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Review

GSK-3β activity and hyperdopamine-dependent behaviors

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ABSTRACT

Dopamine plays important roles in normal brain function and many neuropsychiatric disorders. Classically, dopamine receptors are positively coupled to G protein-mediated signaling to regulate cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA)–dopamine and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) and Ca^{2+} pathways. However, emerging evidence indicates that under hyperdopaminergic conditions, the protein kinase B (Akt)–glycogen synthase kinase 3β (GSK-3β) signaling cascade may mediate dopamine actions via D_2-like receptors. This cAMP-independent signaling pathway involves the regulation of downstream synaptic targets, e.g., AMPA receptor, NMDA receptors, and thus synaptic plasticity. Here we provide an overview of how this novel signaling pathway relays dopamine receptor-mediated responses, particularly hyperdopamine-dependent behaviors. We discuss the relevance of the Akt/GSK-3β signaling cascade for the expression of dopamine-dependent behaviors and the drug actions associated with dopaminergic systems.

Contents

Abbreviations: AC, adenylyl cyclase; Akt, protein kinase B; βArr2, β-arrestin 2; cAMP, cyclic adenosine monophosphate; DA, dopamine; DAT, dopamine transporter; DARPP-32, dopamine and cAMP-regulated phosphoprotein of 32 kDa; ERK, extracellular-signal-regulated kinase; GSK-3, glycogen synthase kinase 3β; GPCRs, G protein-coupled receptors; LTP, long-term potentiation; LTD, long-term depression; KO, knockout; NMDA, N-methyl-D-aspartate; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; PKA, protein kinase A; PKC, protein kinase C; PKA, protein kinase A; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A.

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1. Introduction

Dopamine (DA) is a predominant catecholamine neurotransmitter in the mammalian central nervous system. Neurons containing DA are clustered in the midbrain areas such as the substantia nigra and ventral tegmental area, and in the hypothalamus. These neurons project axons to large areas of the brain, including the dorsal and ventral striatum, as well as to other corticolimbic structures such as the hippocampus, amygdala, and prefrontal cortex (Bjorklund and Dunnett, 2007). Regulation of DA plays a crucial role in our mental and physical health because it controls a variety of functions including locomotor activity, cognition, emotion, reward, food intake, and neuroendocrine reactions (Bjorklund and Dunnett, 2007; Goto et al., 2007; Kienast and Heinz, 2006; Seamans and Yang, 2004; Sesack and Grace, 2010).

2. Dysfunction of dopaminergic transmission – hypodopaminergia and hyperdopaminergia

The dopaminergic systems have been the focus of much research over the past several decades, mainly because several neurological disorders such as Parkinson's disease, schizophrenia, attention-deficit hyperactivity disorder, mood disorders, Tourette's syndrome, and drug addictions have been linked to dysregulation of dopaminergic transmission (Bjorklund and Dunnett, 2007; Goto et al., 2007; Seamans and Yang, 2004). A large body of evidence indicates that either too little DA (hypodopamine) or too much DA (hyperdopamine) is detrimental to the brain functions. For example, dopamine depletion is involved in the pathophysiology of Parkinson's disease. Mice without DA signaling (DA-deficient mice) exhibit deficits in goal-directed behavior due to decreased motivation to obtain rewards (Cannon and Palmiter, 2003; Cannon and Bseikri, 2004), whereas viral restoration of DA signaling in the dorsal striatum is sufficient to restore normal goal-directed behaviors (Robinson et al., 2006, 2007). In addition, restriction of DA signaling to the dorsolateral striatum is sufficient for many cognitive behaviors (Darvas and Palmiter, 2009, 2010) and DA signaling in the dorsal striatum seems to be essential for motivated behaviors (Palmiter, 2008). These results suggest that DA facilitates the output from the dorsal striatum, which may also provide a permissive signal for feeding and other goal-directed behaviors (Palmiter, 2008) as widely reported in the ventral striatum (Carelli, 2004; Di Chiara, 2002; Kelley, 2004; Nicola et al., 2000).

