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Dopamine receptors – IUPHAR Review 13

Jean-Martin Beaulieu[1], Stefano Espinoza[2] and Raul R Gainetdinov[2,3,4]

[1]*Department of Psychiatry and Neuroscience, Faculty of Medicine, Université Laval – IUSMQ, Québec, Québec, Canada,* [2]*Department of Neuroscience and Brain Technologies, Istituto Italiano di Tecnologia, Genova, Italy,* [3]*Skolkovo Institute of Science and Technologies, Skolkovo, Moscow Region, Russia, and* [4]*Faculty of Biology, St. Petersburg State University, St. Petersburg, Russia*

Correspondence
Raul R Gainetdinov, Istituto Italiano di Tecnologia (IIT), Via Morego 30, Genova, 16163, Italy.
E-mail: raul.gainetdinov@iit.it

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This article, written by members of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) subcommittee for the dopamine receptors, confirms the existing nomenclature for these receptors and reviews our current understanding of their structure, pharmacology and functions and their likely physiological roles in health and disease. More information on these receptor families can be found in the Concise Guide to PHARMACOLOGY (http://onlinelibrary.wiley.com/doi/10.1111/bph.12445/abstract) and for each member of the family in the corresponding database http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=20&familyType=GPCR.

The variety of physiological functions controlled by dopamine in the brain and periphery is mediated by the D_1, D_2, D_3, D_4 and D_5 dopamine GPCRs. Drugs acting on dopamine receptors are significant tools for the management of several neuropsychiatric disorders including schizophrenia, bipolar disorder, depression and Parkinson's disease. Recent investigations of dopamine receptor signalling have shown that dopamine receptors, apart from their canonical action on cAMP-mediated signalling, can regulate a myriad of cellular responses to fine-tune the expression of dopamine-associated behaviours and functions. Such signalling mechanisms may involve alternate G protein coupling or non-G protein mechanisms involving ion channels, receptor tyrosine kinases or proteins such as β-arrestins that are classically involved in GPCR desensitization. Another level of complexity is the growing appreciation of the physiological roles played by dopamine receptor heteromers. Applications of new *in vivo* techniques have significantly furthered the understanding of the physiological functions played by dopamine receptors. Here we provide an update of the current knowledge regarding the complex biology, signalling, physiology and pharmacology of dopamine receptors.

Abbreviations

βArr2, β-arrestin 2; BDNF, brain-derived neurotrophic factor; CaMKII, Ca^{2+}/calmodulin-dependent PK II; CDK5, cyclin-dependent kinase 5; DAT, dopamine transporter; DARPP-32, dopamine and cAMP-regulated phosphoprotein, 32 kDa; GluA1, glutamate receptor, ionotropic, AMPA 1 subunit; GluN2B, glutamate receptor, ionotropic, NMDA 2B subunit; GIRKs, G protein coupled inwardly rectifying potassium channels; GSK3, glycogen synthase kinase; HTT, huntingtin; KO, knockout; IP_3, inositol trisphosphate; PDK, phosphatidylinositol-dependent kinase; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; rpS6, ribosomal protein S6; RTK, receptor tyrosine kinases; TCS1/2, tuberous sclerosis proteins 1 and 2; TrkB, neurotrophic tyrosine kinase, receptor, type 2.

Table of Links

TARGETS		
GPCRs[a]	**Enzymes**[b]	**Transporters**[c]
5-HT receptors	adenylyl cyclases	DAT
Adenosine A_1 receptor	Akt	**Catalytic receptors**[d]
Adenosine A_{2A} receptor	calpain	ErbB (epidermal growth factor) receptor family
α_{1B}-Adrenoceptor	CaMKII	
β_1-Adrenoceptor	CDK5	ErbB-1
Dopamine D_1 receptor	ERK	IGFR1
Dopamine D_2 receptor	Epac1	PDGFRβ
Dopamine D_3 receptor	Epac2	RTKs
Dopamine D_4 receptor	GRK2	TrkB
Dopamine D_5 receptor	GSK3	**Ion channels**[e]
Ghrelin receptor	GSK3α	GIRKs
Muscarinic M_4 receptor	GSK3β	$K_{ir}2$ channels
TA_1 receptor	MAPK	IP_3 receptor
	PDK1	**Ligand-gated ion channels**[f]
	PKA	GluA1
	PKC	GluN2B
	PLC	Ionotropic glutamate receptors
	PLCβ	

LIGANDS		
amphetamine	fluoxetine	quetiapine
apomorphine	GABA	quinpirole
aripiprazole	haloperidol	risperidone
asenapine	huntingtin	SCH23390
BDNF	IGF	SKF 38393
blonanserin	IGF-1	SKF 81297
brexpiprazole	iloperidone	thioridazine
bromocriptine	insulin	UNC0006
cAMP	L-DOPA	UNC9975
cariprazine	lithium	UNC9994
chlorpromazine	lurasidone	xanomeline
clozapine	NMDA	ziprasidone
cocaine	olanzapine	
dopamine	perphenazine	

This table lists protein targets and ligands, which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and the Concise Guide to PHARMACOLOGY 2013/14 ([a,b,c,d,e,f]Alexander *et al.*, 2013a,b,c,d,e,f).

Introduction

Five subtypes of dopamine receptors (D_1, D_2, D_3, D_4 and D_5 receptors, encoded in humans by genes *DRD1*, *DRD2*, *DRD3*, *DRD4* and *DRD5*, respectively) are known to mediate essentially all of the physiological functions of dopamine. These functions include, but are not limited to, the following: voluntary movement, reward, sleep regulation, feeding, affect, attention, cognitive function, olfaction, vision, hormonal regulation, sympathetic regulation and penile erection. Dopamine receptors are also known to influence the immune system as well as cardiovascular, renal and gastrointestinal functions. As members of the GPCR superfamily, dopamine receptors have a canonical seven-transmembrane structure and can signal through both G protein-dependent and -independent mechanisms. Based on coupling to either $G\alpha_{s,olf}$ proteins or $G\alpha_{i/o}$ proteins to stimulate or inhibit the production of the second messenger cAMP, respectively, dopamine receptors are classified as D_1-class receptors (D_1 and D_5) or D_2-class receptors (D_2, D_3 and D_4) (Kebabian, 1978; Spano *et al.*, 1978). The alternative splicing of D_2 results in the generation of two major D_2 dopamine receptor variants that differ in the presence of an additional 29 amino acids on the third intracellular loop with distinct physiological, signalling and pharmacological properties, and are classified as D_{2S} (D_2-short) and D_{2L} (D_2-long). Dopamine receptors are well-established targets in the clinical pharmacology of numerous disorders and conditions such as schizophrenia, Parkinson's disease, bipolar disorder, depression, restless leg syndrome, hyperprolactinaemia, pituitary tumours, hypertension, gastroparesis, nausea and erectile dysfunction. The basic principles of dopamine receptor structure, signalling, function and pharmacology are covered in detail in several excellent reviews (Niznik and Van Tol, 1992; Sibley and Monsma, 1992; Sokoloff *et al.*, 1992; Civelli *et al.*, 1993; Missale *et al.*, 1998; Vallone *et al.*, 2000; Carlsson, 2001; Seeman, 2006). Recently, we have provided a comprehensive overview of the field in *Pharmacological Reviews* (Beaulieu and Gainetdinov, 2011). However, although the basic information regarding the structural, genetic and biochemical properties of dopamine receptors has remained essentially unchanged in the last 4 years, a significant amount of new information has emerged on dopamine receptor signalling, functional relevance and pharmacology that requires an update of the status of current knowledge. Here we will focus on newly emerging topics and trends in understanding dopamine receptor biology as well as topics that were not covered or only partially discussed in our previous review (Beaulieu and Gainetdinov, 2011).

Mechanisms of dopamine receptor signalling

The prevailing convention was that dopamine receptors were considered to signal exclusively through G protein-dependent cellular processes. The D_1-class receptors (D_1 and

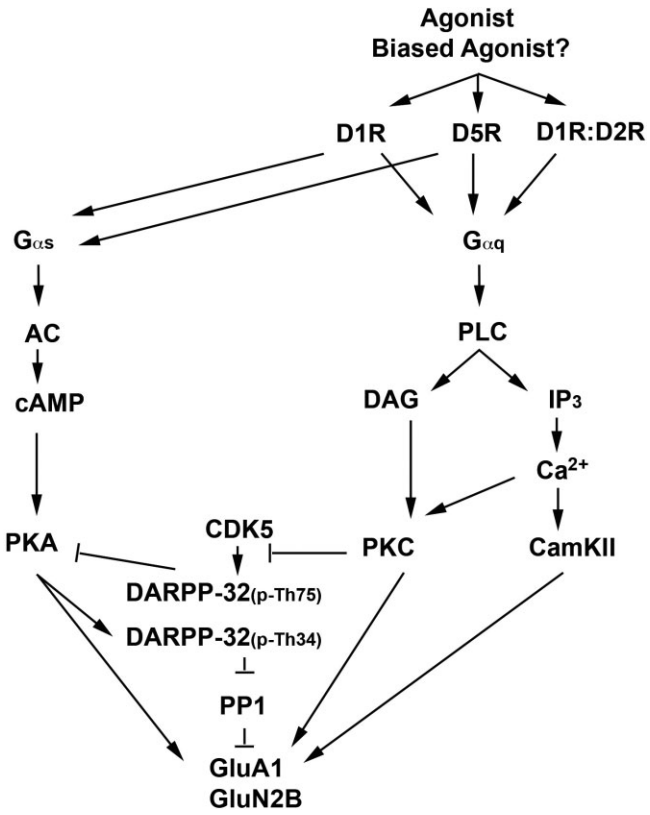

Figure 1

Schematic diagram representing the signalling cascades activated by the D_1 dopamine receptor (D1R). D5R, D_5 dopamine receptor; D1R:D2R, D_1–D_2 receptor heteromer.

D_5 receptors) are primarily coupled to $G\alpha_{s/olf}$ proteins and stimulate the activity of AC and the production of the second messenger cAMP (Figure 1). In contrast, the D_2 class receptors (D_{2S}, D_{2L}, D_3 and D_4 receptors) are associated with $G\alpha_{i/o}$ proteins to inhibit the production of cAMP (Kebabian, 1978; Spano *et al.*, 1978) (Figure 2).

