonist and antipsychotic haloperidol has been independently shown to stimulate Akt phosphorylation and to inhibit GSK-3 in normal animals (Emamian et al., 2004). Pharmacological activation of dopamine receptors also results in the modulation of Akt and GSK-3 activity. In addition, administration of amphetamine, an indirect dopamine receptor agonist that induces potent increases in extracellular dopamine (Jones et al., 1998), led to an inhibition of Akt activity and an activation of GSK-3 in healthy C57BL6 mice (Beaulieu et al., 2004). A similar reduction in Akt activity was also reported after treatment of WT mice with the direct D1/D2 dopamine receptor agonist apomorphine, confirming that dopamine regulates the Akt/GSK-3 pathway in vivo (Beaulieu et al., 2004, 2005). However, neither Akt nor GSK-3 activity was affected by direct modulation of cAMP levels in the striatum of mice, indicating that this signaling pathway is not controlled by cAMP (Beaulieu et al., 2004). In contrast, amphetamine and apomorphine administered to β-arrestin 2 KO mice failed to reduce Akt phosphorylation (Beaulieu et al., 2005). Furthermore, mice lacking both β-arrestin 2 and DAT showed no inhibitory action of excessive dopamine on Akt phosphorylation, demonstrating that dopamine receptors regulate Akt through β-arrestin 2 (Beaulieu et al., 2005). Further investigations of the mechanism through which β-arrestin 2 regulates Akt in response to dopamine have shown that stimulation of the D2-class receptors causes the formation of a protein complex (Figs. 1, 3C, and 4) that is composed of Akt, β-arrestin 2, and PP2A and facilitates the dephosphorylation/deactivation (Andjelković et al., 1996) of Akt by PP2A in response to dopamine (Beaulieu et al., 2004, 2005).

Apart from the deficits in the dopamine-associated behaviors observed in β-arrestin 2 KO mice, data from multiple behavioral assays also support the involvement of the β-arrestin 2/Akt/GSK-3 pathway in the regulation of dopamine-associated behaviors. Inhibition of GSK-3 activity has been shown to reduce locomotor hyperactivity in DAT-KO mice and in amphetamine-treated WT animals (Beaulieu et al., 2004; Gould et al., 2004). Confirmation of these pharmacological observations was obtained using genetically engineered animals. GSK-3β KO mice die during embryogenesis, whereas GSK-3β heterozygote mice develop normally without overt phenotypes (Hoeflich et al., 2000). An evaluation of the behavioral actions of amphetamines revealed that GSK-3β heterozygote mice are less responsive to amphetamine over a range of doses than WT mice, supporting the involvement of GSK-3β in the development of dopamine-associated behaviors (Beaulieu et al., 2004). In addition, transgenic mice expressing a GSK-3β mutant that lacks an inhibitory phosphorylation site develop a locomotor hyperactivity phenotype that is reminiscent of DAT-KO mice (Prickaerts et al., 2006), whereas knockin mice lacking GSK-3α and a β inhibitory phosphorylation site are hyperresponsive to amphetamine (Polter et al., 2010). Finally, mice lacking the Akt isoform Akt1 exhibit an enhanced disruption of sensory motor gating (prepulse inhibition) after amphetamine but not after the glutamate NMDA receptor blocker MK-801 compared with WT mice (Emamian et al., 2004). The disruption of sensory motor gating by amphetamine has been used as a behavioral paradigm to model psychosis in rodents and is efficiently blocked by antipsychotics such as haloperidol. Because Akt1 is inhibited after the stimulation of D2-class receptors (Beaulieu et al., 2007b), the increased behavioral effect of amphetamine in Akt1 KO mice compared with WT mice further supports the involvement of Akt inhibition in the development of dopamine-related behavioral responses. However, dopamine regulates more than locomotor activity and sensory motor gating (Carlsson, 1987). Further behavioral characterization of different dopamine-associated behavioral paradigms that use traditional or tissue-specific knockout mice should be conducted to further elucidate the functions of β-arrestin 2, Akt, and GSK-3 in the expression of dopamine-associated behaviors.

2. Two Signaling Modalities of Slow Synaptic Transmission. β-arrestin- and G protein-mediated responses to GPCR stimulation are characterized by different kinetics, suggesting that dopamine receptor signaling may be composed of two separate modalities that develop differently over time. In cultured fibroblasts, β-arrestin-mediated ERK signaling has a slower onset and a more prolonged duration than G protein-mediated GPCR signaling (Ahn et al., 2004). In addition, the β-arrestin 2-dependent inhibition of Akt by dopamine in the mouse striatum displays a very different kinetic timeline (Fig. 1) compared with the signaling events that are regulated by the cAMP/PKA pathway (Beaulieu et al., 2004, 2005). After administration of dopaminergic drugs, such as amphetamine and cocaine, the cAMP-dependent phosphorylation of ERK and DARPP-32 peaks and returns to baseline within the first 30 min (Valjent et al., 2000 2005; Svenningsson et al., 2003). In contrast, β-arrestin 2-dependent inhibition of Akt by amphetamine develops

progressively over the first 30 to 60 min of the drug's action (Beaulieu et al., 2004, 2005). It is noteworthy that no difference in the behavioral response to amphetamine was observed when mutant mice lacking one copy of the GSK-3β gene and WT mice were compared over the first 30 min after drug administration. However, after this time point, the intensity of the locomotor activation was significantly reduced in the mutant animals. This difference persisted until the behavioral drug effects were no longer observed at 2 h after administration of the drug (Beaulieu et al., 2004). This finding suggests that the regulation and maintenance of a subset of dopamine-associated behaviors and the action of drugs might depend upon two complementary phases of GPCR signaling responses (Fig. 1). The early phase of this response would involve cAMP-mediated and other G protein-mediated responses that have a rapid onset and desensitization. In contrast, the second or late phase of the response would be characterized by β-arrestin-mediated cell signaling that has a slower onset, a longer duration, and no known desensitization mechanism (Fig. 1). β-Arrestin-mediated mechanisms seem to be a key determinant to separate these two phases of cellular responses in slow synaptic transmission because these mechanisms are responsible for both the termination of the early phase and the initiation of the late phase of the receptor signaling responses. G protein and β-arrestin 2 signaling modalities may also provide mechanisms for neurons to distinguish between bursts of repeated neurotransmitter stimulation and prolonged, continuous stimulation of their receptors by dopamine. As a result, the early and late phases of slow synaptic transmission may be compatible with differential responsiveness to rapid/phasic and long-lasting/tonic changes in dopamine concentrations, respectively, and may thus provide molecular mechanisms that support signaling responses to different modalities of dopamine neurotransmission.