In contrast, hyperfunction of the dopaminergic system plays a fundamental role in generating endophenotypes associated with schizophrenia (Abi-Dargham and Moore, 2003; Dzirasa et al., 2009a; Howes and Kapur, 2009; Kellendonk et al., 2006; Simpson et al., 2010). Hyperdopaminergia may also occur under various physiological and pathological conditions, including acute severe stress (Andersen, 2002; Arnsten and Goldman-Rakic, 1998; Arnsten, 2000, 2009; Goto et al., 2007), psychostimulant drug abuse (Robinson et al., 1988; Robinson and Kolb, 1997), and in mice with gene-knockout (KO) of the DA transporter (DAT) (Gainetdinov and Caron, 2003; Kalueff et al., 2007; Spielewoy et al., 2000b; Zhuang et al., 2001), α-synuclein and γ-synuclein (Senior et al., 2008), the GABAa receptor α3 subunit (Yee et al., 2005), the GABAb1 subunit (Vacher et al., 2006), the GluR1 receptor (Wiedholz et al., 2008), the DA D_3 receptor (Le Foll et al., 2005), and the NR1 subunit in DA neurons (Zweifel et al., 2008, 2009).

Among these hyperdopaminergic conditions, DAT-KO or knockdown (KD) mice appears to be a particularly useful model for examining the behavioral consequences of a chronically dysregulated DA system and for elucidating the molecular adaptive changes accompanying pathological states associated with hyperdopaminergic function. Genetic deletion of the DAT gene in mice results in a persistent extracellular hyperdopaminergic tone, functional hyperactivity, and impaired response inhibition in a number of paradigms. Extracellular levels of DA are reported to be elevated fivefold, and clearance of released DA is 300 times slower than in control mice (Gainetdinov et al., 1999; Gainetdinov and Caron, 2003; Kalueff et al., 2007). Despite the increased DA levels, mice genetically modified to be hyperdopaminergic do not learn faster than normal mice. They do, however, demonstrate increased motivation for food (Cagniard et al., 2006a,b), morphine (Spielewoy et al., 2000a), endocannabinoid (Tzavara et al., 2006), and cocaine (Morice et al., 2009). In addition, persistent hyperdopaminergia could also change many other functions, including various behavioral disturbances (Spielewoy et al., 2000b) such as disrupted responses in social interaction (Rodriguiz et al., 2004), enhanced resistance to extinction (Hironaka et al., 2004), reduced behavioral lateralization (Morice et al., 2005), and reduced cognitive flexibility (Morice et al., 2007); marked changes in functional interaction between DA and glutamate (Gainetdinov et al., 2001a); motor dysfunction and selective degeneration of striatal GABAergic neurons (Cyr et al., 2003); and decreased hippocampal theta oscillations (Dzirasa et al., 2009b) and disrupted neural phase signaling (Dzirasa et al., 2009a).

3. Signaling pathways of DA receptors

The major challenge in the past 50 years has been to elucidate the molecular and cellular mechanisms associated with the DA-related disorders and to discover selective dopaminergic drugs for the treatment of these diseases. These efforts have led to the cloning of various DA receptors, the characterization of G protein-coupled signaling, and the development of a number of new therapeutic agents that target on DA receptors. For instance, DA receptor antagonists have been developed to block hallucinations and delusions that occur in schizophrenic patients, and DA receptor agonists are effective in alleviating the hypokinesia of Parkinson's disease. However, direct blockade of DA receptors can induce extrapyramidal effects, and high doses of DA agonists can cause psychoses. The therapies for disorders associated with DA imbalances thus have severe side effects (Maguire, 2002; Missale et al., 1998; Miyamoto et al., 2005; Reynolds, 2001). It is therefore imperative to elucidate the molecular mechanisms and to characterize the complex signaling pathways related to DA receptors and DA-dependent behaviors in order to develop new drugs to attain the desired therapeutic actions while avoiding the undesired side effects.

All of the DA receptors cloned thus far, including D_1, D_2, D_3, D_4, and D_5 receptors, are a class of G protein-coupled receptors (GPCRs) that typically possess seven transmembrane domains (Missale et al., 1998; Neve et al., 2004). All GPCRs are essentially slow metabotropic receptors that functionally modulate other receptor systems and ion channels (Gainetdinov et al., 2004; Greengard, 2001; Premont and Gainetdinov, 2007; Tan et al., 2004). DA is the primary endogenous ligand for DA receptors. Unlike the fast ionotropic receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, DA receptors are prototypic GPCRs mediating slow neurotransmission (Greengard, 2001; Missale et al., 1998). Based on the length of the third cytoplasmic loop and the carboxy tail of the receptors, and most importantly, the G protein coupling, DA receptors are subdivided into the Gs- or Gq-coupled D_1-like (D_1 and D_5 receptors with longer third cytoplasmic loop and carboxyl tail) and Gi/o-coupled D_2-like family (D_2, D_3, and D_4 receptors with shorter third cytoplasmic loop and carboxyl tail) (Missale et al., 1998; Neve et al., 2004).