Modulation of cAMP synthesis by dopamine receptors results in the regulation of PKA and potentially of other exchange proteins activated by cAMP (Epac1 and Epac2) (Svenningsson *et al.*, 2004; Beaulieu and Gainetdinov, 2011). Among PKA substrates, the multifunctional dopamine and cAMP-regulated phosphoprotein (DARPP-32/PPP1R1B) has been extensively studied over the last 30 years. When phosphorylated on Thr^{34} by PKA, DARPP-32 is a negative regulator of protein phosphatase 1 (PP1). In contrast, phosphorylation of DARPP-32 on Thr^{75} by cyclin-dependent kinase 5 (CDK5), in response to sustained D_1 receptor activation, results in PKA inhibition (Figures 1 and 2). The roles of PKA and DARPP-32 in dopamine receptor signalling are well characterized, and strong evidence supports their contribution to the physiological functions of dopamine receptors (Svenningsson *et al.*, 2004; Girault, 2012).

cAMP-mediated signalling and mRNA translation

An interesting development in the characterization of cAMP-mediated dopamine receptor signalling involves its recently appreciated contribution to the regulation of mRNA translation mechanisms. Either D_1 receptor activation or D_2 receptor blockade by haloperidol has been shown to promote the phosphorylation of the ribosomal protein S6 (rpS6) on $Ser^{235/236}$ and $Ser^{240/244}$ (Santini *et al.*, 2009; Valjent *et al.*, 2011). Phosphorylation of rpS6 on these and adjacent residues results in enhanced CAP-dependent mRNA translation (Roux *et al.*, 2007; Hutchinson *et al.*, 2011). Increased phosphorylation of rpS6 via D_1 receptors would involve activation of PKA, subsequent inhibition of PP1 by DARPP-32 and activation of the mammalian target of rapamycin (mTOR) complex 1 (Santini *et al.*, 2009; 2012; Bonito-Oliva *et al.*, 2013). In medium spiny neurons expressing D_2 receptors, activation of PKA and DARPP-32 by the adenosine A_{2A} receptors also plays a role (Valjent *et al.*, 2001; 2011; Santini *et al.*, 2009), whereas activation of ERK signalling by a DARPP-32-dependent mechanisms are thought to be involved in D_1 receptor-expressing medium spiny neurons (Santini *et al.*, 2012). Interestingly, D_1 receptor stimulation also promotes rpS6 phosphorylation in the dentate gyrus, albeit through a different, mTOR-independent, pathway involving ERK activation (Gangarossa and Valjent, 2012). Understanding the overall importance of dopamine receptor-mediated regulation of rpS6 on mRNA translation and behaviour is still in its infancy. However, preliminary evidence supports its involvement in the development of L–DOPA-induced dyskinesia (Santini *et al.*, 2009; 2012; Subramaniam *et al.*, 2012) and cocaine sensitization, seeking and relapse behaviours (Wu *et al.*, 2011).

cAMP-independent dopamine receptor signalling

In addition to the regulation of cAMP, several studies have revealed that dopamine receptors can exert some of their biological effects through alternative signalling pathways (Beaulieu *et al.*, 2004; 2005; Hasbi *et al.*, 2009). For instance, there are indications that both D_1 and D_2 receptors can transactivate the brain-derived neurotrophic factor (BDNF) receptor in neurons (Swift *et al.*, 2011). These two dopamine receptors can also regulate calcium channels through a direct protein–protein interaction *in vivo* (Kisilevsky and Zamponi, 2008; Kisilevsky *et al.*, 2008). Direct interaction of D_1 and D_2 receptors and Na^+-K^+-ATPase has also been demonstrated (Hazelwood *et al.*, 2008; Blom *et al.*, 2012). Under certain circumstances, dopamine receptors can also regulate IP_3-mediated signalling (Medvedev *et al.*, 2013; Perreault *et al.*, 2014), and there is evidence for alternative coupling of D_1-class receptors to $G\alpha_q$ (Figure 1).

The D_2-class D_2 and D_3 receptors have been shown to signal through both G protein-dependent and G protein-independent mechanisms (Beaulieu and Gainetdinov, 2011). G protein-dependent mechanisms for D_2 dopamine receptors are represented by the well-known $G\alpha_{i/o}$ subunit-mediated cAMP-PKA-DARPP32 cascade (Svenningsson *et al.*, 2004) and the Gβγ-mediated activation of PLC, leading to increased cytoplasmic calcium and downstream signalling events (Hernandez-Lopez *et al.*, 2000; Beaulieu and Gainetdinov, 2011). Furthermore, Gβγ-mediated mechanisms are involved in the regulation of activity of the L- and N-type calcium channels (Yan *et al.*, 1997) as well as G protein coupled inwardly rectifying potassium channels (GIRKs) (Kuzhikandathil *et al.*, 1998; Beaulieu and Gainetdinov,

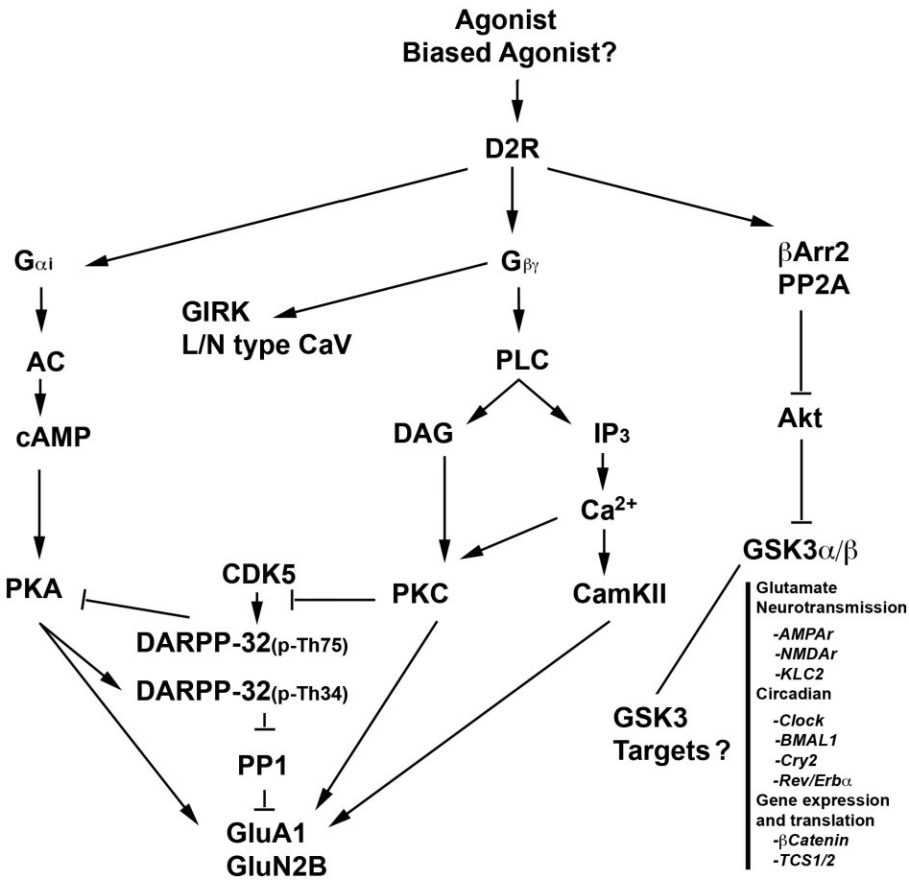

Figure 2

Schematic diagram representing the signalling cascades activated by the D_2 dopamine receptor (D2R). BMAL1, aryl hydrocarbon receptor nuclear translocator-like protein; *Clock*, circadian locomotor output cycles kaput gene; Cry2, cryptochrome 2; KLC2, kinesin light chain 2; Rev/Erbα, nuclear receptor subfamily 1, group D, member 1.

2011). Recent evidence indicates that all of these G protein-mediated signalling cascades converge on, among other targets, phosphorylation of two subunits of ionotropic glutamate receptors, GluA1 and GluN2B, which are critically involved in glutamatergic transmission (Jenkins and Traynelis, 2012; Dell'anno *et al.*, 2013; Hobson *et al.*, 2013; Jia *et al.*, 2013; Song *et al.*, 2013; Flores-Barrera *et al.*, 2014; Jenkins *et al.*, 2014; Murphy *et al.*, 2014) (Figure 2).

Finally, there is strong evidence that D_2 dopamine receptors can signal *in vivo* by activating cAMP-independent mechanisms involving the multifunctional adaptor protein β-arrestin 2 (βArr2) (Beaulieu *et al.*, 2004; 2005; 2008b; Urs *et al.*, 2012) (Figure 2). In the remaining parts of this subsection, we will provide an overview of recent evidence underscoring the importance of cAMP-independent mechanisms in dopamine receptor function.

Coupling of dopamine receptors to $G\alpha_q$

Several lines of evidence support the regulation of PLC and calcium signalling by dopamine receptors. As early as 1989, Felder *et al.* reported that the D_1 receptor agonist SKF 82526 stimulates PLC activity independently of cAMP in renal tubular membranes (Felder *et al.*, 1989). Activation of PLC leads to the production of inositol trisphosphate (IP_3) and DAG. This results in the activation of PKC by DAG and an increased mobilization of intracellular calcium in response to IP_3 (Berridge, 2009). The increase of intracellular calcium in the cytoplasm leads to the activation of calcium-dependent PKC variants as well as calcium-regulated enzymes, such as the calcium/calmodulin-dependent PK II (CaMKII) and the protein phosphatase calcineurin/protein phosphatase 2B (PP2B).

The most common way for a GPCR to regulate PLC activity is by coupling to $G\alpha_q$. Putative D_1–D_2 receptor heterodimers have been suggested to regulate DAG and IP_3 signalling by activating $G\alpha_{q/11}$ in transfected cells as well as in striatal membrane preparations (Lee *et al.*, 2004; Rashid *et al.*, 2007b). The physiological relevance of D_1–D_2 receptor heterodimers is supported by the co-expression of D_1 and D_2 receptors in small populations of medium spiny neurons of the nucleus accumbens in the mouse (Rashid *et al.*, 2007b) and in other regions of the basal ganglia (Perreault *et al.*, 2010). Notably, analysis of BAC transgenic mice that express fluorescent gene-reporter proteins driven by D_1 and D_2 receptor promoters showed that the majority of D_1 receptor-positive pyramidal neurons in the prefrontal cortex also express low

levels of D_2 receptors (Zhang *et al.*, 2010). In addition to co-expression studies, FRET studies conducted with fluorescent proteins in transfected cells and treatments of tissue sections with labelled antibodies have produced results that suggest the formation of receptor heterodimers (Rashid *et al.*, 2007b; Perreault *et al.*, 2013).

Despite accumulating evidence, the involvement of D_1–D_2 receptor heterodimers in the regulation of PLC-mediated signalling *in vivo* remains poorly understood. It should be noted that recent studies have questioned the selectivity (Chun *et al.*, 2013) and PLC activity (Lee *et al.*, 2014) of the putative D_1–D_2 receptor heteromer agonist SKF 83959 that was used to characterize the role of D_1–D_2 receptor heterodimers in the regulation of PLC *in vivo* (Rashid *et al.*, 2007b). One important aspect of D_1–D_2 heterodimer signalling in cells is the requirement of co-activation of both the D_1 and D_2 receptor moiety to activate $G\alpha_{q/11}$. Furthermore, the formation of the D_1–D_2 receptor heterodimers would prevent coupling of either receptors to $G\alpha_{s/olf}$ or $G\alpha_{i/o}$ (Perreault *et al.*, 2014). This theory, however, is in contrast with several *in vivo* observations supporting the regulation of PLC by D_1-class receptors without the need for D_2 receptor involvement. It was recently reported that acute systemic administration of cocaine, amphetamine, apomorphine or the D_1-class receptor agonist SKF 81297 to wild-type mice increases striatal IP_3 synthesis (Medvedev *et al.*, 2013). Co-treatments with selective antagonists as well as the use of D_1 and D_2 receptor knockout (KO) animals revealed that the production of IP_3 in response to these pharmacological treatments requires D_1, but not D_2 receptor activation. Importantly, PLCβ inhibition suppressed spontaneous locomotor hyperactivity in hyperdopaminergic mice lacking the dopamine transporter (DAT) and antagonized the effects of amphetamine, cocaine, SKF 81297 and apomorphine on forward locomotion. Furthermore, the restoration of locomotion by L-DOPA in dopamine-depleted mice (Sotnikova *et al.*, 2005) is also reduced by inhibition of PLCβ resulting in mostly vertical activity following these treatments (Medvedev *et al.*, 2013). These data strongly support a contribution of PLC in mediating the effects of dopamine on forward locomotion. However, further investigation is necessary to decipher the relative contribution of different modes of PLC regulation on the various aspects of dopamine-related behaviours.