3. Glycogen Synthase Kinase-3 Targets Involved in the Effects of Dopamine. GSK-3 has multiple substrates, including proteins involved in diverse cellular processes (Cohen and Frame, 2001; Frame and Cohen, 2001; Scheid and Woodgett, 2001; Woodgett, 2001). A thorough review of the role of GSK-3 substrates in the regulation of behavior can be found in the literature (Beaulieu et al., 2009; Karam et al., 2010). Direct in vivo evidence supports the role of GSK-3 in the regulation of at least two important brain functions by dopamine (Fig. 4). Ionotropic glutamate receptors are heteromultimeric ion channels for which trafficking and expression are closely related to the regulation of synaptic plasticity (Sheng and Hoogenraad, 2007). Dopamine is known to regulate ionotropic glutamate receptors and their associated proteins in neurons (Esteban et al., 2003; Svenningsson et al., 2004; Yao et al., 2004). Inhibition of GSK-3 prevents the development of long-term depression (LTD) in rat hippocampal slices (Peineau et al., 2007, 2008), whereas GSK-3 activation reduces the expression of the NMDA

receptor subunits NR2A/B on the cell surface in hippocampal slices and cultured cortical neurons (Chen et al., 2007; Zhu et al., 2007). In agreement with this finding, GSK-3 activity has recently been shown to be required for the inhibition of synaptic NMDA receptor functioning by D2 dopamine receptors in the rat prefrontal cortex (Li et al., 2009), suggesting a role for GSK-3-mediated D2 dopamine receptor signaling in the regulation of NMDA receptor synaptic plasticity by dopamine. In addition, recent evidence indicates that GSK-3 also contributes to the regulation of LTD by disrupting the normal transport of AMPA receptors at the synapse through the kinesin cargo system (Du et al., 2010). Although the contribution of D2 dopamine receptors to this new type of AMPA receptor regulation has not yet been studied, these results suggest an exciting new mechanism through which these receptors can contribute to the regulation of mood and synaptic plasticity. Overall, the results obtained concerning the regulation of LTD and the inhibition of glutamate receptor functions by GSK-3 isoforms also suggest that activation of these kinases in response to D2 receptor stimulation in a subpopulation of MSNs may prevent the depolarization of these neurons in response to glutamate. The results of a recent study using optogenetic stimulation of MSNs that express D2 receptors (i.e., MSNs involved in the indirect striatopalidal pathway) showed that the depolarization of these neurons reduces locomotion in mice compared with controls (Kravitz et al., 2010). This suggests that the inhibition of excitatory glutamate receptors by GSK-3 in response to dopamine in MSNs expressing D2 dopamine receptors could stimulate locomotion.

D2 dopamine receptor signaling through GSK-3 may also contribute to the regulation of circadian responses by dopamine. The results from studies conducted using mice lacking D2 dopamine receptors have revealed a role for this receptor in the regulation of circadian behavior by light (Doi et al., 2006). Furthermore, D2 dopamine receptor signaling enhances the transcriptional capacity of the circadian transcription factor CLOCK-BMAL1 complex, and the activity of this complex in the regulation of *mPer1* gene transcription in response to light is reduced in the retinas of D2-KO mice compared with WT mice (Yujnovsky et al., 2006). The phosphorylation of BMAL1 by GSK-3 results in the ubiquitination and degradation of this transcription factor, and reduced GSK-3 activity in D2-KO mice (Beaulieu et al., 2007b) correlates with an increase in BMAL1 protein levels in the striatum of these mice (Sahar et al., 2010). These findings strongly suggest that molecules involved in circadian regulation might also represent downstream targets of GSK-3-mediated D2 dopamine receptor signaling that are involved in the regulation of behavior. It is noteworthy that such regulation of circadian mechanisms might also contribute to long-lasting changes in gene expression that are involved in the regulation of synaptic plasticity (Borrelli et al., 2008). However, the regulation of other signaling cascades, including MAP kinases,
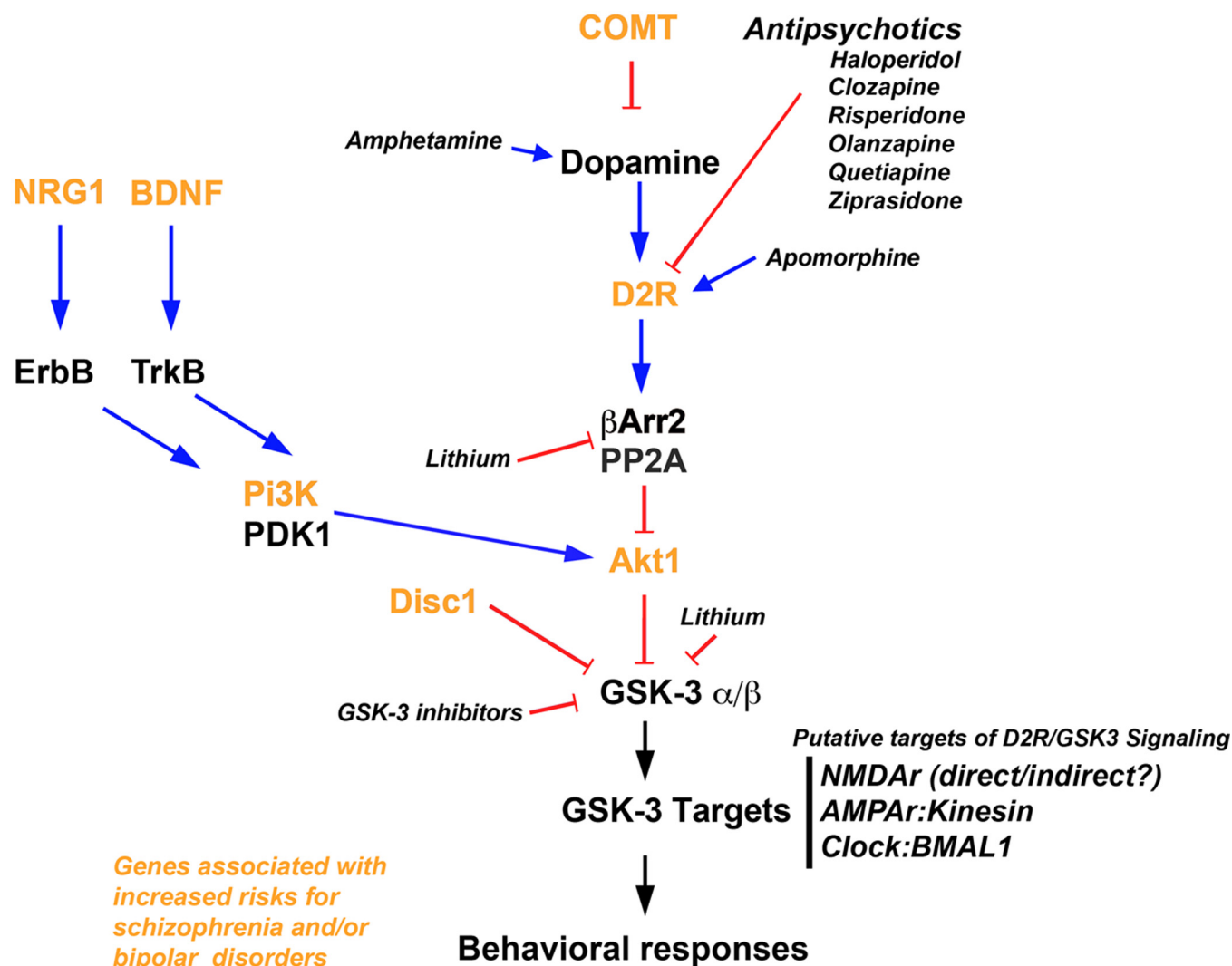
FIG. 4. Regulation of Akt/GSK-3 signaling by psychoactive drugs and related network of gene products associated with mental disorders. Proteins labeled in orange are the product of genes associated with an increased risk of developing schizophrenia and/or bipolar disorders. Blue arrows indicate activation, and the red T-arrows indicate inhibition. Black arrows indicate actions that can either be activatory or inhibitory on the function of specific substrates. Behavioral changes in dopaminergic responses have been reported in Akt1 and β-arrestin 2 KO mice and in GSK-3β-HET mice. COMT, catechol-O-methyltransferase; D2R, D2 dopamine receptor; Disc1, Disrupted-in-Schizophrenia 1; NRG1, neuregulin 1; PDK1, phosphatidylinositol-dependent kinase 1; Pi3K, phosphatidylinositol 3-kinase.