The coupling of DA receptors to second messenger pathways through GPCRs has been a subject of intensive interest since the 1970s. It has been recognized that activations of DA receptors

regulate the activity of adenylyl cyclase (AC) in DA-rich brain regions, such as the striatum, nucleus accumbens, and prefrontal cortex (Greengard, 2001; Missale et al., 1998; Neve et al., 2004; Seamans and Yang, 2004). Classically, the functions of the DA receptors have been associated with the regulation of the cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA)–DA- and cAMP-regulated phosphoprotein with molecular weight kDa 32 (DARPP-32) cascade through G protein-mediated signaling (Greengard, 2001; Missale et al., 1998; Svenningsson et al., 2004). The D_1-like receptors couple to Gs and stimulate the production of AC/cAMP and the activity of PKA. By contrast, the D_2-like receptors couple to Gi/o to inhibit the production of AC/cAMP, resulting in a reduction of PKA activity. D_2 receptors also regulate intracellular Ca^{2+} levels by modulating Ca^{2+} channels or intracellular Ca^{2+} release (Greengard, 2001; Missale et al., 1998). DARPP-32 has important functions in regulating the efficacy of DA receptor signaling and its integration with other signaling modalities (Greengard, 2001; Svenningsson et al., 2004). Furthermore, extracellular-signal-regulated kinase (ERK) has also been identified as an important mediator of cAMP signaling that is involved in the development of acute and chronic responses to dopaminergic drugs (Beaulieu et al., 2007a, 2006; Valjent et al., 2005, 2006). ERK signaling is particularly prominent under conditions of extremely high dose of psychostimulant stimulation (Beaulieu et al., 2006).

In addition to these canonical actions on G protein-mediated signaling and the regulation of the cAMP/PKA/DARPP-32 pathway, recent studies have shown that D_2 receptors also exert their effects *in vivo* through cAMP-independent mechanisms, i.e., the protein kinase B (Akt)–glycogen synthase kinase 3 (GSK-3) signaling cascade (Beaulieu et al., 2007b, 2009; Li et al., 2009). This novel mode of DA receptor signaling involves the expression of dopamine-associated behaviors and the action of numerous dopaminergic drugs (Beaulieu et al., 2007a; Li et al., 2009). Most importantly, this cAMP-independent DA receptor signaling pathway may display distinctly different kinetic properties and dose range and might therefore serve as an integrator of DA receptor signaling and signaling events that derive from other neurotransmitter receptors (see Fig. 1). Below we summarize recent work and discuss the relevance of the Akt/GSK-3 signaling cascade for the expression of DA-dependent behaviors and the drug actions associated with dopaminergic systems.

Interestingly, Susan George and colleagues (George and O'Dowd, 2007; Lee et al., 2004; Rashid et al., 2007) also reported that the D1 and D2 receptors in the striatal neurons can form a heterooligomer, which is coupled to Gq to activate phospholipase C (PLC) and to generate intracellular Ca^{2+} release. The activation of Gq by the D1–D2 heterooligomer has been shown to occur in cells expressing both receptors, distinct from Gs/olf or Gi/o activation by the D1 and D2 receptor homooligomers, respectively. However, because the co-expression of D1 and D2 receptors is restricted to a small number of cells in the striatum, the role of D1 and D2 receptor heterooligomers on the DA-mediated behaviors remains to be explored. Further study is needed to determine whether the D1 and D2 receptor heterooligomers and the associated Gq/PLC/Ca^{2+} signaling pathway exist in other brain regions.