At the same time, expression of D_1 receptors in transfected HEK293 cells does not affect intracellular calcium signalling. However, expression of D_5 receptors in the same cells induces extensive calcium mobilization after stimulation (So *et al.*, 2009), and the D_1-class receptor agonist SKF 38393 activates PLC-mediated signalling in D_1 receptor KO mice (Friedman *et al.*, 1997). Furthermore, this same agonist, as well as dopamine and SKF 83959, failed to increase IP_3 levels in brain slices prepared from mice lacking D_5 receptors (Sahu *et al.*, 2009). A similar lack of responsiveness of PLC-mediated signalling to SKF 83959 was also reported following systemic administration of this compound to D_5 receptor KO mice (Sahu *et al.*, 2009), suggesting that activation of D_5 receptors is sufficient to activate $G\alpha_{q/11}$ in response to selected doses of certain D_1-class receptor agonists.

Thus, several independent studies support the regulation of PLC-mediated signalling through dopamine receptors, however, these studies are in disagreement with regard to the detailed mechanism of this regulation. Current evidence does not allow us to rule out the contributions of D_1 receptors, D_5 receptors or D_1–D_2 receptor heterodimers in this phenomenon (Figure 1). Discrepancies between the results of different research groups raise the possibility that several mechanisms may be involved, perhaps in different neuronal populations. It is also conceivable that different D_1-class receptor agonists may be functionally selective for PLC-mediated mechanisms when activating D_1 receptors, D_5 receptors or D_1–D_2 receptor heterodimers.

Beyond the question of its detailed mechanism, activation of PLC-mediated signalling by dopamine also raises the question of possible crosstalk between this modality of signalling and cAMP-mediated mechanisms. Among several possibilities, activation of PKC and CaMKII through calcium signalling could affect glutamate receptors concomitantly with PKA (Figure 1). Different mechanisms involving either positive or negative regulation of CDK5 by calcium may also be an important nexus for crosstalk. For instance, PKC has previously been shown to prevent the phosphorylation of DARPP-32 and other substrates by CDK5 (Sahin *et al.*, 2008). Because the global activity of DARPP-32 is modulated by an equilibrium between its phosphorylation by CDK5 and PKA (Bibb *et al.*, 1999) it is possible that $G\alpha_{q/11}$-mediated dopaminergic signalling may reduce the phosphorylation of DARPP-32 by CDK5 and potentiate PKA-mediated signalling (Figure 1). In contrast, cleavage of the CDK5 co-activator p35 by the calcium-regulated protease calpain (Lee *et al.*, 2000; Beaulieu and Julien, 2003) may result in CDK5 hyperactivity and an inhibition of PKA signalling. Furthermore, changes in calcium concentration may also affect the activity of PP2B (calcineurin), which is involved in the dephosphorylation of DARPP-32 at Thr^{34} (Halpain *et al.*, 1990). Overall, the full understanding of the regulation of PLC activity by dopamine remains incomplete yet holds promise for exciting future investigations.

Coupling of D_2-class receptors to βArr2, Akt and glycogen synthase kinase (GSK3)

G protein-independent D_2 receptor signalling is represented by βArr2-mediated mechanisms. Arrestins are a family of four molecular adaptor proteins that were originally characterized for their role in mediating GPCR desensitization and internalization (Lohse *et al.*, 1990; Ferguson *et al.*, 1996). In addition to these functions, the two ubiquitous arrestins, βArr1 and βArr2, have also been shown to act as molecular scaffolds for signalling molecules such as kinases and phosphatases (Luttrell *et al.*, 2001; Beaulieu *et al.*, 2005).

Several lines of evidence have pointed towards the contribution of a βArr-mediated mechanism in the regulation of the serine/threonine kinases Akt and GSK3 by dopamine. Akt is involved in several cellular processes such as glucose metabolism, gene transcription, cell proliferation, migration and neurotrophin action through the stimulation of receptor tyrosine kinases (RTKs) (Cross *et al.*, 1995; Alessi *et al.*, 1996; Scheid and Woodgett, 2001). Activation of RTKs and some GPCRs regulates PI3K, which converts phosphatidylinositol-2-phosphate (PIP_2) to phosphatidylinositol-3-phosphate (PIP_3) (Martelli *et al.*, 2010). This newly formed PIP_3 interacts with the pleckstrin homology domain of Akt, inducing the recruitment of Akt to the plasma membrane. This, in turn,

results in the phosphorylation of Akt at the Thr^{308} and Ser^{473} residues by two phosphatidylinositol-dependent kinases, PDK1 and PDK2/rictor-mTOR respectively (Scheid and Woodgett, 2001; Jacinto *et al.*, 2006). Once activated, Akt phosphorylates several substrates including GSK3 (Rossig *et al.*, 2002). Mammalian cells express two isoforms of GSK3, GSK3α and GSK3β, which are constitutively active and can phosphorylate several cellular substrates (Woodgett, 1990; Kaidanovich-Belin and Woodgett, 2011). Phosphorylation by Akt inhibits both isoforms of GSK3 in response to growth factors and hormones, including insulin, IGF, and BDNF (Yamada *et al.*, 2002; Altar *et al.*, 2008). Specifically, Akt phosphorylates Ser^{21} on GSK3α and Ser^{9} on GSK3β, which are located on their respective N-terminal domains (Stambolic and Woodgett, 1994; Frame and Cohen, 2001).

Experiments using dopamine receptor agonists/antagonists, dopamine depletion and hyperdopaminergic DAT-KO mice have provided converging evidence for the negative regulation of Akt, resulting in the activation of both GSK3 isoforms by D_2-class receptors in mammals and other vertebrates (Beaulieu *et al.*, 2004; Bychkov *et al.*, 2007; Chen *et al.*, 2007; Souza *et al.*, 2011). Consequently, D_2-class receptor antagonists induce Akt activation and subsequent GSK3 inhibition (Beaulieu *et al.*, 2004; Emamian *et al.*, 2004). Additional investigations conducted using mice lacking various dopamine receptors have shown that a loss of D_2, but not D_1 receptors prevents the inactivation of striatal Akt by drugs acting on dopamine neurotransmission (Beaulieu *et al.*, 2007b). In contrast, D_3 receptor-deficient mice exhibit a reduction of Akt phosphorylation in response to dopaminergic drugs. This suggests that D_2 receptors are critical for the inhibition of Akt by dopamine, whereas the D_3 receptors appear to potentiate the D_2 receptor-mediated dopamine response (Beaulieu *et al.*, 2007b).

The role of βArr2 in mediating the regulation of Akt and GSK3 by D_2 receptors is supported by direct *in vivo* biochemical observations in pharmacological and genetic models of enhanced dopaminergic neurotransmission (Beaulieu *et al.*, 2004; 2005). Amphetamine and apomorphine have been shown to inhibit the phosphorylation and activation of Akt in the striatum of wild-type mice, whereas these two drugs failed to inhibit Akt in βArr2-KO mice. Furthermore, regulation of Akt and GSK3 signalling observed in mice with genetically increased dopaminergic tone caused by a lack of DAT, was absent in double mutant mice deficient for both DAT and βArr2, suggesting an important role of this scaffolding protein in Akt regulation by dopamine (Beaulieu *et al.*, 2005). Further characterization of the molecular mechanisms underlying the regulation of Akt by D_2 receptors, following receptor stimulation has shown that βArr2 is involved in the formation of a protein complex composed of Akt, βArr2 and protein phosphatase 2A (PP2A) (Beaulieu *et al.*, 2005). Formation of this complex allows PP2A to dephosphorylate and inactivate Akt, resulting in the activation of GSK3 (Beaulieu *et al.*, 2004; 2005).

It is worth mentioning that the formation of the Akt : βArr2 : PP2A signalling complex in response to D_2 receptor activation represents a mechanism through which dopamine can trigger the inactivation of PI3K/Akt signalling in a regulated fashion. Importantly, the Akt : βArr2 : PP2A signalling complex dissociates in response to lithium, thus providing a probable explanation for the early behavioural observations of the antagonistic effect of lithium on dopaminergic behaviours as well as a reasonable mechanism for the activation of Akt by lithium (Beaulieu and Caron, 2008a; O'Brien *et al.*, 2011; Pan *et al.*, 2011). The details of the mechanism(s) by which lithium triggers this dissociation are not yet fully understood. Current evidence suggests that lithium may affect the stability of this complex by acting on several of its components, possibly in a synergistic fashion. First, lithium has been shown to interfere with the interaction of Akt1 and βArr2 (Beaulieu *et al.*, 2008b). Direct investigation of the Akt–βArr2 interaction using recombinant proteins have demonstrated that this interaction is dependent upon the presence of magnesium ions and that excess magnesium can prevent the dissociation of Akt and βArr2 upon treatment with a therapeutic dose of lithium (1 mM). Second, GSK3β has also been shown to interact with βArr2. Recent evidence obtained from transgenic mice overexpressing *Xenopus* GSK3β in neurons indicate that activated GSK3 can act as a feed-forward mechanism for its own activation (Figure 2) by stabilizing the Akt : βArr2 : PP2A signalling complex (O'Brien *et al.*, 2011). According to this model, direct inhibition of GSK3 by lithium would thus constitute a mechanism that can promote the disassembly of the Akt : βArr2 : PP2A.

The effect of βArr2-mediated Akt/GSK3 signalling on dopaminergic behaviours is supported by several experimental observations *in vivo*. βArr2-KO mice have been shown to display spontaneous locomotor hypoactivity, reduced apomorphine-induced climbing and amphetamine-induced hyperlocomotion (Gainetdinov *et al.*, 2004; Beaulieu *et al.*, 2005). These mice also have a reduced responsiveness to the dopamine-dependent locomotor effects of morphine (Bohn *et al.*, 2003). In addition, novelty-driven locomotor hyperactivity, a phenotype that is typical of hyperdopaminergic DAT-KO mice, is less pronounced in double mutant mice lacking both βArr2 and DAT (Beaulieu *et al.*, 2005). Administration of lithium exerts multiple actions on behaviours in DAT-KO and normal mice, including suppression of spontaneous locomotor activity, but this was not observed in βArr2-KO mice (Beaulieu *et al.*, 2004; 2005). In line with these data, mice lacking Akt1 demonstrate an enhanced sensitivity to amphetamine with regard to the disruption of sensorimotor gating in the pre-pulse inhibition (PPI) test, which is used to model psychosis in rodents (Emamian *et al.*, 2004). As described above, Akt1 is inhibited following the stimulation of D_2 receptors, thus the increased behavioural effect of amphetamine in Akt1-KO mice is likely to result from the involvement of Akt in dopaminergic behavioural responses.