also seems to play an important role in the complex mechanisms through which the D2 dopamine receptor contributes to the regulation of circadian rhythm functions (Yujnovsky et al., 2006).

V. Pharmacology of Dopamine Receptors and Human Diseases

A. Abnormalities in Dopamine Receptor Physiology in Human Disorders

Numerous studies have focused on abnormalities in dopamine receptor biology as an underlying cause of mental disorders. Understanding the role of dopamine receptors in human diseases began with the development of receptor binding techniques that provided an opportunity to measure dopamine receptor binding characteristics in postmortem tissues of patients with various disorders (Seeman and Van Tol, 1994). However,

after multiple attempts, it has become obvious that receptor density measurements provide an extremely variable picture of the alterations that are likely to reflect particularities in postmortem tissue collection rather than underlying pathological mechanisms. Likewise, measurements of dopamine receptor mRNA levels or protein levels have generally provided ambiguous results that failed to provide convincing evidence connecting a dopamine receptor abnormality with a disorder. However, these studies were instrumental in generating several important hypotheses on the pathophysiology of human disorders. Among these hypotheses, the most notable is the postulated enhanced sensitivity of postsynaptic D2 dopamine receptors in schizophrenia (Seeman et al., 2005, 2007). Seeman at al. (2005, 2007) postulated, on the basis of observations that patients with schizophrenia are generally supersensitive to dop-

amine-related psychostimulants and of selected publications that report an increase in the proportion of D2 dopamine receptors that are in the high-affinity state in the brain of these patients, that the D2 (high) state is a common basis for the dopamine supersensitivity leading to psychotic reactions in schizophrenia. Another interesting hypothesis suggests that the anhedonia observed in patients with depression is related to a decrease in the sensitivity of postsynaptic D2/D3 dopamine receptors in the limbic brain areas that are responsible for reward, connecting the therapeutic effects of long-term antidepressant administration with an increase in the sensitivity of D2/D3 dopamine receptors in these brain areas (Willner, 1997). Further mechanistic studies would be necessary to explore these intriguing hypotheses in detail.

In vivo imaging studies using numerous recently developed selective radioligands have provided more consistent observations. A recent detailed analysis of in vivo imaging studies of synaptic function using positron emission tomography and single-photon emission computer tomography has highlighted several important abnormalities in the level of dopamine receptor expression in patients suffering from mental and affective disorders (Frankle and Laruelle, 2002; Nikolaus et al., 2009b; Volkow et al., 2009). In general, no consistent changes in D1 dopamine receptor binding were observed in schizophrenia patients; however, a significant portion of studies have shown a higher level of D2 dopamine receptor density in the basal ganglia of these patients compared with healthy control subjects. In patients with major depression, one report noted a decrease in D1 dopamine receptor binding, whereas the majority of the studies demonstrated unaltered or increased D2 dopamine receptor binding in the basal ganglia. In patients with bipolar disorder, no alterations in D1 dopamine receptor binding were observed, but two studies reported an increase in the D2 dopamine receptor density compared with healthy control subjects. Decreased striatal D2 dopamine receptor binding was observed in drug abusers; in some, but not all, studies in patients with Tourette's syndrome; and no changes in D2 dopamine receptor binding were observed in patients with ADHD (Frankle and Laruelle, 2002; Nikolaus et al., 2009b; Volkow et al., 2009).

An analysis of in vivo imaging studies performed in patients with movement disorders and/or dementias revealed more pronounced alterations in dopamine receptor expression (Nikolaus et al., 2009a). In patients with PD, the D2 dopamine receptor density in the basal ganglia was found to be altered in the majority of the studies, with no changes observed in the density of postsynaptically localized D1 dopamine receptors. In general, the pattern of the changes in D2 dopamine receptor expression is extremely complex and is likely to depend on the stage of the disease, with a slight increase in D2 dopamine receptor binding observed at the earlier

stages and a decrease observed at the later stages. Significantly decreased striatal D1 and D2 dopamine receptor densities were consistently reported in patients with multiple system atrophy, and a selective reduction in D2 dopamine receptor binding was observed in patients with progressive supranuclear palsy. However, in diseases such as dementia with Lewy bodies and corticobasal degeneration, there is little evidence for significant alterations in D1 and/or D2 dopamine receptor binding. Strikingly, in patients with Huntington's disease, in which postsynaptic degeneration occurs in GABA-ergic MSNs, significant reductions compared with healthy control subjects in the level of striatal D1 and D2 dopamine receptor binding have been observed in essentially all of the studies. Little to no change in dopamine receptor expression was observed in patients with Alzheimer's disease or PD dementia (Felicio et al., 2009; Nikolaus et al., 2009a).