4. GSK-3 is an important player for many biological functions

GSK-3 is a multifunctional serine/threonine (ser/thr) kinase that was originally identified as a regulator of glycogen metabolism (Woodgett, 2001). It plays a fundamental role in a wide variety of functions, including cell division, proliferation, differentiation, and adhesion (Forde and Dale, 2007; Frame and Cohen, 2001; Grimes and Jope, 2001). It is also associated with the regulation of receptor trafficking (Li et al., 2009) and synaptic plasticity (Forde and Dale, 2007; Peineau et al., 2008). Two isoforms of GSK-3, GSK-3α and GSK-3β, exist in mammals and are encoded by different genes, and both isoforms are closely related kinases associated with the regulation of glycogen synthesis in response to insulin (Frame and Cohen, 2001). These proteins are highly homologous in their kinase domains but differ in other regions. Both enzymes are highly regulated by phosphorylation. Phosphorylation of tyr216 is required for basal activity of GSK-3β and high levels of phosphorylation of this residue result in GSK-3β being active (Hughes et al., 1993). By contrast, regulation of phosphorylation of ser9 by ser/thr protein phosphatases such as protein phosphatase 1 (PP1) and protein phosphatase 2A (PP2A) leads to inactivation of GSK-3β, overriding the activation induced by phosphorylation of tyr216 (Woodgett, 2001). Similarly, GSK-3α is regulated via phosphorylation sites tyr279 and ser21. In glycogen metabolism, insulin stimulates phosphatidylinositol 3-kinase (PI3K), which activates Akt, and this in turn inhibits GSK-3β activity by phosphorylation of ser9, allowing for dephosphorylation of glycogen synthase and the stimulation of glycogen synthesis (Doble and Woodgett, 2003; Frame and Cohen, 2001; Grimes and Jope, 2001).

GSK-3α and GSK-3β are constitutively active and can be inactivated through the phosphorylation of a single residue at serine 21 (GSK-3α) or serine 9 (GSK-3β), which are located in their regulatory N-terminal domains, by Akt and other kinases (Frame and Cohen, 2001; Grimes and Jope, 2001). Akt has been shown to inhibit GSK-3α and GSK-3β in response to insulin, insulin-related peptides such as insulin-like growth factor (IGF), and neurotrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin 3 (Frame and Cohen, 2001; Grimes and Jope, 2001; Scheid and Woodgett, 2001). In addition to Akt, PKA can phosphorylate both GSK-3α and GSK-3β whereas protein kinase C (PKC) is able to phosphorylate GSK-3β (Fang et al., 2000). Other regulators of GSK-3β include the mammalian target of the rapamycin (mTOR) pathway, the Wnt signaling pathway, and the mitogen-activated protein kinase (MAPK) cascade (Frame and Cohen, 2001; Grimes and Jope, 2001).

5. Involvement of GSK-3β in neurological and psychiatric disorders

Although both isoforms of GSK-3 are implicated in neurological and psychiatric disorders, most studies have focused on GSK-3β because it is highly enriched in the brain (Grimes and Jope, 2001; Woodgett, 2001). GSK-3β has been implicated in various disorders including Alzheimer's disease (Bhat et al., 2000; Eldar-Finkelman, 2002; Grimes and Jope, 2001; Jope and Johnson, 2004), schizophrenia (Freyberg et al., 2009; Jope and Roh, 2006; Koros and Dorner-Ciossek, 2007; Kozlovsky et al., 2002; Molteni et al., 2009), bipolar disorders (Gould et al., 2006; Harwood, 2003), and drug addictions (Chen et al., 2009; Miller et al., 2009; Perrine et al., 2008). Therefore, GSK-3β has been proposed to be a prime therapeutic target for a variety of brain disorders (Beaulieu et al., 2009; Cohen and Goedert, 2004; Gould et al., 2006; Harwood, 2003; Jope et al., 2007; Koros and Dorner-Ciossek, 2007; Molteni et al., 2009). Of particular relevance to neurological disorders, GSK-3β phosphorylates both presenilin-1 and tau, the proteins implicated in Alzheimer's disease (Balaraman et al., 2006; Forde and Dale, 2007; Grimes and Jope, 2001; Jope et al., 2007; Rayasam et al., 2009). It has also been linked to the etiology of schizophrenia (Freyberg et al., 2009; Jope and Roh, 2006; Koros and Dorner-Ciossek, 2007; Kozlovsky et al., 2002; Lovestone et al., 2007; Molteni et al., 2009) and to hyperdopamine-dependent behaviors (Beaulieu et al., 2007a, 2009).