Genetic suppression of GSK3 activity also inhibits locomotor hyperactivity related to excessive dopaminergic tone in amphetamine-treated mice (Beaulieu *et al.*, 2004). Similarly, several GSK3 inhibitors as well as GSK3β haploinsufficiency can block amphetamine-induced hyperactivity (Beaulieu *et al.*, 2004; Gould *et al.*, 2004; Kalinichev and Dawson, 2011). In contrast, mice overexpressing GSK3β show pronounced locomotor hyperactivity (Prickaerts *et al.*, 2006), and transgenic mice expressing a GSK3β mutant that lacks an inhibitory phosphorylation site (thus is constitutively active) demonstrate increased novelty-driven and amphetamine-induced hyperactivity (Polter *et al.*, 2010).

More recent evidence obtained using strains of cell type-specific conditional GSK3β-KO mice have generated a more nuanced portrait of the contribution of GSK3β in the regulation of dopaminergic behaviour. Ablation of GSK3β expression specifically in D_1 or D_2 receptor-expressing striatal neurons (Urs *et al.*, 2012) confirmed the selective contribution of GSK3β to the acute action of amphetamine on locomotion in D_2 but not D_1 receptor-expressing neurons. The antagonistic action of the D_2 receptor partial agonist aripiprazole and lithium on amphetamine-induced locomotion is also curbed in mice lacking GSK3β in D_2 receptor-expressing neurons. In contrast, haloperidol-induced catalepsy is not affected by diminished GSK3β expression in either D_1 or D_2 receptor-expressing striatal neurons, whereas the disruptive effects of amphetamine on sensory motor gating is abolished by in either D_1 or D_2 receptor-expressing neuron-selective GSK3β gene inactivation. Taken together, these observations confirm the role of βArr2-mediated regulation of GSK3β in D_2 receptor-expressing neurons in the effects of amphetamine, lithium and aripiprazole on locomotion. The fact that haloperidol-induced catalepsy remains intact in mice lacking GSK3β suggests the involvement of at least two separate signalling pathways mediating the effects of antipsychotics and strengthens the rationale for the development of biased D_2 receptor antagonists to selectively target these pathways in schizophrenia (Beaulieu *et al.*, 2007a; Beaulieu, 2012). Further confirmation of these hypotheses should come from repeating these experiments in mice lacking βArr2 in specific neuronal populations.

Selective ablation of GSK3β post-natally in forebrain pyramidal neurons revealed other functions of GSK3β in the regulation of dopamine-associated behaviours (Latapy *et al.*, 2012). The locomotor effects of amphetamine are marginally increased in these mice, which suggests a minor role of cortical neurons in the modulation of amphetamine action and further indicates that the opposing effect of GSK3β inhibition on amphetamine-induced locomotion is mediated by GSK3β in subcortical structures. Additionally, these mice display reduced anxiety and enhanced social interactions. Investigation of the possible contribution of GSK3β in behavioural responses to social defeat stress (Wilkinson *et al.*, 2011; Latapy *et al.*, 2012) using either conditional forebrain KO mice, GSK3β haplo-insufficient mice or mice expressing a dominant negative GSK3 in the nucleus accumbens also revealed a role for subcortical GSK3β inhibition in mediating resilience to this form of stress. This emphasizes the need to further examine the contribution of GSK3-mediated dopamine receptor signalling in coping behaviours.

Beyond its potential involvement in the action of lithium, βArr2-mediated D_2 receptor signalling can also contribute to effects of antipsychotics. Characterization of the effects of different antipsychotics using BRET in transfected HEK293 cells revealed that first-generation antipsychotics (chlorpromazine, haloperidol), as well as second- (clozapine, quetiapine, olanzapine, risperidone, ziprasidone) and third-(aripiprazole) generation antipsychotics potently antagonize quinpirole-induced βArr2 recruitment to D_2 receptors (Masri *et al.*, 2008). In contrast, strong differences existed in the potency of these drugs in preventing inhibition of cAMP synthesis by D_2 receptors. Of interest, D_2 receptor partial agonist aripiprazole displayed partial D_2 receptor agonist activity for cAMP-mediated signalling in the absence of quinpirole while functioning as an antagonist for cAMP when quinpirole was applied concomitantly. Because second- and third-generation antipsychotics are characterized by fewer extrapyramidal side effects, this study led to the hypothesis that identification of functionally selective D_2 receptor antagonists that specifically prevent βArr2 recruitment to D_2 receptors may pave the way for the development of new antipsychotics that would have fewer side effects while retaining their therapeutic activity.

This hypothesis led to the development of new aripiprazole derivative compounds: UNC9975, UNC0006 and UNC9994, which display antipsychotic-like activity in rodents (Allen *et al.*, 2011). In the absence of a full agonist, these three compounds have the distinction of acting as partial D_2 agonist for βArr2 recruitment without affecting cAMP. It should be noted, however, that these compounds may not be fully functionally selective as Allen *et al.* also reported that they can act as neutral antagonists for cAMP-mediated D_2 signalling. It is also noteworthy that aripiprazole behaves as a partial agonist for βArr2 recruitment when applied alone on cells (Allen *et al.*, 2011) while acting as an antagonist of βArr2 recruitment when simultaneously applied with quinpirole (Masri *et al.*, 2008). It is thus possible that the UNC compounds may display different pharmacological properties when applied alone *in vitro* and in the context of an active dopamine tone *in vivo* where they might antagonize both cAMP and βArr2 mediated D_2 receptor signalling through a combination of neutral antagonism and partial agonism.

Overall, βArr2-mediated D_2 receptor signalling provides interesting avenues for the development of new drugs targeting dopamine neurotransmission. However, it is unclear at the moment whether this type of intervention will be more suited for clinical interventions in schizophrenia or bipolar disorder. Indeed, this form of signalling is directly targeted by lithium (Beaulieu *et al.*, 2004; 2008b), a drug that has very limited efficacy for the treatment of schizophrenia.

Protein phosphatase metallo-dependent (PPM/PP2C) and $G\alpha_{i/o}$ mediated regulation of huntingtin (HTT) protein phosphorylation by D_2 receptors

Recent investigation has revealed a role of D_2 receptors in the regulation of the phosphorylation of the HTT protein on Ser^{421} (Marion *et al.*, 2014). It is known that phosphorylation of HTT on this residue by Akt in response to IGF-1 leads to reduction of the formation of nuclear inclusions and HTT toxicity (Humbert *et al.*, 2002; Rangone *et al.*, 2004). Intriguingly, D_2 receptor stimulation reduces the phosphorylation of HTT on this residue in heterologous cells and in the mouse striatum (Marion *et al.*, 2014). The molecular mechanism of this regulation appears not to involve the regulation of Akt by D_2 receptors. Instead, the regulation of HTT phosphorylation by D_2 receptors involves the activation of $G\alpha_{i/o}$ and the formation of a protein complex between HTT and D_2 receptors. Indeed, treatment of transfected cells with the $G\alpha_{i/o}$ inhibitor, *Pertussis* toxin, prevented the dephosphorylation of HTT in response to D_2 receptor stimulation. Furthermore, the study revealed the formation of a protein complex comprising D_2

receptors, HTT and two members of the PPM/PP2C family. The first of these phosphatases, PPM1A, was shown to interact directly with HTT *in vivo* whereas the second phosphatase, PPM1B as well as HTT interact directly with the D_2 receptors. While it is not clear at the moment if PPM1A and B both participate in HTT dephosphorylation and the contribution of cAMP-mediated mechanisms has remained unexplored, the potential involvement of this mechanism in the regulation of HTT toxicity certainly warrants further investigations.

Transactivation of RTK by dopamine receptors

RTKs are a major family of cell surface receptors involved in many functions in neuronal and non-neuronal cell types (Lemmon and Schlessinger, 2010). Members of this family include, among others, the BDNF receptor neurotrophic tyrosine kinase, receptor, type 2 (TrkB), EGF/neuregulin family receptors (ErbB family) and receptors for insulin and insulin-like growth factor 1 (IGFR1). Activation of RTKs by their cognate ligands enhances receptor dimer formation, internalization, and recruitment of monomeric receptors to the cell surface. RTK activation generally results in a concomitant rapid activation of several signalling pathways, including PI3K/Akt, Ras/MAPK and PLC-mediated signalling (Figure 2).

In addition to direct activation by their ligands, RTKs can also be transactivated by GPCRs (Eguchi *et al.*, 1998; Maudsley *et al.*, 2000; Rajagopal *et al.*, 2004). However, the molecular mechanisms of this transactivation are not clearly understood. Independent investigations conducted in different systems have underscored the possible contribution of both G protein- and arrestin-mediated mechanisms involving either direct activation of RTK by intracellular processes or autocrine/paracrine RTK activation following ligand shedding in response to GPCR activation.

Dopamine receptors have been shown to transactivate RTKs in different experimental systems (Figure 3). The D_4 receptor was shown to transactivate the platelet-derived growth factor β (PDGFβ) receptor, and D_2 receptors were able to transactivate IGF receptors in heterologous cell systems (Chi *et al.*, 2010; Mannoury la Cour *et al.*, 2011). Furthermore, both D_1 and D_2 receptors can transactivate ErbB-1 in transfected CHO-K1 cells (Swift *et al.*, 2011) and primary neuron cultures (Iwakura *et al.*, 2011; Yoon and Baik, 2013). Finally, D_1, D_2 and potentially D_1–D_2 receptor heteromers have been shown to transactivate the BDNF receptor in cultured striatal neurons (Iwakura *et al.*, 2008; Swift *et al.*, 2011; Barbeau *et al.*, 2013). Systemic administration of the D_1-class receptor agonist SKF 38393 also increased TrkB activation at 3 and 6 h following drug injection in 4-day-old rats (Iwakura *et al.*, 2008). The treatment of rats with the D_1 receptor antagonist SCH23390 reduced striatal TrkB activation, suggesting that transactivation of TrkB by D_1 receptors occurs in response to normal endogenous dopamine tone.