Multiple genetic studies have focused on the role of dopamine receptor dysfunctions in human disorders. Although no conclusive association has been found thus far, there are several indications that polymorphisms could contribute to the pathogenesis of the disorder or to the response to pharmacological treatments. For example, variants in the D2, D3, and D4 dopamine receptor genes have been linked to schizophrenia or to the response to antipsychotic treatments (Parsons et al., 2007; Bertram, 2008; Rondou et al., 2010), *DRD4* and *DRD5* have been consistently linked to candidate genes for ADHD (Coghill and Banaschewski, 2009; Gizer et al., 2009), and the D2 dopamine receptor gene has been associated with substance abuse (Le Foll et al., 2009), prolactin-secreting pituitary adenomas (Filopanti et al., 2010), and several other conditions. However, as noted by Wong et al. (2000), "while there is some evidence that polymorphisms and mutations in dopamine receptors can alter functional activity and pharmacological profiles, no conclusive data link these gene variants to drug response or disease." Unfortunately, this situation has little changed over the past decade.

B. Abnormalities in G Protein-Related Dopamine Signaling in Human Disorders

A growing understanding of a complex array of dopamine receptor signaling events has led to the focus on the abnormalities in intracellular signaling mechanisms as a potential cause or a modifier of pathological processes that lead to dopamine-related disorders. However, because most intracellular signaling molecules (such as kinases and phosphatases) are involved in multiple functions in many cells in response to the activation of receptors and channels, the pathologic evidence of these molecules' involvement in dopamine receptor-mediated functions will most likely be only indirect.

The notable exception may be DARPP-32, which is involved in the modulation of the selective population of dopamine-receptive neurons via the regulation of signal-

ing events that are triggered by a small number of receptors and channels (Greengard et al., 1999). DARPP-32, which is encoded by the *PPP1R1B* (protein phosphatase 1, regulatory/inhibitor subunit 1B) gene, is particularly enriched in neostriatal MSNs and has been extensively investigated in association with several dopamine-related disorders. It has been reported that protein and mRNA levels of DARPP-32 are down-regulated in the dorsolateral prefrontal cortex of patients with schizophrenia or bipolar disorder (Albert et al., 2002; Ishikawa et al., 2007). A decrease in DARPP-32 mRNA in the prefrontal cortex was observed in a small cohort of suicide victims with schizophrenia compared with healthy control subjects (Feldcamp et al., 2008). A recent investigation has shown that the expression of DARPP-32 is also reduced in the leukocytes of patients with schizophrenia and bipolar disorder compared with healthy control subject, further suggesting that a deficiency in the DARPP-32-mediated signaling pathways may occur in conjunction with these disorders (Torres et al., 2009). Furthermore, genetic evidence exists that implicates DARPP-32 in human frontostriatal structure, function, and cognition (Meyer-Lindenberg et al., 2007). It should be noted, however, that direct attempts to find a genetic association between the SNPs in *PPP1R1B* and schizophrenia or bipolar disorder failed to observe allelic, genotypic, or haplotypic associations (Hu et al., 2007; Yoshimi et al., 2008). Multiple preclinical studies using various experimental models have suggested that DARPP-32 may be critically involved in the response to several drugs of abuse (Bibb et al., 1999; Girault and Greengard, 2004); however, no clinical studies that have supported these observations have been published to date. Although no significant alterations in DARPP-32 levels were found in Parkinson's disease patients (Girault et al., 1989b), substantial evidence exists that indicates a role of the DARPP-32-related signaling network in the development of L-DOPA-induced dyskinesia in these patients (Santini et al., 2007).

Several intriguing observations have been made about the proteins that are involved in the DARPP-32-mediated signaling network. In particular, genetic clinical studies using knockout mice have indicated that protein phosphatase calcineurin, also known as PP2B, is involved in the regulation of DARPP-32 dephosphorylation and could be a candidate molecule in the pathogenesis of schizophrenia (Gerber et al., 2003; Miyakawa et al., 2003). In fact, several other groups have also reported genetic associations of the genetic variants of the human PP2B/calcineurin γ-subunit gene (*PPP3CC*) with schizophrenia (Liu et al., 2007; Kyogoku et al., 2011), bipolar disorder (Mathieu et al., 2008), and drug abuse (Kinoshita et al., 2008). In addition, the variants in the gene encoding CK1 that phosphorylate DARPP-32 are associated with the subjective response to amphetamine in normal volunteers (Veenstra-VanderWeele et al., 2006). The other kinases that are related to the DARPP-32 sig-

naling network, CDK5 and ERK, have been shown to contribute to the abnormal plasticity that leads to drug abuse and L-DOPA-induced dyskinesia (Aubert et al., 2005; Girault et al., 2007; Santini et al., 2007; Lebel and Cyr, 2011); however, further observations in clinical settings are necessary to support these hypotheses.

C. Abnormalities in β-Arrestin 2/Akt/Glycogen Synthase Kinase-3 Signaling in Human Disorders

A growing body of consistent evidence exists that indicates that the Akt/GSK-3 signaling cascade plays a critical role in the pathogenesis and treatment of psychiatric disorders (Fig. 4). At the pharmacological level, both first- and second-generation antipsychotics have been shown to affect GSK-3 signaling in mice (Emamian et al., 2004; Alimohamad et al., 2005; Li et al., 2007). In addition, first-generation antipsychotics have been shown to correct the signaling imbalance in psychiatric patients by preventing the reduction in Akt activity that results from the activation of D2-class receptors (Beaulieu et al., 2007a). In addition, GSK-3 activity has also been shown to be regulated by 5-HT neurotransmission, through the activation of 5-HT2A receptors (Li et al., 2004; Beaulieu et al., 2007a, 2008c). It is therefore possible that atypical antipsychotics, which are antagonists of D2 dopamine receptors and 5-HT2a serotonin receptors, might inhibit GSK-3 activity by acting on dopamine and 5-HT receptor functions (Beaulieu, 2007). It is noteworthy that first- and second-generation antipsychotics and the partial D2 dopamine receptor agonist aripiprazole, which differ remarkably in their actions on cAMP-mediated D2 dopamine receptor signaling, share the common property of preferentially inhibiting the recruitment of β-arrestin 2 to D2 dopamine receptors in transfected HEK293 cells, suggesting that clinically effective antipsychotics may act as preferential antagonists for D2 dopamine receptor β-arrestin-mediated signaling (Masri et al., 2008).

Furthermore, Akt and GSK-3 have also been associated with the action of the mood stabilizer lithium (Fig. 4). Lithium is a direct inhibitor of GSK-3 that can also inhibit GSK-3 activity in cells through an indirect mechanism that involves Akt activation (Chalecka-Franaszek and Chuang, 1999; Zhang et al., 2003; Beaulieu et al., 2004). Short- and long-term administration of lithium has been shown to indirectly inhibit brain GSK-3 activity in mice, as revealed by an increase in the level of regulatory N-terminal domain phosphorylation compared with control subjects (De Sarno et al., 2002; Beaulieu et al., 2004). In the mouse striatum, this indirect effect of lithium on the activity of GSK-3 results from a disruption of the signaling complex that is composed of Akt, β-arrestin 2, and PP2A, which mediates some of the D2 receptor's signaling functions (Beaulieu et al., 2005, 2008a) (for a more detailed review on the actions of lithium, see (Beaulieu and Caron, 2008). Last, GSK-3 inhibition or a reduction in GSK-3β expression repro-

duces some of the dopamine-dependent behavioral actions of lithium and/or antipsychotics in rodents (Cox et al., 1971; Beaulieu et al., 2004; Gould et al., 2004; O'Brien et al., 2004; Beaulieu et al., 2008b). Taken together, these findings provide direct in vivo evidence that lithium, and potentially antipsychotics and other psychoactive drugs, exert some of their biochemical and behavioral effects by interfering with the regulation of Akt and GSK-3β.