6. GSK-3β is critical for DA-dependent actions, particularly hyperdopaminergic behaviors

Both Akt and GSK-3β have multiple substrates, including proteins involved in cellular processes as diverse as metabolism, cell survival and death, cytoskeletal organization, and regulation of gene expression (Cohen and Frame, 2001; Frame and Cohen, 2001; Grimes and Jope, 2001; Scheid and Woodgett, 2001). Numerous potential substrates for GSK-3β have been identified, including several different transcription factors, metabolic enzymes, proteins that bind to microtubules and components of the machinery involved in cell division and cell adhesion (Cohen and Frame, 2001; Doble and Woodgett, 2003; Frame and Cohen, 2001; Grimes and Jope, 2001).

Although extensive studies have been reported on the regulation of Akt and GSK-3 by monoamines, the identity of the downstream targets of Akt/GSK-3 signaling involved in the regulation of DA-mediated behaviors remains elusive. It was not known until recently whether GSK-3 has neuronal-specific functions under normal conditions. Evidence indicates that the Akt/GSK-3 signaling pathway possibly plays a role in the regulation of synaptic plasticity and ionotropic glutamate receptor functions (Hooper et al., 2007; Peineau et al., 2007, 2008, 2009; Zhu et al., 2007). These receptors and glutamate neurotransmission in general are strongly implicated in the etiology of psychiatric disorders such as schizophrenia (Carlsson et al., 2001; Gainetdinov et al., 2001b; Mohn et al., 1999; Sharp et al., 2001), Alzheimer's disease (Farber et al., 1998), bipolar disorders (Schloesser et al., 2008), and drug addictions (Hyman et al., 2006).

Recent studies indicate that activation of GSK-3 inhibits the development of long-term potentiation (Zhu et al., 2007) and presynaptic release of glutamate (Zhu et al., 2010), whereas its inhibition prevents the development of long-term depression in rat hippocampal slices (Peineau et al., 2007, 2008). GSK-3 also appears to affect the trafficking and reduce the cell surface expression of the NMDA receptor subunits NR2A and NR2B both in hippocampal slices and in cultured cortical neurons (Chen et al., 2007a; Zhu et al., 2007). We recently found that, under hyperdopaminergic conditions, the synaptic NMDA receptor-mediated currents are significantly attenuated by excessive DA stimulation