The mechanisms by which dopamine receptors transactivate RTKs are not fully understood. Quantitative pharmacological characterization of ErbB-1 receptors by various GPCRs has shown that these phenomena are not restricted by the coupling of the GPCR to a different G protein (Swift *et al.*, 2011). Increased release of the RTK ligand BDNF does not appear to be essential for the transactivation of TrkB by D_1 receptors (Iwakura *et al.*, 2008). However, release of EGF appears to play a role in the transactivation of ErbB-1 by D_2 receptors in cultured neurons (Iwakura *et al.*, 2011; Yoon and Baik, 2013). Interestingly, stimulation of either frontal cortex D_5 receptors (Perreault *et al.*, 2013) or striatal D_1–D_2 receptors (Hasbi *et al.*, 2009) has also been reported to increase BDNF levels, therefore potentially leading to increased TrkB activation in response to dopamine receptor stimulation.

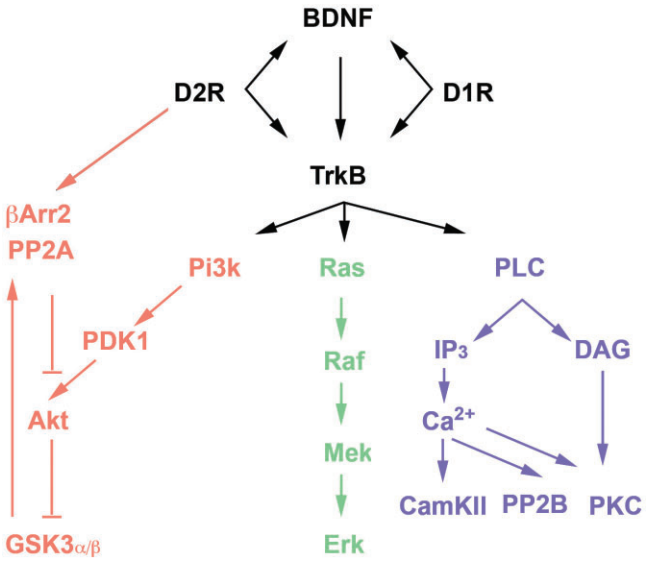

Figure 3

Mechanisms and signalling events involved in the transactivation of RTK by dopamine receptors. Raf, proto-oncogene serine/threonine-PK; Ras, rat sarcoma family of small GTPases.

Transactivation of RTKs by dopamine receptors can have a major effect on our understanding of dopamine receptor signalling *in vivo*. RTKs are coupled to several signalling mechanisms that can elicit cellular responses, which are beyond the direct effect of G protein or arrestin-mediated cellular responses. For instance, although D_2 receptor stimulation leads to a βArr2-dependent inactivation of Akt and concomitant activation of GSK3 *in vivo*, the opposite has been reported to occur in heterologous cell systems and, in some cases, cultured neurons (Brami-Cherrier *et al.*, 2005; Beaulieu, 2012). It has recently been shown that activation of Akt by recombinant D_2 receptors in transfected cells can be attributed to the transactivation of IGFR and concomitant activation of PI3K-mediated signalling by this RTK (Mannoury la Cour *et al.*, 2011). It is also possible that some instances of MAPK and PLC-mediated signalling in response to dopamine receptor activation may also result from RTK transactivation (Figure 3). The apparent involvement of RTK ligand release in the transactivation of some RTKs by dopamine receptors also raises the possibility that activation of dopamine receptors in dopaminoceptive neurons may elicit paracrine signalling responses to dopamine in either non-dopaminoceptive neurons or non-neuronal cells, possibly leading to indirect regional effects of dopamine receptor stimulation. This type of regional responses may be important considering the potential role of TrkB, and probably other RTKs, in regulating drug-induced reward (Lobo *et al.*, 2013).

Dopamine receptor oligomerization

Historically, GPCRs are believed to function as monomeric units, but now there is mounting evidence indicating that several GPCRs can exist in oligomeric forms (Perreault *et al.*, 2014). Regarding dopamine receptors, they can form both homomers and heteromers with several receptors, including other GPCRs and ionotropic glutamate receptors (Guo *et al.*, 2008; Van Craenenbroeck *et al.*, 2011; Perreault *et al.*, 2014). Some of these interactions may be regulated via mechanisms likely orchestrated by AC and cAMP (Woods and Jackson, 2013). A study by the Javitch group suggested that D_2 receptor homodimers and a G protein exist as the minimal single functional unit, which is maximally activated by the binding of an agonist to only one protomer and is either negatively or positively modulated by the ligand to the other protomer of an agonist or an inverse agonist respectively (Han *et al.*, 2009). This allosteric modulation between the two protomers of the complex is mediated through intermolecular interactions by the direct association among receptors and not by downstream effects. The development of RET-based techniques has been of fundamental importance in the discovery and characterization of many homomers and heteromers and is now considered to be the preferred biophysical method in describing complex formations (Milligan, 2004; Pfleger and Eidne, 2006; Marullo and Bouvier, 2007; Salahpour *et al.*, 2012). Both BRET and FRET rely on the principle of a non-radiative energy transfer between a donor protein and a fluorescent acceptor. In case of FRET, the donor is also a fluorescent protein (e.g., CFP), whereas in BRET, the donor is an enzyme (*Renilla* luciferase) that produces bioluminescence upon the degradation of a substrate (coelenterazine *h* or derivatives) (Pfleger and Eidne, 2006). Because the energy transfer is only possible when the donor and the acceptor are closer than 10 nm, when two proteins fused to a donor and an acceptor produce a BRET or FRET signal, it is an indication of a physical contact (Pfleger and Eidne, 2006; Marullo and Bouvier, 2007; Lohse *et al.*, 2012). However, a simple BRET or FRET signal is insufficient to distinguish true heterodimerization from a random collision; thus many experimental approaches have been adopted to characterize a putative heterodimer, such as saturation curves, competition assays and others (Marullo and Bouvier, 2007; Salahpour and Masri, 2007). Although these approaches have been extremely useful to study various complexes in cellular systems, these methods cannot simply be applied directly in native tissue, although there are some examples of successful applications *in vivo* using FRET with selective fluorescent ligands (Albizu *et al.*, 2010) or antibodies (Perreault *et al.*, 2010). After the *in vitro* description of the heterodimer and the characterization of its functional features, it is more common to prove the existence of the complex in native tissue using indirect evidence, such as identifying the 'biochemical fingerprint' and reproducing the specific characteristics of the complex and/or analysing physiological or behavioural responses to co-activation of the receptors (Ferre and Franco, 2010). In this section, we limit our discussion only to the heterodimers formed by dopamine receptors that have at least partial validation in studies in native tissue and/or *in vivo*.

D_1–D_2 receptor heterodimer

As mentioned earlier, D_1 and D_2 receptors can form a heterodimer complex that has been shown to exist in a heterologous system and in primary striatal neurons as well as *in vivo* in the rodent brain (Perreault *et al.*, 2013; 2014). Several techniques have been used to characterize this complex, ranging from classic biochemical approaches, including co-immunoprecipitation of the two proteins (Lee *et al.*, 2004), to more accurate techniques such as quantitative FRET (Dziedzicka-Wasylewska *et al.*, 2006; Hasbi *et al.*, 2009; Perreault *et al.*, 2010). The expression and cellular localization of D_1–D_2 receptor heterodimers has been characterized not only in cells, but also *in vivo*, primarily in rat striatum. Studies from BAC transgenic mice demonstrate that the majority of the D_1- and D_2 receptor-expressing neurons are segregated in two different populations, although a small percentage of neurons express both receptors, ranging from a 6% in caudate putamen to a 15–30% in nucleus accumbens (Bertran-Gonzalez *et al.*, 2008; Perreault *et al.*, 2010). These MSNs expressing D_1 and D_2 receptors are interesting in that they express both dynorphin and enkephalin; thus, one might consider them to be a third, distinct subset on MSNs. Among these, not all of the neurons show constitutive D_1–D_2 receptor heterodimer formation. Although a small proportion of caudate putamen MSNs revealed a D_1–D_2 receptor complex, in most of the neurons (90%) expressing both D_1 and D_2 receptors in the nucleus accumbens, these receptors are present as heterodimers (Perreault *et al.*, 2010). As mentioned earlier, this occurs under basal conditions, and it has been shown that several stimuli and pathological conditions could alter the state and the proportion of D_1–D_2 heterodimers (Dziedzicka-Wasylewska *et al.*, 2006; Perreault *et al.*, 2010). A peculiar aspect of this heterodimer is that it has a unique pharmacology that is distinct from that of its single protomer (Figure 1). Activation of the D_1–D_2 receptor complex induces the recruitment of the $G\alpha_{q/11}$ protein, leading to the release of calcium from the internal stores (Rashid *et al.*, 2007a,b; Hasbi *et al.*, 2009). It appears that D_1 and D_2 receptors are both necessary for this pathway, thus the application of dopamine or a combination of two selective D_1 and D_2 receptor agonists are able to increase intracellular calcium, whereas treatment with either a D_1 or D_2 receptor antagonist can abolish this effect (Hasbi *et al.*, 2009).

A selective D_1–D_2 receptor heteromer agonist (SKF 83959) has also been described: (Rashid *et al.*, 2007b). It should be noted, however, that a recent report argues the selectivity of this compound by showing that this effect is dependent on the level of $G\alpha_{q/11}$ expression in cells and there could be a contribution from the $G\beta\gamma$ subunits and GRK2 on the calcium increase induced by the D_1–D_2 receptor heterodimer (Chun *et al.*, 2013), while another report questioned in general the ability of SKF 83959 to influence PLC (Lee *et al.*, 2014). It has been suggested that this heteromer may play a role in brain disorders such as addiction (Perreault *et al.*, 2010), schizophrenia (Dziedzicka-Wasylewska *et al.*, 2008) and major depression (Pei *et al.*, 2010), although additional evidence is needed to support these hypotheses.

D_1-D_3 receptor heterodimers

D_1 and D_3 receptors are co-expressed in the majority of the substance P – expressing GABAergic medium spiny neurons,

suggesting that there could be functional crosstalk between these two receptors. Two independent studies have demonstrated that D_1 and D_3 receptors can form a constitutive heterodimer (Fiorentini *et al.*, 2008; Marcellino *et al.*, 2008). Using BRET and FRET techniques in transfected cells, it has been shown that D_1 and D_3 receptors can physically interact with no change in complex formation upon agonist treatment. Moreover, using co-immunoprecipitation, it was possible to isolate the D_1–D_3 complex from striatal membranes, confirming the existence of this heteromer in the brain. This cooperativity between D_1 and D_3 receptors is also evident in behavioural experiments. It is known that activation of D_1 receptors stimulates locomotor activity, whereas the role of D_3 receptors is less clear. In reserpinized mice (a model to isolate postsynaptic effects), D_3 receptor agonists can potentiate the stimulatory effects of D_1, but not D_2 receptor agonists. Furthermore, this potentiation can be counteracted with a D_3 receptor antagonist and is not present in D_3 receptor KO mice (Marcellino *et al.*, 2008). It has been suggested that the functional synergy of the D_1–D_3 dimer could be important for processes related to drug addiction and L–DOPA-induced dyskinesia in Parkinson's disease. It will be of interest to further characterize the physiological relevance of the D_1–D_3 heterodimer in other dopamine-related functions and pathologies.