Several independent studies have reported a link between the deregulation of Akt signaling and schizophrenia. A significant association of Akt1 haplotypes and schizophrenia has been reported in independent cohorts of patients with schizophrenia (Toyota et al., 2003; Emamian et al., 2004; Lai et al., 2006; Thiselton et al., 2008; Beaulieu et al., 2009; Freyberg et al., 2010). Furthermore, a reduction in Akt protein levels has been observed in the hippocampus and frontal cortex in postmortem brain samples and lymphocytes from patients with schizophrenia compared with healthy control subjects (Emamian et al., 2004). In addition, Disrupted-In-Schizophrenia 1 (*DISC1*) and Neuregulin 1 (*NRG1*), the genetic variants that have been shown to contribute to the pathogenesis of schizophrenia (Ross et al., 2006), have been shown to affect the Akt/GSK-3 signaling pathway in various experimental models (Mao et al., 2009; Prata et al., 2009; Kéri et al., 2010, 2011; Sei et al., 2010; Lipina et al., 2011), indicating that complex interactions exist among the network of schizophrenia-related proteins (Beaulieu et al., 2009; Karam et al., 2010). Recent evidence has indicated that a decrease in Neuregulin 1-induced Akt phosphorylation is associated with an impaired sensory gating mechanism in first-episode patients with schizophrenia (Kim et al., 2009). Furthermore, Tan et al. (2008) presented convincing evidence for an association of a coding variation in *AKT1* that affects protein expression with an increased risk for schizophrenia and with differences in the specific domains of cognitive function in healthy subjects. In addition, it has been shown that frontostriatal gray-matter volume was altered in subjects with this *AKT1* variation and a significant epistatic interaction was found between this *AKT1* variant and a functional polymorphism (V158M) of the catechol-*O*-methyltransferase gene that is also associated with schizophrenia (Meyer-Lindenberg et al., 2006). An association between the *AKT1* gene and Parkinson's disease has been also reported (Xiromerisiou et al., 2008).

At present, there is little clinical evidence demonstrating an association between the genetic locus encoding GSK-3α and psychiatric disorders. However, the levels of phosphorylated GSK-3β have been found to be significantly reduced in the frontal cortex of people with schizophrenia compared with healthy control subjects (Emamian et al., 2004; Karege et al., 2007). Furthermore, recent evidence indicates that temporal lobe gray matter volume in patients with schizophrenia is associated with a GSK-3β polymorphism (Benedetti et al., 2004). Several reports have also indicated that an association exists between a polymorphism in the GSK-3β gene promoter and the responsiveness to lithium therapy or the occurrence of psychotic symptoms in patients with mood disorders (Beaulieu et al., 2009; Freyberg et al., 2010).

The identification of the role of β-arrestin 2 in G protein-independent D2 dopamine receptor signaling suggests that the deregulation of β-arrestin 2 functions may be involved in the development of dopamine-related disorders. Although there are currently no published reports of associations of the gene encoding β-arrestin 2 (*ARRB2*) and mental disorders, one recent report has indicated that the coding-synonymous polymorphism (S280S) in *ARRB2* could be associated with tardive dyskinesia in patients with schizophrenia (Liou et al., 2008). Furthermore, evidence for the possible association of a polymorphism in *ARRB2* with methamphetamine use has been presented (Ikeda et al., 2007).

D. Current and Future Dopaminergic Treatments: a Shift from Receptor Pharmacology to the Targeting of Postreceptor Mechanisms

The pharmacological targeting of dopamine receptors has proven to be a very effective approach to affect deficient functions in several pathological conditions (Table 3). Starting from the remarkable success of the use of the dopamine precursor and indirect dopamine receptor agonist L-DOPA in patients with PD (Birkmayer and Hornykiewicz, 1961), a number of highly effective compounds that activate dopamine receptors have been developed for the symptomatic treatment of this disorder. Dopamine replacement therapy in PD has led to the clinical utility of several dopamine receptor agonists, including apomorphine, bromocriptine, pramipexole, piribedil, pergolide, ropinirole, rotigotine, and other compounds (Bonuccelli and Pavese, 2007; Millan, 2010). However, it should be noted that none of these dopamine agonists can be compared in efficacy to the first choice in PD treatment, L-DOPA. The D2 dopamine receptor agonists bromocriptine and cabergoline have also been shown to be effective in the treatment of pituitary tumors, hyperprolactinemia, and related conditions (Colao et al., 2006). Ropinirole and pramipexole have been approved for clinical indication for the treatment of restless legs syndrome (Zintzaras et al., 2010). An ergoline derivative, bromocriptine, has been used in the treatment of type 2 diabetes (Scranton and Cincotta, 2010), and pramipexole and rotigotine have been shown to have been effective in proof-of-concept studies in the treatment of bipolar disorder and depression (Aiken, 2007). The nonselective D1/D2 dopamine receptor agonist apomorphine has become a valuable tool in the treatment of erectile dysfunction (Carson, 2007). Furthermore, the synthetic benzazepine derivative fenoldopam acts as an agonist at peripheral D1 dopamine re-

TABLE 3
*Dopamine receptor agonists and antagonists that have been
used clinically*

The table was compiled from information presented in articles cited in the text and from the references cited therein.