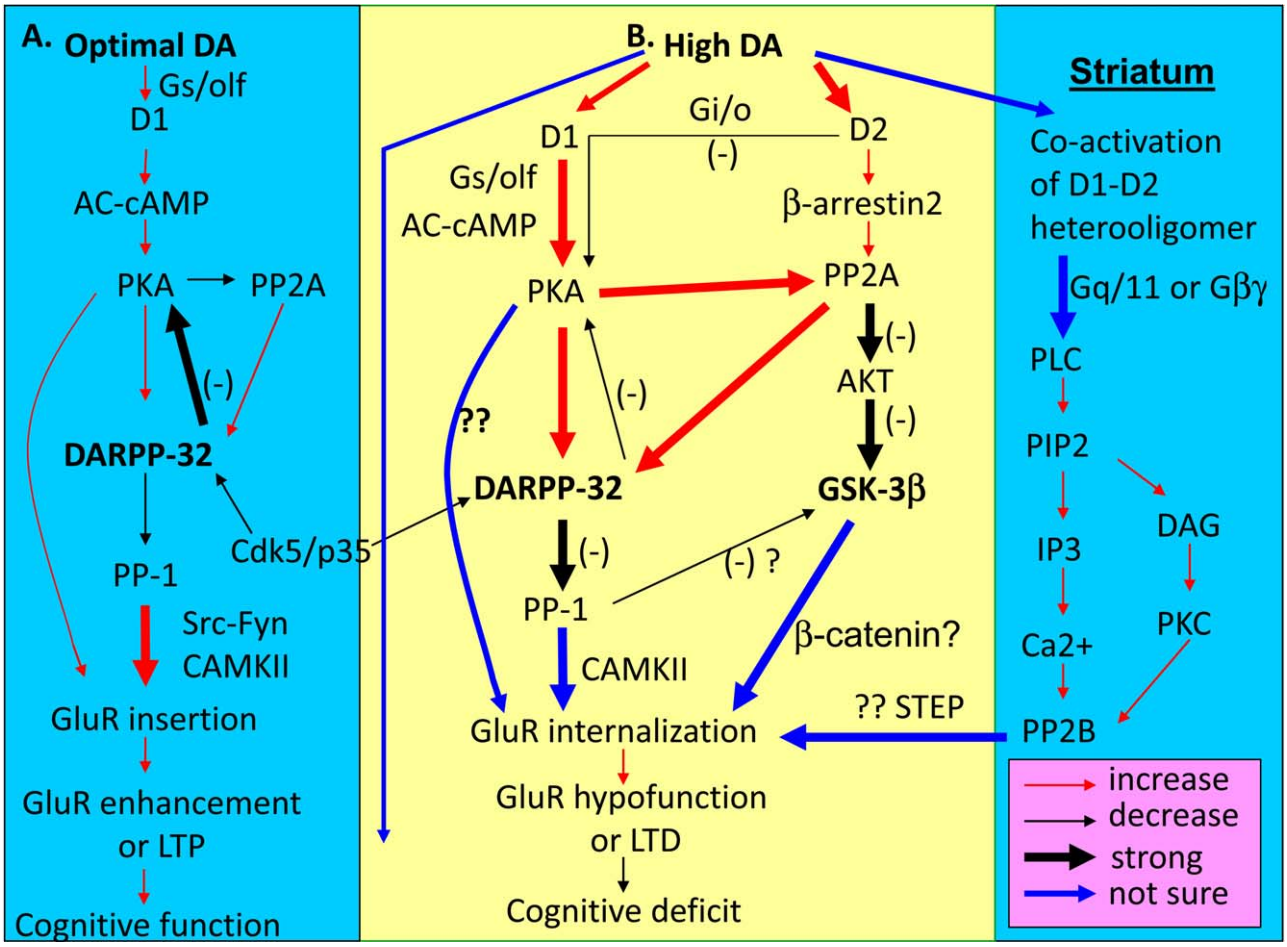

Fig. 1. Model illustrating the signaling pathways activated by optimal DA and hyperdopamine. A, under normal conditions, optimal DA through activation of D1-coupled Gs/olf protein activates the classic AC/cAMP/PKA/DARPP-32 pathway, which reduces the activity of protein phosphatase 1 (PP1). In addition, phosphorylation of DARPP-32 by Cdk5 causes inhibition of PKA, inactivation of protein phosphatase 2A (PP2A), and decreased dephosphorylation of DARPP-32. Inhibition of PKA also results in decreased phosphorylation of DARPP-32 and, therefore, inactivation of PP1. Inhibition of PKA and activation of PP1 synergistically regulate the phosphorylation of various substrates, such as AMPA and NMDA receptors, and thus induce long-term plasticity and enhance cognitive functions. B, under hyperdopaminergic conditions, however, the signaling pathways activated by DA are much more complicated. On the one hand, by sequentially activating DA D1 receptors, PKA and PP2A reduce the level of DARPP-32. Dephosphorylation of DARPP-32 by PP-2A removes the inhibition of PKA. Activation of PKA also results in increased phosphorylation of DARPP-32 and inhibition of PP1. Activation of PKA and inhibition of PP1 synergistically increase the phosphorylation of various substrates such as glutamate receptors. On the other hand, emerging evidence indicates that a high concentration of DA likely activates D2 receptors more than it does D1 receptors. Under hyperdopaminergic conditions, Akt/GSK-3β signaling cascade critically mediates DA actions via D_2-like receptors. This cAMP-independent signaling pathway involves β-arrestin and PP2A in the upstream and regulation of glutamate receptors and synaptic plasticity in the downstream. Consequently, increase of GSK-3β activity would cause a cognitive deficit. In the striatum, it has also been reported that under a high concentration of DA, the D1/D2 heterooligomer couples to Gq/11 or Gβγ to activate the phospholipase C/IP3/PP2B pathway and to regulate synaptic functions.

through activation of D_2 receptors (Li et al., 2009). The high-dose DA/D_2 receptor-mediated suppression of NMDA receptors is involved in the increase of GSK-3β activity, which in turn phosphorylates β-catenin and disrupts β-catenin-NR2B interaction. Moreover, the hyperdopamine induced by the DA reuptake inhibitor GBR12909 significantly decreases the surface expression of NR2B proteins, as well as the NR2B mRNA levels. These effects are completely reversed by administration of either GSK-3β inhibitor or D_2 receptor antagonist. These results suggest that GSK-3β is required for the hyperdopamine/D_2 receptor-mediated inhibition of NMDA receptors in the prefrontal neurons and that these actions may underlie D_2 receptor-mediated psychostimulant effects and hyperdopamine-dependent behaviors in the brain (Li et al., 2009). Our data are consistent with those from other recent studies, indicating that DA affects synaptic plasticity by regulating the expression, phosphorylation, and trafficking of ionotropic glutamate receptors and associated proteins in neurons (Esteban et al., 2003; Svenningsson et al., 2004; Yao et al., 2004).