D_2–D_4 receptor heterodimers

Both the long and the short D_2 receptor isoforms can associate with D_4 receptors, (Borroto-Escuela *et al.*, 2011b; Gonzalez *et al.*, 2012b). Using BRET, co-immunoprecipitation and proximity ligation assay, it has been shown in cell culture that D_{2L} receptors can exist in a heterodimeric form with the major variants of the D_4 receptors: $D_{4.2}$, $D_{4.4}$ and $D_{4.7}$, with $D_{4.7}$ being the least effective in forming the complex (Borroto-Escuela *et al.*, 2011b). Ferrè and colleagues showed with BRET that D_{2S} receptors can also associate in a heterodimer complex with the two variants $D_{4.2}$ and $D_{4.4}$, but not with the variant $D_{4.7}$ (Gonzalez *et al.*, 2012b). This study revealed a biochemical fingerprint for this heteromer that could potentiate D_4 receptor activation of MAPK. In the mouse striatum, although the single activation of either D_2 or D_4 receptors had no effect on MAPK, co-administration of D_2 and D_4 receptor agonists induced a strong ERK phosphorylation response (Gonzalez *et al.*, 2012b). This synergistic activity was lost in knock-in mice carrying the $D_{4.7}$ variant, demonstrating the lack of mutual functional interaction between these two receptors. Moreover, the same synergistic effect was observed as regard to the ability of D_4 receptors to modulate glutamate release in the striatum (Gonzalez *et al.*, 2012b).

Dopamine receptor/NMDA receptor heteromer

Many studies have reported D_1 receptor-mediated modulation of NMDA activity, primarily through a G protein-dependent mechanism involving the cAMP/PKA pathway and proteins such as DARPP-32 (Blank *et al.*, 1997). However, there is evidence indicating that NMDA receptors and D_1 receptors could also interact physically. A first study demonstrated the existence of this complex in hippocampal extracts by co-immunoprecipitation (Lee *et al.*, 2002). It has been described that there are two sites of interaction in the carboxy-terminal domain of D_1 receptor: one interacts with the GluN1 (NR1) subunit and the other with the GluN2A (NR2A) subunit. Each of these sites is responsible for a specific functional characteristic of the complex. These data were confirmed by another group in BRET studies that showed D_1 receptors and GluN1 forming a constitutive heterodimer in cells (Fiorentini *et al.*, 2003). Interestingly, the D_1–GluN1 complex is formed early in the ER and is translocated to the membrane only upon association with the GluN2B (NR2B) subunit (Fiorentini *et al.*, 2003). When at the cell membrane, the D_1 receptors involved in this complex lose the ability to desensitize and internalize upon stimulation, suggesting a dual role of this receptor in native tissue depending on microdomain localization and aggregation with NMDA receptors, as previously reported (Dumartin *et al.*, 1998). The activation of D_1 receptors leads to a decrease of NMDA receptor functionality, as measured by NMDA-mediated currents in HEK cells and hippocampal neurons. This loss of activity is likely due to a decrease of NMDA receptor expression to the plasma membrane mediated by GluN2A subunit (Lee *et al.*, 2002). D_1 receptor agonists could reduce the cytotoxicity induced by an overactivation of the NMDA receptors. This effect appears to be mediated through a PI3K mechanism dependent on the GluN1 subunit instead of the reduction of the calcium influx (Lee *et al.*, 2002). In another study (Nai *et al.*, 2010), D_1 receptor activation in hippocampal slices increased the NMDA-dependent long-term potentiation, as previously reported (Huang and Kandel, 1995). This effect could be abolished by disrupting the heteromer with specific interfering peptides. This interaction can have important functional consequence on cognition, as disruption of the D_1–NMDA complex led to working memory impairment (Nai *et al.*, 2010).

Another reported interaction with NMDA receptors is between D_2 receptors and GluN2B (Liu *et al.*, 2006). It has been demonstrated that in both the dorsal striatum and nucleus accumbens, D_2 receptors and GluN2B are clustered in the PSD and form a complex that is more prevalent upon systemic cocaine treatment. Cocaine is also able to produce a selective decrease in the phosphorylation of Ser^{1303} on the GluN2B subunit. This decrease is D_2 receptor-dependent, blocked by antagonist treatment, enhanced by agonist treatment and mediated by CaMKII. Cocaine treatment induces a D_2 receptor-dependent decrease in CaMKII activity, and its association with GluN2B results in the decrease of phosphorylation of Ser^{1303}. Functionally, cocaine application to striatal neurons causes a decrease in NMDA-mediated currents, an effect that can be abolished by heteromer disruption using a selective peptide that prevents the binding between the third intracellular loop of D_2 receptors and the carboxy-terminal tail of GluN2B. Furthermore, disruption of the D_2-GluN2B heteromer prevents phosphorylation of GluN2B and reduces cocaine-stimulated locomotor activity.

Adenosine receptor/dopamine receptor complexes

Many studies have shown that adenosine and dopamine exert opposing effects in the basal ganglia, with adenosine receptor agonists generally suppressing motor response and antagonists inducing motor activation (Ferre *et al.*, 1997). Because the adenosine A_1 receptor is expressed mainly in striato-nigral neurons, which also express dopamine D_1 receptors, and the adenosine A_{2A} receptor is expressed

predominantly in striato-pallidal neurons, which express D_2 receptors, it is suggested that A_1-D_1 and A_{2A}-D_2 heteromers might exist and have discrete localization in the basal ganglia (Fuxe *et al.*, 2010). Thus, heterodimer formation has been reported and extensively characterized for the A_1–D_1 complex (Gines *et al.*, 2000; Toda *et al.*, 2003) and the A_{2A}–D_2 complex (Hillion *et al.*, 2002; Canals *et al.*, 2003) using different biophysical approaches. In both complexes, both A_1 and A_{2A} receptor activation can antagonize the cAMP responses upon either D_1 or D_2 receptor stimulation in transfected cells (Ferre *et al.*, 1991; Gines *et al.*, 2000). For these reasons, it has been proposed that these complexes could be of importance as novel approach to treat some dopamine-related diseases such as Parkinson's disease and schizophrenia. Particularly, A_{2A} receptor antagonists, which can act as potentiators of the dopamine response, could be applied as adjunct therapy with D_2 receptor agonists and L-DOPA for the locomotor impairments present in Parkinson's disease patients (Fuxe *et al.*, 2007). In fact, A_{2A} receptor antagonists have been shown to improve motor deficits in several animal models of Parkinson's disease as well as demonstrate anti-parkinsonian properties in clinical trials (Fuxe *et al.*, 2008) and reduce L–DOPA-induced dyskinesia (Chase *et al.*, 2003). At the same time, A_{2A} receptor agonists showed an antipsychotic-like profile in different schizophrenia models, both in rodents (Rimondini *et al.*, 1997) and non-human primates (Andersen *et al.*, 2002). The mechanism proposed on the basis of these effects is the ability of A_{2A} receptor agonists to reduce D_2 receptor agonist binding and G protein coupling, particularly in the nucleus accumbens. Because the A_{2A}–D_2 heteromer can internalize as one unit, these agonists can also reduce D_2 receptor availability at the plasma membrane (Hillion *et al.*, 2002).

Other dopamine receptor heterodimers

Another example how dopamine receptors can alter their signalling pathways comes from a study on the D_2 -ghrelin receptor heterodimer (Kern *et al.*, 2012). The ghrelin receptor is a GPCR expressed in different regions of the brain that can be activated by the stomach peptide ghrelin (Kojima *et al.*, 1999). In the hypothalamus, the ghrelin receptor and D_2 receptors are co-expressed, and using time-resolved FRET experiments, it has been shown that these two receptors form a heterodimer in native tissue (Kern *et al.*, 2012). Moreover, when co-expressed with the ghrelin receptor, D_2 receptors are able to elicit a calcium response dependent on PLC activation, IP_3 receptors and intracellular calcium stores. Interestingly, $G\alpha_q$ is not responsible for this increase, but rather the $G\beta\gamma$ subunit, derived from $G\alpha_i$ activation, mediates this effect likely through the direct association with GRK2 and direct stimulation of PLC (Inglese *et al.*, 1994; Koch *et al.*, 1994). This heterodimer formation appears to have an important role in appetite, as the suppression of food intake induced by a dopamine D_2 receptor agonist was prevented by a ghrelin antagonist and was absent in ghrelin-KO mice, demonstrating the importance of this heterodimer in physiology.

One interesting example how dimerization can alter the physiological functions of each protomer is the case of the D_4-β_1 adrenoceptor and D_4-α_{1B} adrenoceptor heteromers (Gonzalez *et al.*, 2012a). D_4 receptors are highly expressed in the pineal gland, and their expression follows a circadian rhythm, being high at the beginning of the light cycle and low at the end (Bai *et al.*, 2008). The role of the pineal gland is to translate light inputs from the retina by producing and secreting melatonin, a product of serotonin. In this brain region, β_1 and α_{1B} adrenoceptors are the primary receptors that control this mechanism. In transfected cells, Gonzalez and colleagues proved the existence of these two heterodimers using BRET, and they also used a proximity ligation assay to demonstrate their presence *in vivo* in the pineal gland. Similar to the circadian nature of D_4 receptors, these complexes were found only at the beginning of the light cycle (Gonzalez *et al.*, 2012a). A distinctive biochemical property of these heterodimers was the modulation of ERK and Akt activity. When co-expressed in the same cells or when naturally present in native tissue, treatment with a D_4 receptor agonist was able to reduce ERK and Akt phosphorylation induced by β_1 and α_{1B} adrenergic receptors. Similarly, D_4 receptor antagonists prevent MAPK and Akt activation induced by β_1 or α_{1B} adrenoceptors, and adrenoceptor antagonists could block D_4 receptor stimulation of these pathways, showing a cross-antagonist property of this heterodimer. This functional interaction between D_4, β_1 and α_{1B} receptors was also reflected by the production and release of serotonin and melatonin, with a circadian regulation mediated by D_4 receptors and its modulation of β_1 and α_{1B} adrenoceptor activity (Gonzalez *et al.*, 2012a).

One GPCR that has emerged as a novel modulator of the dopamine system is the trace amine-associated receptor 1 (TA_1, known also as TAAR1) (Borowsky *et al.*, 2001; Sotnikova *et al.*, 2009; Espinoza *et al.*, 2011). The TA_1 receptor is expressed in several areas innervated by dopaminergic terminals such as the basal ganglia and frontal cortex, as well as in regions containing monoaminergic nuclei, including dopaminergic neurons in the ventral tegmental area (Lindemann *et al.*, 2008). Several studies have shown that the TA_1 receptor can modulate dopaminergic activities such as D_2 receptor function and the firing rate of dopaminergic neurons (Lindemann *et al.*, 2008; Bradaia *et al.*, 2009; Espinoza *et al.*, 2011). Moreover, TA_1 receptor agonists have been shown to influence effects of a wide range of dopaminergic agents and related behaviours such as amphetamine-induced hyperactivity (Revel *et al.*, 2011) and cocaine self-administration (Revel *et al.*, 2012), and are effective as antipsychotic compounds in several models of schizophrenia against positive, negative and cognitive symptoms (Revel *et al.*, 2013). One mechanism through which TA_1 receptors can influence the dopamine system is by forming a heterodimer with D_2 receptors. Using BRET, it has been demonstrated that TA_1 receptors can form a constitutive heterodimer with D_2, but not with D_1 receptors (Espinoza *et al.*, 2011; 2013), and that this heteromer can be disrupted by the D_2 receptor antagonist haloperidol. This functional interaction exerts its effect in modulating the cAMP pathway and haloperidol could potentiate TA_1 receptor-mediated cAMP signalling in cells. Furthermore, haloperidol's effects, such as *c-Fos* induction in the striatum and catalepsy, were reduced in TA_1 receptor-KO mice indicating prominent interaction between D_2 and TA_1 receptors at the levels of postsynaptic structures (Espinoza *et al.*, 2011). The D_2–TA_1 receptor interaction can also play an important role in presynaptic regulation of dopaminergic transmission by modulating D_2 receptor autoreceptor functions via TA_1 receptors (Leo *et al.*, 2014).