Drugs	Major Clinical Application
Dopamine agonists	
Apomorphine	PD, erectile dysfunction
Bromocriptine	PD, pituitary tumors, hyperprolactinemia, type 2 diabetes
Cabergoline	Pituitary tumors, hyperprolactinemia
Fenoldopam	Hypertension
Pramipexole	PD, restless legs syndrome, bipolar disorder, depression
Piribedil	PD
Pergolide	PD
Ropinirole	PD, restless legs syndrome
Rotigotine	PD, bipolar disorder and depression
Dopamine antagonists	
Amisulpride	Schizophrenia, bipolar disorder, depression
Aripiprazole	Schizophrenia, bipolar disorder, depression
Benperidol	Schizophrenia
Bromopride	Nausea, gastroparesis
Chlorpromazine	Schizophrenia
Clopenthixol	Schizophrenia
Clozapine	Schizophrenia
Domperidone	Nausea
Droperidol	Schizophrenia, nausea
Fluphenazine	Schizophrenia
Flupentixol	Schizophrenia, depression
Fluspirilene	Schizophrenia
Haloperidol	Schizophrenia
Quetiapine	Schizophrenia, bipolar disorder, depression
Metoclopramide	Nausea, gastroparesis
Olanzapine	Schizophrenia, bipolar disorder, depression
Penfluridol	Schizophrenia
Perazine	Schizophrenia
Perphenazine	Schizophrenia
Pimozide	Schizophrenia
Prochlorperazine	Schizophrenia, nausea
Promazine	Schizophrenia
Risperidone	Schizophrenia, bipolar disorder
Remoxipride	Schizophrenia
Sertindole	Schizophrenia
Sulpiride	Schizophrenia, depression
Sultopride	Schizophrenia
Thiethylperazine	Nausea
Thiothixene	Schizophrenia
Thioridazine	Schizophrenia
Tiapride	Schizophrenia
Trifluperidol	Schizophrenia
Triflupromazine	Schizophrenia, nausea
Trifluoperazine	Schizophrenia
Ziprasidone	Schizophrenia, bipolar disorder, depression

ceptors and is used clinically to treat hypertensive crisis (Varon, 2008).

The discovery of the potent antipsychotic activity of the D2 dopamine receptor antagonist chlorpromazine in patients with schizophrenia led to remarkable progress in the development of antipsychotic drugs that are based on D2 dopamine receptor antagonism. First-generation antipsychotic drugs, also commonly defined as typical antipsychotics, are characterized by potent antipsychotic activity accompanied by pronounced side effects such as extrapyramidal syndrome, tardive dyskinesia, and neuroleptic malignant syndrome (Lindenmayer and Khan, 2004; Miyamoto et al., 2005; Lieberman et al., 2008). In addition to chlorpromazine, this group of compounds includes fluphenazine, prochlorperazine, promazine, triflupromazine, perazine, trifluoperazine,

perphenazine, haloperidol, benperidol, clopenthixol, droperidol, flupentixol, fluspirilene, sultopride, trifluperidol, penfluridol, pimozide, thiothixene, thioridazine, and tiapride (Arnt, 1998; Lindenmayer and Khan, 2004; Miyamoto et al., 2005; Awouters and Lewi, 2007; Lieberman et al., 2008). Atypical antipsychotics, also known as second-generation antipsychotics, generally have a lower propensity to develop extrapyramidal side effects and include clozapine, sulpiride, amisulpride, remoxipride, ziprasidone, risperidone, quetiapine, olanzapine, sertindole, aripiprazole, and other compounds (Lindenmayer and Khan, 2004; Miyamoto et al., 2005; Agid et al., 2008; Lieberman et al., 2008; Gründer et al., 2009). In general, these atypical antipsychotics retain the ability not only to antagonize D2 dopamine receptors, but they also have activity at other neurotransmitter receptors, most notably at the serotonin 5-HT2A receptors (Miyamoto et al., 2005; Agid et al., 2008; Lieberman et al., 2008; Marek et al., 2010).

Some of these drugs (amisulpride, aripiprazole, quetiapine, olanzapine, ziprasidone and risperidone) are also effective in the treatment of episodes of mania in bipolar disorder or in the treatment of depression (amisulpride, sulpiride, aripiprazole, flupentixol, quetiapine, olanzapine and ziprasidone) (DeBattista and Hawkins, 2009; Tohen and Vieta, 2009). Several D2 dopamine receptor antagonists, such as bromopride, domperidone, droperidol, metoclopramide, prochlorperazine, thiethylperazine, and triflupromazine, have found clinical application as antiemetic drugs in the treatment of nausea and vomiting (Axelrod, 1997). Metoclopramide and bromopride are also used clinically as prokinetic drugs for the gastrointestinal tract to increase muscle contractions in the upper digestive tract (Sanger and Alpers, 2008). The list of dopamine receptor agonists and antagonists that have been used clinically is presented in Table 3. A number of other selective and nonselective dopamine receptor agonists and antagonists are currently being developed for the treatment of these and other disorders; however, a majority of these compounds target primarily D2 dopamine receptors. Although some of the compounds that are primarily used as an antiparkinsonian drugs are also active at D1 and D3 dopamine receptors, the clinical utility of D4 dopamine receptor-selective compounds remains to be established. However, with an increasing number of compounds that are being developed to act directly on dopamine receptors as agonists and antagonists, it has become evident that the general approach of targeting these receptors by selective ligands has its own limitations, and it is unlikely that the future development of even more selective compounds will significantly broaden their therapeutic applications.

There is growing understanding that signaling effects mediated by dopamine receptors may represent a more "soft" target than receptors themselves for the pathological processes that lead to human disorders (Neve et al.,

2004; Beaulieu et al., 2009; Freyberg et al., 2010). This comprehension has shifted the focus from the direct targeting of dopamine receptors with selective agonists and antagonists to attempts to exert modulatory effects on the receptor's regulatory and signaling mechanisms. Although these signaling approaches have not yet had similar clinical success to the ligand-based pharmacology of dopamine receptors, there are certain developments that demonstrate significant progress in the field. One of the most notable examples of such development is the growing appreciation of role of the Akt/GSK-3 signaling cascade in psychiatric disorders and actions of psychotropic drugs (Beaulieu et al., 2004, 2009). These findings have led to a translation toward novel pharmacological strategies to bipolar disorder treatment based on targeting GSK-3 and related pathways (Beaulieu, 2007; Catapano and Manji, 2008; O'Brien and Klein, 2009). The recently recognized roles of the D1 dopamine receptor-related abnormalities in ERK and CDK5 activity in L-DOPA-induced dyskinesia in patients with PD (Santini et al., 2007) led to the idea that these proteins could be targeted as a possible therapy to counteract this debilitating condition either genetically or through the use of mTOR complex 1 (Santini et al., 2009b). Studies in mice lacking GRK6 indicated that this kinase plays a role in D2 dopamine receptor desensitization (Gainetdinov et al., 2003), and significant changes in the level of expression of this kinase have been observed in the striatum of experimental models of PD or in patients with PD (Ahmed et al., 2008a). A direct demonstration of the possibility to significantly reduce L-DOPA-induced dyskinesias by genetically manipulating the levels of GRK6 in the striatum has been conducted in experimental rat and monkey models of PD (Ahmed et al., 2010). As a result of these studies, a novel therapeutic strategy to counteract these dyskinesias has been suggested.