It is known that acute stress induces excessive DA release (Goto and Grace, 2006; Gresch et al., 1994; Morrow et al., 2000), which in turn overstimulates D1 receptors in the prefrontal cortical circuitry. The acute excess DA could shut down recurrent excitation between prefrontal pyramidal neurons (Gao et al., 2001) and thus disrupt working memory function (Williams and Goldman-Rakic, 1995). The information processing mediated by hippocampal-prefrontal cortex interactions could also be disrupted because the synaptic plasticity induced by stress is DA-dependent (Jay et al., 2004). Although it is unclear whether an increase in DA persists during long-term potentiation induction, the DA-induced changes in the phosphorylation of second messenger molecules such as CREB and DARPP-32 could outlast the period of DA receptor stimulation (Hotte et al., 2007; Xu et al., 2009). Whether Akt/GSK-3 signaling is involved in the DA-dependent synaptic plasticity remains unknown.

It should be noted that, although we emphasize the role of GSK-3β in DA-associated actions, recent studies have suggested that GSK-3α is also regulated by DA receptor stimulation, such as under conditions of cocaine administration in normal rats (Perrine et al., 2008) and of methamphetamine administration in D3 receptor-KO mice (Chen et al., 2007b). In addition, the work conducted by the Caron and Borrelli groups in D2 receptor-KO mice indicated that basal Akt (Thr308) and GSK-3β (Ser-9) phosphorylation were increased by an absence of D2 receptors (Beaulieu et al., 2007b). Furthermore, Emamian et al. (2004) reported that phosphorylation of GSK-3β (Ser-9) was increased by the chronic treatment of D2 antagonist haloperidol in wild-type animals. Together these data suggest that while GSK-3β is involved in behavioral responses to elevated DA, it may also be affected by D2 receptors under normal conditions.

7. The β-arrestin/Akt/GSK-3 pathway mediates DA-dependent behaviors via activation of D_2 receptors

DA D_2 supersensitivity has been reported under numerous conditions, including schizophrenia, hippocampal lesions, and gene KOs of DA beta-hydroxylase, D_4 receptors, GRK6 (G protein-coupled receptor kinase 6), and catechol-O-methyltransferase (COMT). The functional state of D_2, or the high-affinity state for DA, was increased by about 40–900% in the striatal tissues under these conditions (Seeman et al., 2005). Other studies indicate that several typical and atypical antipsychotics are potent antagonists for agonist-induced recruitment of β-arrestin 2 (βArr2) to the D_2 receptor while having divergent pharmacological effects on the regulation of cAMP by this same receptor (Beaulieu et al., 2005; Gainetdinov et al., 2004; Masri et al., 2008).

Arrestins are a small family of proteins important for regulating signal transduction (Lefkowitz and Whalen, 2004; Lefkowitz and Shenoy, 2005; Moore et al., 2007), especially for regulating the activity of GPCRs (Gurevich and Gurevich, 2006, 2008). One of the important steps is the phosphorylation induced by a class of serine/threonine kinases and GRKs. GRK phosphorylation then specifically prepares the activated receptor for arrestin binding, which blocks G protein-mediated signaling, targets receptors for internalization, and redirects signaling to alternative G protein-independent pathways. Evidence from heterologous cellular systems demonstrates that β-arrestins can act as G protein-independent mediators of signaling by scaffolding other proteins such as kinases and their substrates (Beaulieu et al., 2007a, 2009; Beaulieu et al., 2005; Freyberg et al., 2009). It is therefore possible that antipsychotics may exert their therapeutic effects by blocking βArr2-mediated D_2 signaling (Masri et al., 2008) while inducing some of their divergent side effects through modulation of other signaling pathways.