Other developments and emerging trends

Newly identified functions mediated by dopamine receptors

Recent studies that often employed newly developed approaches and tools have revealed novel functions mediated by dopamine receptors and clarified the contribution of specific subtypes to previously established functions. Several observations regarding the functional role of dopamine receptors have been made using transgenic techniques. In addition to gene KO studies, which have been described in previous reviews (Sibley, 1999; Holmes *et al.*, 2004; Beaulieu and Gainetdinov, 2011), mice overexpressing D_2 and D_3 receptors have been recently characterized. Particularly, mice selectively overexpressing D_2 receptors in the striatum have persistent abnormalities in prefrontal cortex function and deficits in working memory and behavioural flexibility (Kellendonk *et al.*, 2006), as well as motivation (Simpson *et al.*, 2012) and timing precision (Ward *et al.*, 2009) deficits that are often found of schizophrenia models. These mutants also demonstrated altered dendritic morphology of medium spiny neurons via involvement of $K_{ir}2$ channels (Cazorla *et al.*, 2012), and a deficit in inhibitory GABA-mediated transmission and dopamine sensitivity in the prefrontal cortex (Li *et al.*, 2011b). Taken together, these studies indicated an important role for the striatal processes in the pathogenesis of the cognitive symptoms of schizophrenia. Based on this model, overstimulation or excessive D_2 receptor activity in the striatum leads to altered functioning of prefrontal cortex neurons via several mechanisms, culminating in deficiencies in executive function and working memory – key components of schizophrenia-related deficits (Simpson *et al.*, 2010). In contrast, mice overexpressing D_3 receptors in the striatum have less pronounced, but still significant phenotype. They do not demonstrate cognitive deficits, but show disrupted motivation, suggesting that targeting D_3 receptors may have effect on motivational symptoms, which are not improved by the currently available antipsychotics in schizophrenic patients (Simpson *et al.*, 2014).

In another study, a role of subpopulation of D_1 receptor-expressing cholinergic neurons in putative antipsychotic action of the M_4 muscarinic receptor agonist xanomeline was demonstrated (Dencker *et al.*, 2011). In mutant mice lacking the M_4 muscarinic receptors only in D_1 dopamine receptor-expressing cells, the antipsychotic-like effects of xanomeline were completely abolished suggesting that M_4 muscarinic receptors co-localized with D_1 receptors are involved.

Several recent observations have indicated that the direct modulation of the DAT function by D_2 receptors might occur (Chen *et al.*, 2013) and this interaction has physiological or pathological relevance (Bowton *et al.*, 2010; Owens *et al.*, 2012); however, no alterations in DAT function were found in D_2 autoreceptor KO mice (Bello *et al.*, 2011). Based on studies involving mice that constitutively express only the short isoform D_{2S} or lacking both isoforms, it has been proposed that D_{2L} is the major postsynaptic isoform expressed in medium spiny GABA neurons while D_{2S} is predominantly expressed on presynaptic terminals and involved in autoreceptor function (Lindgren *et al.*, 2003). However, recent study with virus-mediated receptor restoration in D_2 receptor KO mice has indicated that both these alternatively spliced forms of the D_2 receptors are equally capable of acting as postsynaptic receptors and autoreceptors (Neve *et al.*, 2013). Interestingly, while the role of presynaptic D_2 receptors in autoreceptor regulation of dopamine neuron firing rate, as well as dopamine synthesis and release is well established (Bello *et al.*, 2011), a recent study involving cell-specific KO mice has shown a significant contribution of postsynaptic D_2 receptors in the local feedback regulation of dopaminergic transmission in the dorsal striatum as well (Anzalone *et al.*, 2012). As D_3 receptors are also shown to contribute to the regulation of dopamine release and are expressed both at the presynaptic terminals and postsynaptic structures (Gainetdinov *et al.*, 1996; Joseph *et al.*, 2002; Gross *et al.*, 2013), it would be of interest to explore if postsynaptic D_3 receptors could be involved in the regulation of presynaptic transmission via similar local feedback mechanisms.

Application of optogenetic techniques has allowed for more precise anatomical and cellular dissection of the role of specific dopamine receptors in dopamine-related functions. An important advance in understanding the complex interplay of basal ganglia output by direct and indirect pathway projection neurons in regulating movement has been achieved (Kravitz *et al.*, 2010; Freeze *et al.*, 2013). Application of optogenetic and pharmacological approaches in transgenic mice has highlighted an important role of striatal D_2 receptors in the concerted balance of the striatal output system and structural plasticity (Cazorla *et al.*, 2014). Distinct roles for striatal neurons in the direct and indirect pathways in reinforcement have been shown by demonstrating that optogenetic stimulation of D_1 receptor-expressing neurons induce persistent reinforcement whereas stimulation of D_2 receptor-expressing neurons induce transient punishment (Kravitz *et al.*, 2012). The role of medial prefrontal D_1 receptor-expressing neurons in the control of food intake (Land *et al.*, 2014) and temporal control (Narayanan *et al.*, 2012) has also been demonstrated. Recent evidence indicates that optogenetic inhibition of D_1 but not D_2 receptor-expressing medium spiny neurons in the nucleus accumbens alters cocaine-mediated regulation of the T-lymphoma invasion and metastasis 1 (Tiam1) protein, which has been implicated in structural and synaptic plasticity (Chandra *et al.*, 2013). Furthermore, using a combination of optogenetic and chemogenetic approaches based on designer receptors exclusively activated by designer drugs (DREADD) technology (Lee *et al.*, 2013), it has been shown that strengthening the accumbal indirect pathway via D_2 receptors promotes resilience to compulsive cocaine use (Bock *et al.*, 2013).

A role of D_2 receptor-related signalling in suppressing human osteoclastogenesis has been recently identified (Hanami *et al.*, 2013), which may provide a plausible mechanism for the skeletal effects of antipsychotics observed in children and adolescents (Calarge *et al.*, 2013). A complex role of D_1 and D_2 receptors has been demonstrated for epileptogenesis (Bozzi and Borrelli, 2013), and cohlear functions (Maison *et al.*, 2012). Evidence gained from humans and mice also indicates that D_4 receptors may contribute to longevity (Grady *et al.*, 2013). Studies involving D_4 receptor KO mice and selective D_4 receptor agonists and antagonists in animal models of drug-seeking and drug-taking behaviours have sug-

gested that treatments based on antagonism of the D_4 receptor may be effective approaches for the management of psychostimulant and nicotine abuse (Di Ciano *et al.*, 2014). That presynaptic D_2 receptors might be involved in cocaine- and nicotine-induced structural plasticity in mesencephalic dopaminergic neurons via mechanism involving ERK and Akt signalling is also intriguing (Collo *et al.*, 2012; 2013). A novel mechanism for D_1 receptor-mediated regulation of ERK signalling involving the tyrosine phosphatase Shp-2, that is required for ERK activation by tyrosine kinase receptors, has been recently shown (Fiorentini *et al.*, 2011), and this mechanism appears to be involved in L–DOPA-induced dyskinesia in the experimental model of Parkinson's disease (Fiorentini *et al.*, 2013).

Recent evidence also indicated that dopamine receptors are involved in immune system regulation and processes related to inflammation and autoimmune reactions. It has been shown that astrocytic D_2 receptors modulate innate immunity through αB-crystallin, which results in suppression of neuroinflammation (Shao *et al.*, 2013). A role of D_2 receptors in renal inflammation has been demonstrated as well (Zhang *et al.*, 2012). It has been also observed that stimulation of D_5 receptors expressed on dendritic cells potentiates Th17-mediated immunity, thus indicating that D_5 receptors are able to modulate the development of an autoimmune response *in vivo* (Prado *et al.*, 2012).

Although the role of retinal dopamine and dopamine receptors in the regulation of vision and related processes is well established, recent studies have uncovered previously unappreciated mechanisms. Studies involving KO mice lacking specific dopamine receptors have shown that in addition to the role of dopamine in suppressing rod-driven signals in bright light, it also enhances the same signals under dim illumination via D_1 receptor-dependent sensitization of rod bipolar cells by GABA (Herrmann *et al.*, 2011). A role of both D_1 and D_4 receptors in various dimensions of light-adapted vision has been demonstrated as well (Jackson *et al.*, 2012). In a mouse model of type 1 diabetes, which develops early visual dysfunction because of dopamine deficiencies, acute treatment with either D_1 or D_4 receptor agonists improved overall retinal and visual function (Aung *et al.*, 2014). Retinal dopamine plays a critical role in the development of myopia predominantly via the D_2 receptor, but there is recent evidence suggesting that the balance of D_2 and D_1 receptor activation is important (Feldkaemper and Schaeffel, 2013). Evidence from KO mice suggests that not only retinal, but also central dopamine could play a role in the regulation of retinal function via differential involvement of D_1 and D_2 receptors (Lavoie *et al.*, 2014a). Furthermore, D_2 receptor-regulated GSK3 signalling also appears to contribute to electroretinogram anomalies observed in subjects at high genetic risk for schizophrenia and bipolar disorder, suggesting that electroretinograms can serve as a biomarker for central dopamine abnormalities related to psychiatric disorders (Lavoie *et al.*, 2014b).

It is well known that dopamine acting through D_2 receptors controls lactotroph proliferation and prolactin levels; however, the role of the D_{2S} and D_{2L} receptor isoforms was unknown. Recent investigations have shown that the presence of either the D_{2S} or D_{2L} isoforms *in vivo* prevents hyperprolactinaemia, the development of lactotroph hyperplasia, and tumourigenesis, all of which are observed when both isoforms are deleted in mice (Radl *et al.*, 2013). However, the protective function of a single D_2 receptor isoform is overridden when single isoform-KO mice are challenged by chronic estrogen treatments, suggesting that signalling from both isoforms is necessary in conditions that simulate pathological states (Radl *et al.*, 2013).