Because several intracellular signaling pathways that can be affected by dopamine receptors are also critical for a host of cellular events related to cell cycle, growth, proliferation, or general homeostasis, pharmacotherapeutic approaches based on affecting such pathways directly in the whole body could be less specific and may potentially have more unwanted side effects than receptor targeting with ligands. However, there is currently a growing list of clinically effective compounds that target a particular function that are based on broad kinase inhibition (Catapano and Manji, 2008). For psychiatric disorders, this concept is best illustrated by the well established therapeutic benefit of lithium in bipolar disorder despite the generally nonselective mechanism of action of lithium on several kinases (O'Brien and Klein, 2009). The recently demonstrated ability of lithium to disrupt the β-arrestin 2-mediated signaling complex suggests that the search for compounds that may possess a similar disruptive ability for β-arrestin-mediated complexes may identify novel effective compounds to treat this disorder (Beaulieu and Caron, 2008; Beaulieu

et al., 2009). Furthermore, recent evidence indicates that beyond directly targeting the signaling pathways via kinases and phosphatases, there is a distinct possibility of achieving the desired signaling effect by developing biased ligands that act on specific receptors but only affecting a subset of cell signaling responses.

E. Biased Ligand Pharmacology of Dopamine Receptors

The assumption that a receptor is engaged in exclusively one type of signaling event regardless of its cellular composition has been the basis of the definition of the intrinsic efficacy of the drug. The concept of intrinsic efficacy suggests that the ligands of receptors should be classified as full agonists, partial agonists, neutral antagonists, or inverse agonists based on the ability of the ligand to cause a specific intracellular response. However, in most cases, agonist binding to a receptor causes a parallel or consecutive activation of multiple downstream signaling pathways, thus exerting pluridimensional efficacy (Rajagopal et al., 2010). As discussed above, the most critical determinant of the dynamic choice of intracellular pathways that are triggered by receptor activation is the cellular composition of the interacting proteins, such as the isoforms of the β-arrestins, GRKs, RGSs, or G proteins. In addition, this molecular environment in the cells that express a particular receptor provides the basis for the selection of the signaling mechanisms that are induced. Furthermore, it is clear that receptors can exist in multiple active states, which are determined by variations in their ligand-induced intermediate conformational states (Urban et al., 2007; Kenakin and Miller, 2010). Ligands can either induce or stabilize a receptor in different active conformations, leading to the involvement of different downstream signaling pathways. The possibility of the oligomerization of GPCRs further complicates this situation because of the variety of intracellular signaling events that might be evoked by heterodimers of receptors (Maggio et al., 2005; Fiorentini et al., 2010; Fuxe et al., 2010; Hasbi et al., 2010). The variety of signaling events that can be induced by the action of a ligand on a single GPCR implies that the classification of ligands that is based on a single signaling pathway may be misleading and that the same ligand could be a full agonist for one signaling pathway and an antagonist or an inverse agonist for another (Galandrin et al., 2007). Thus, any attempt to classify a ligand based on its intrinsic efficacy should be followed by the clarification of the specific pathway to which it is related. In addition, growing evidence suggests that certain ligands that act on the same receptor can cause preferential involvement of selected signaling pathways over other pathways. Such preference of one signaling pathway over another has been described as "functional selectivity," "collateral efficacy," "stimulus trafficking," or "biased agonism" (Urban et al., 2007; Kenakin and Miller, 2010).

For dopamine receptor ligands, biased agonism was first noted for the dopamine receptor agonists dihydrexidine and propylnorapomorphine (with regard to D2 dopamine receptors) and for apomorphine (with regard to D1 dopamine receptors) (Urban et al., 2007). The atypical antipsychotic drug aripiprazole has a functionally selective profile of action on dopamine receptors. This clinically effective compound was postulated to have "dopamine system stabilization" or "normalization" actions that could be effective in normalizing both hypoactive and hyperactive dopaminergic transmission (Tamminga and Carlsson, 2002; Lieberman, 2004). Aripiprazole exerts properties of a partial agonist on D2 dopamine receptor-mediated inhibition of cAMP accumulation. However, this drug exerts potent antagonistic actions in other functional assays such as D2 dopamine receptor-mediated guanosine 5′-O-(3-thio)triphosphate binding, GIRK channel activity, and β-arrestin 2 recruitment, and it acts as a full agonist with regard to D2-mediated inhibition of tyrosine hydroxylase (Shapiro et al., 2003; Urban et al., 2007; Klewe et al., 2008; Masri et al., 2008). It has been suggested that the specific pharmacological profile of this drug could be related to the antagonism of postsynaptic D2 dopamine receptors combined with its ability to activate presynaptic D2 autoreceptors (Kikuchi et al., 1995). However, it has also been reported that the ability of aripiprazole to engage different intracellular signaling events via action on the same population of D2 receptors is responsible for the unique pharmacological profile of this drug (Mailman, 2007). Such biased agonism may be also involved in the effects of other putative atypical antipsychotic drugs that partially activate D2-dopamine receptors, such as bifeprunox, N-desmethylclozapine, preclamol, (3S)-3-[3-(methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride (OSU6162), and huntexil (ACR16) (Mailman, 2007; Kara et al., 2010); however, the possibility of the involvement of D2/D3 dopamine receptor heterodimers in the actions of these compounds cannot be fully excluded (Maggio and Millan, 2010).

The recent discovery of the G protein-independent β-arrestin-mediated signaling of GPCRs has demonstrated that these distinct G protein- and β-arrestin-mediated signaling modalities may provide an important framework to understand the biased agonism of certain compounds (Luttrell and Gesty-Palmer, 2010; Rajagopal et al., 2010). The preferential ability of a receptor to engage G protein signaling or to initiate β-arrestin-mediated signaling may be determined by the ability of β-arrestin to adopt multiple active conformations that can occur even in the absence of receptor phosphorylation after receptor activation by a ligand (Shukla et al., 2008). It is believed that such biased agonism can have important implications for drug development because intracellular signaling events mediated by these parallel pathways may have distinct physiological consequences. As discussed above, D2 dopamine receptors have been shown to be one of the best examples of this duality in receptor signaling, because they are involved in the regulation of the G protein-mediated functions and the β-arrestin 2-mediated Akt/GSK-3 signaling cascade (Beaulieu et al., 2009). Although currently there are no D2 dopamine receptor ligands known to affect specifically one or the other of these signaling modalities, it may be possible to develop drugs to selectively target one of these pathways. In fact, the ability of the mood stabilizer drug lithium to disrupt β-arrestin 2-mediated Akt/GSK-3 signaling and to suppress the behavioral effects that are related to enhanced dopaminergic transmission provides the first evidence for the activity of clinically effective compounds on β-arrestin 2 scaffolded signaling complexes downstream of the D2 dopamine receptor (Beaulieu et al., 2008a, 2009; Rajagopal et al., 2010).