Selective disruption of D_2 receptors in pituitary lactotrophes in conditional mutant mice results in an increase in body weight and adiposity (Perez Millan *et al.*, 2014), indicating that D_2 receptors might be involved in the metabolic side effects of antipsychotic drug treatment such as obesity, cardiovascular complications and increased incidence of type 2 diabetes (Reynolds and Kirk, 2010). Interestingly, the D_2 receptor agonist bromocriptine has been recently approved for clinical use for the management of type 2 diabetes mellitus, particularly in forms associated with cardiovascular deficits (Grunberger, 2013).

The general role of D_2 receptors and dopamine in endocrine tumours is supported by reports that D_2 receptor agonists are effective in controlling hormone secretion and cell proliferation in experimental studies (Gatto and Hofland, 2011). Furthermore, dopamine agonists have been found to be efficacious in a subgroup of patients with pituitary adenomas and a few reported cases of carcinoids (Gatto and Hofland, 2011). It has also been shown that dopamine, acting via D_2 receptors, blocks stress-mediated ovarian carcinoma growth (Moreno-Smith *et al.*, 2011) in part through the antiangiogenic effect of dopamine and in part through D_1 receptors that stimulates vessel stabilization by increasing pericyte recruitment to tumour endothelial cells (Moreno-Smith *et al.*, 2013). Interestingly, recent unbiased screening attempts to identify novel anti-cancer therapies yielded dopaminergic compounds such as the D_2 receptor antagonist thioridazine, which selectively targets cancer stem cells by inducing differentiation to overcome neoplastic self-renewal (Sachlos *et al.*, 2012), and perphenazine, which was found to be effective in T-cell acute leukaemia by inducing PP2A-mediated apoptosis (Gutierrez *et al.*, 2014).

Influence on glutamate and GABA transmission

One recurrent topic that has received significant attention recently is related to signalling mechanisms involved in the convergence of dopamine receptor-mediated signalling with glutamatergic and GABA neurotransmission. It is well known that, as a slow neurotransmitter, dopamine exerts its actions through the modulation of the effects of fast neurotransmitters such as glutamate and GABA. This multi-transmitter interaction is critical for many vital functions mediated by dopamine as well as related disorders such as schizophrenia. As presented in Figures 1 and 2, both D_1 and D_2 receptors have multiple potential signalling mechanisms that may be involved in this modulation. Dopamine receptors can alter the phosphorylation of critical subunits of glutamate AMPA receptors (GluA1) and NMDA receptors (GluN2B), via the Gα subunit-mediated cAMP-PKA-DARPP32 signalling cascade (Dell'anno *et al.*, 2013; Hobson *et al.*, 2013; Song *et al.*, 2013; Flores-Barrera *et al.*, 2014; Murphy *et al.*, 2014), as well as $G\alpha_q$ and Gβγ subunit-mediated PLC signalling and subsequent Ca^{2+}-dependent events (Jenkins and Traynelis, 2012; Jenkins

et al., 2014). Activation of the G protein-independent Akt/GSK3 signalling cascade by D_2 receptors could lead to significant alterations in glutamatergic signalling mediated by NMDA and AMPA receptors (Li *et al.*, 2009; Li and Gao, 2011a) as well as changes in kinesin-mediated AMPA receptor trafficking (Du *et al.*, 2010). Similar mechanisms can also affect GABA transmission (Li *et al.*, 2012). As discussed earlier, the direct interaction of dopamine receptors with GluN1 and GluN2B subunits of NMDA receptors has been demonstrated (Fiorentini *et al.*, 2003; Liu *et al.*, 2006). Several mechanisms of direct and indirect interaction of D_3 receptors with glutamate neurotransmission have also been documented (Sokoloff *et al.*, 2013).

Further understanding of the mechanisms of the intricate interaction of dopamine receptor-mediated signalling events with glutamate and GABA signalling could manifest into exciting new molecular targets for novel pharmacological approaches to dopamine-related disorders.

Search for biased ligands of dopamine receptors

The growing realization of the complexity of signalling mediated by GPCRs in general, and dopamine receptors in particular, has provided a theoretical framework for the development of pathway-specific biased ligand pharmacology of D_2 receptors (Beaulieu *et al.*, 2007a; Beaulieu and Gainetdinov, 2011). In addition to the studies described earlier (Masri *et al.*, 2008; Allen *et al.*, 2011), a structure–activity analysis of pathway-specific biased agonism at D_2 receptors based on aripiprazole derivatives (Chen *et al.*, 2012) and search for novel potential antipsychotic cariprazine derivatives (Shonberg *et al.*, 2013) and other D_2 receptor targeting compounds (Hiller *et al.*, 2013) have been performed. These studies have recently resulted in identification of several functionally selective D_2 receptor agonists that are biased towards G protein- versus βArr2-dependent signalling (Free *et al.*, 2014; Möller *et al.*, 2014). Future characterization of the biochemical and behavioural effects of these biased compounds could eventually result in the development of improved antipsychotic drugs with reduced propensity of undesirable side effects. It should be noted that although the majority of current studies are focused on the development of biased ligands targeting either G protein-dependent or βArr2-dependent signalling mechanisms, it might be expected that biased ligands that, for example, will specifically target one, but not another modality of G protein-independent signalling could be identified in future (Figures 1 and 2).

Allosteric modulators of dopamine receptors

Another exciting direction in the pharmacology of GPCRs that is gaining attention recently is related to the development of allosteric modulators (Nickols and Conn, 2014). Although classic drug discovery approaches targeting GPCRs have traditionally focused on developing ligands for orthosteric sites, which bind endogenous ligands, more recent efforts have been aimed at modulating receptor function via allosteric modulators, which target a site distinct from the orthosteric site. It is expected that the development of such positive or negative allosteric modulators or 'bitopic' ligands that interact with both the allosteric and the orthosteric sites could eventually result in increased drug selectivity for therapeutic action and potentially decreased adverse side effects. Thus, a specific allosteric modulator of D_2 receptors, the peptidomimetic 3(R)-[(2(S)-pyrrolidinylcarbonyl) amino]-2-oxo-1-pyrrolidineacetamide (PAOPA), has been recently characterized as binding to a site on the D_2 receptor that is distinct from the endogenous ligand binding site (Tan *et al.*, 2013). PAOPA can influence several signalling and cellular events characteristic of D_2 receptor activation (Basu *et al.*, 2013), and in preclinical models, can attenuate schizophrenia-like behavioural manifestations without causing significant motor abnormalities common with many current antipsychotics (Tan *et al.*, 2013).

Based on the crystal structure of D_3 receptors (Chien *et al.*, 2010) a virtual screen targeting allosteric sites of this receptor has been recently performed (Lane *et al.*, 2013). This screening resulted in the identification of a number of allosteric ligands for D_3 receptors, including chemically diverse compounds with a variety of functional activity profiles and high affinities and ligand efficiencies. It is believed that identification of the allosteric structural features of D_3 receptors that are essential to selectivity and efficacy could be critical for the identification of highly selective D_3 receptor ligands, which are notorious for their difficulty in development (Newman *et al.*, 2012). Allosteric modulation of certain ligands can also occur at the level of receptor heterodimers as demonstrated by the ability of a newly identified dopamine agonist to negatively modulate adenosine A_{2A} receptor binding properties by interacting with the A_{2A}–D_2 receptor heteromer (Trincavelli *et al.*, 2012). Interestingly, A_{2A} receptor agonist-induced modulation of D_2 receptor agonist-induced βArr2 recruitment has been described, suggesting the involvement of a possible A_{2A}–D_2–βArr2 complex in this allosteric modulation (Borroto-Escuela *et al.*, 2011a).

New dopamine receptor-based drugs

In addition to the clinically approved compounds targeting dopamine receptors that were discussed in our recent review (Beaulieu and Gainetdinov, 2011), several new compounds have either been approved for clinical use or are in the last stages of clinical trials. Essentially all of these compounds are antipsychotics targeting D_2 receptors. It should be noted that no clinically approved antipsychotic drugs exist to date that are not D_2 receptor blockers. Among the newer antipsychotics recently approved for the treatment of schizophrenia, the most conspicuous are iloperidone, asenapine, lurasidone and blonanserin, considered to be atypical antipsychotics (George *et al.*, 2013). These compounds at least partially target D_2 receptors with additional influence on other receptors, particularly 5-HT_{2A} receptors. Although they exert clear antipsychotic activity, essentially all of them produce metabolic side effects and hyperprolactinaemia, which require appropriate monitoring (Wang *et al.*, 2014). In addition to the olanzapine-fluoxetine combination, quetiapine, lurasidone is now FDA-approved for the acute treatment of bipolar depression (McIntyre *et al.*, 2013). Among several emerging antipsychotic compounds, cariprazine has attracted the most attention because this drug has partial agonist activity at D_2 and D_3 receptors, with a six- to eightfold higher affinity for the human D_3 receptor over the D_2 receptor. Cariprazine is at latest stages of development, and an application has been submitted to the FDA for approval as a treatment for schizo-

phrenia, bipolar mania and depression (Veselinovic *et al.*, 2013). Another interesting compound is brexpiprazole, a novel drug candidate in clinical development for psychiatric disorders with high affinity for D_2 dopamine, 5-HT_{2A} and adrenoceptors (Maeda *et al.*, 2014). Brexpiprazole was showing significant antipsychotic-like properties in several preclinical models suggesting that brexpiprazole is a 5-HT-dopamine activity modulator with a unique pharmacology that might provide novel treatment option for psychiatric disorders.

D_2 receptor antibodies in autoimmune encephalitis

One exciting direction in the current neuropsychiatry is the emergence of novel class of disorders related to autoantibodies against critical synaptic proteins such as NMDA receptors and D_2 receptors (Lancaster and Dalmau, 2012). Remarkably, some patients with these autoantibodies have symptoms virtually indistinguishable from schizophrenia or other neuropsychiatric or movement disorders. Antibodies to surface D_2 receptors were found in patients with autoimmune movement and psychiatric disorders (Dale *et al.*, 2012). D_2 receptor autoantibodies were found also in patients with Sydenham chorea (Cox *et al.*, 2013), and recent study reported that herpes simplex encephalitis relapse with chorea was associated with autoantibodies against D_2 receptors and the NMDA receptors (Mohammad *et al.*, 2014). This recently emerging field is growing monthly, with more patients identified, and it is expected that the autoimmune theory of neuropsychiatric and movement disorders will have significant support in the future.

Conclusions

The studies described here show the significant progress made in understanding dopamine receptor functions, the complexity of their signalling mechanisms and potential new applications of dopamine receptor-based pharmacological strategies. Using a variety of the most up-to-date approaches, multidimensional analysis of dopamine receptor biology will eventually provide an opportunity for the precise targeting of desired components of post-receptor intracellular processes either via receptor-related mechanisms or post-receptor signalling cascades, thereby providing an exciting opportunity to target pathological processes with minimal propensity of developing side effects. Such approaches involving 'biased agonism', allosteric-based targeting of receptors and heteromers and downstream intracellular signalling events could eventually result in emergence of a new generation of dopamine receptor-based therapies for a variety of dopamine-related disorders.

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Author contributions

All authors contributed equally to this work.

Conflict of interest

The authors declare no conflict of interest in writing this paper.

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