It is noteworthy that a direct comparison of the ability of several clinically effective antipsychotics to affect D2 dopamine receptor-stimulated $G\alpha_i/G\alpha_o$ protein activation and β-arrestin 2 recruitment to the receptor revealed remarkable differences between different compounds in regard to $G\alpha_i/G\alpha_o$-related cAMP signaling; these compounds ranged from inverse to partial agonists with highly variable efficacies and potencies (Masri et al., 2008). At the same time, haloperidol, clozapine, aripiprazole, chlorpromazine, quetiapine, olanzapine, risperidone, and ziprasidone were all extremely potent in antagonizing the interaction of β-arrestin 2 with the D2 dopamine receptor, suggesting that antagonism of the D2 dopamine receptor/β-arrestin 2 interaction, rather than of cAMP-mediated signaling, may be a common function of these clinically effective antipsychotics (Masri et al., 2008). These intriguing observations suggest that approaches aimed at biased targeting of the D2 dopamine receptor/β-arrestin 2 complex and/or related signaling pathways may reveal new opportunities for the development of future antipsychotic treatments (Masri et al., 2008; Beaulieu et al., 2009; Houslay, 2009; Freyberg et al., 2010). Future development of transgenic mice that express D2 dopamine receptors that are unable to bind β-arrestins (Lan et al., 2009a) may represent a good approach to validate this type of activity of potential biased drugs in an animal model.

VI. Summary and Future Directions

Remarkable developments occurred in the 1980s and 1990s in the understanding of the basic genetic and structural features of dopamine receptors. More recently, we have witnessed an explosion of information on the regulatory and signaling mechanisms that are involved in dopamine receptor functioning. One major conclusion from these studies is that signaling events that are caused by the activation of specific receptors are extremely complex and may depend on the cellular composition of accessory proteins such as kinases and phos-

phatases and the receptor conformation that is caused by a specific ligand. Thus, intracellular responses may differ from one cell group to another after activation of the same receptor. To fully understand the complexity of dopamine receptor actions, a multilevel analysis is necessary that involves, among other approaches: cellular biochemical studies, multidimensional functional assays in vitro and in vivo, an assessment of the physiological functions that are caused by specific pathways at the level of whole organism, and the identification of the pathological or therapeutic effects that are associated with specific signaling events in patients suffering from dopamine-related disorders.

Such comprehensive analysis will undoubtedly demand the development of new tools to study dopamine receptor biology in vivo. Studies using BAC transgenic mice that express recombinant proteins in D1 or D2 dopamine receptor-expressing cells (Gong et al., 2003; Shuen et al., 2008; Valjent et al., 2009) indicate that this may be one promising approach for this type of research. This method has been used to express fluorescent gene reporter proteins, such as enhanced green fluorescent protein and tdTomato, in specific populations of dopaminoceptive neurons. These fluorescent BAC transgenic mice have been used for basic neuroanatomical studies (Gong et al., 2003; Shuen et al., 2008; Zhang et al., 2010) and for studies of cell signaling (Valjent et al., 2006b, 2009; Bertran-Gonzalez et al., 2009) and electrophysiological responses (Flores-Barrera et al., 2010) in optically phenotyped neuronal populations. The use of this BAC transgenic technology has also permitted the expression of tagged recombinant proteins that serve as neuron-type specific reporters of protein phosphorylation (Bateup et al., 2008) or mRNA translation (Doyle et al., 2008). Finally, a combination of the BAC transgenic approach with the Cre/Lox system has allowed for the suppression of DARPP-32 expression (Bateup et al., 2010) in D1 or D2 dopamine receptor expressing MSNs, underscoring the possibility of using BAC transgenic mice in more functional studies of dopamine receptors. In addition to these new transgenic mouse approaches, rapid developments in the field of optogenetics involve the expression of light-activated ion channels in specific neuronal populations that provide exciting opportunities to study the functions of neurons that express specific dopamine receptor subtypes at a system level (Kravitz et al., 2010).

For drug development, new screening assays for the identification of compounds that are effective for dopamine-related disorders should be developed to incorporate the possibility of biased signaling and should be designed to detect multiple signaling events downstream of G proteins, such as alterations in the intracellular calcium or cAMP levels, and to detect the indications of β-arrestin-mediated signaling in direct biochemical assays in vitro and in vivo. A necessary step in designing biased drugs would be to decipher which

signaling pathways would be most relevant for therapeutic efficacy and, conversely, which pathways might lead to side effects. Assessing these multidimensional aspects of receptor signaling would make it possible to identify the compounds that stabilize the unique conformational ensembles and bias signaling events and thus will possess enhanced therapeutic efficacy and fewer side effects (Beaulieu et al., 2007a; Rajagopal et al., 2010).

We conclude this review by providing a short list of outstanding questions that might prove important to further our understanding of dopamine receptor functions. First, although striatal D1 and D2 dopamine receptors have been studied extensively, knowledge is still limited regarding the roles of the D3, D4, and D5 dopamine receptors. Further characterization of the physiological functions of these receptors may provide new opportunities for pharmacological interventions and a better understanding of the multiple roles of dopamine outside of the striatum. Another important question is to understand the relative roles played by G protein- and arrestin-mediated signaling mechanisms in the regulation of dopamine responses that are mediated by D2 and potentially by other subtypes of dopamine receptors. With regard to the already defined roles of arrestin-mediated D2 and D3 dopamine receptor signaling, it is particularly important to identify the molecular targets of Akt and GSK-3 that are involved in the regulation of dopamine-regulated behaviors. Among these downstream targets, the possible inhibition of the ionotropic glutamate receptor currents by GSK-3 is of particular interest because it could provide a framework to understand the action of psychostimulants such as amphetamine that increase dopamine tone and those such as ketamine that act by blocking ionotropic glutamate receptors. However, Akt and GSK-3 have multiple known molecular targets, and it is probable that the dopamine signaling-related action of these kinases will involve activation of several such molecules. Finally, the multifaceted view of dopamine receptors that emerges from the current literature underscores the need to understand these receptors as individual units and as components of receptor signaling complexes that act on highly integrated signaling pathways at a system level. Dopamine receptors have been shown to interact with several scaffolding proteins, ion channels, kinases, and phosphatases. They also have the potential to form diverse types of receptor complexes with each other (e.g., D1/D2 heterodimers) and with other GPCRs. The characterization of these complexes, the cellular conditions leading to their formation, and the impact of such complexes on the integration of dopamine functions with those of other neurotransmitters may also lead to important new developments in the future.

Considering the fast pace at which new technologies are being developed in neuroscience, pharmacology, and cell biology, it is likely that our knowledge of dopamine

receptor signaling function in vivo will continue to evolve in exciting ways in the future. Such a multidimensional model of investigation could lead to critical information that identifies abnormal dopamine receptor-related signaling pathways as promising targets for future pharmacological approaches and thus provides novel therapeutic opportunities to managing dopamine-related disorders.

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Wrote or contributed to the writing of the manuscript: Beaulieu and Gainetdinov.

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