Multiple lines of evidence indicate that the βArr2/Akt/GSK-3 pathway plays a role in the regulation of behaviors mediated by DA. βArr2-KO (βArr2-KO) mice display reduced responsiveness to the DA-dependent actions of amphetamine and novelty-induced locomotor hyperactivity that is analogous to the phenotype characteristics of hyperdopaminergic DAT-KO mice (Beaulieu et al., 2005). Several other observations also support the involvement of the βArr2/Akt/GSK-3 pathway in the regulation of DA-related behaviors and antipsychotic drug actions (Amar et al., 2008; Beaulieu et al., 2007a; Del'guidice and Beaulieu, 2008; Molteni et al., 2009). In particular, mice lacking the Akt1 show enhanced disruption of sensorimotor gating in prepulse inhibition (PPI) tests by amphetamine but not by the NMDA receptor antagonist MK-801 (Emamian et al., 2004). Disruption of sensorimotor gating by amphetamine has been used as a behavioral paradigm to model psychosis in rodents (Castner and Williams, 2007; Featherstone et al., 2007; Javanbakht, 2006; Tenn et al., 2003), and this effect can be potently blocked by antipsychotic agents such as haloperidol (Freyberg et al., 2009; Sutton et al., 2007). Because Akt1 is inhibited following the stimulation of D_2-like receptors, the increased behavioral effect of amphetamine in Akt1-KO mice gives further support for the involvement of Akt inhibition in DA-related behavioral responses (Beaulieu et al., 2007b). Finally, it has been shown that GSK-3 inhibitors can reduce locomotor hyperactivity both in DAT-KO mice and in amphetamine-treated wild-type animals (Beaulieu et al., 2004; Gould et al., 2004). GSK-3 inhibitors are also effective in blocking the DA reuptake inhibitor GBR12909-induced NMDA receptor trafficking (Li et al., 2009). These pharmacological studies are further supported by the observations gained in genetically engineered animals. It has been reported that GSK-3β KO is lethal during embryogenesis due to a disruption of NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells), whereas GSK-3β heterozygotes (+/−) develop normally without overt phenotypes (Hoeflich et al., 2000). However, GSK-3β transgenic mice usually exhibit developmental deficits and neuropathies associated with Tau hyperphosphorylation (Lucas et al., 2001; Spittaels et al., 2002). Evaluation of the behavioral effects of amphetamine revealed that GSK-3β heterozygote mice are less responsive to this psychostimulant, which supports the involvement of GSK-3β in the expression of DA-associated behaviors (Beaulieu et al., 2004). Conversely, transgenic mice expressing a GSK-3β mutant at an inhibitory phosphorylation site display a constitutively active GSK-3β and exhibit hyperlocomotor activity that is parallel to that seen in hyperdopaminergic DAT-KO mice (Prickaerts et al., 2006). Yet, DA regulates more than just sensorimotor gating and locomotor activities. Further detailed characterization of DA-related behaviors in various KO mice are necessary to fully understand the functions of βArr2, Akt, and GSK-

3 in the expression of DA-related behaviors (Beaulieu et al., 2009, 2004, 2006).

8. Regulation of brain Akt/GSK-3β signaling by psychostimulant-induced hyperdopamine through activation of D_2-like receptors

DAT-KO mice exhibit a persistent fivefold increase in extracellular DA levels (Dzirasa et al., 2009b). Studies of altered cell signaling in response to persistently elevated extracellular DA levels identified a reduction of Akt phosphorylation/activity and a concomitant activation of both GSK-3α and GSK-3β in the striatum of DAT-KO mice (Beaulieu et al., 2009, 2004, 2006). Administration to normal mice of psychostimulants such as cocaine, amphetamine, and methamphetamine also resulted in an inhibition of Akt activity, whereas striatal DA depletion had the opposite effect, thus firmly establishing the regulation of the Akt/GSK-3 pathway by DA (Beaulieu et al., 2005; Bychkov et al., 2007; Carlson et al., 2003; Chen et al., 2007b; Miller et al., 2009; Perrine et al., 2008). It has been shown that cocaine activated GSK-3β in the caudate putamen and that pharmacological inhibition of GSK-3β reduced both the acute behavioral responses to cocaine and the long-term neuroadaptations produced by repeated administration of cocaine, suggesting a role for GSK-3β in the behavioral and neurochemical manifestations associated with cocaine exposure (Miller et al., 2009; Perrine et al., 2008). Further characterization of these signaling responses using the D_1 antagonist SCH23390 and the D_2 antagonist raclopride in DAT-KO mice shows that Akt, GSK-3α, and GSK-3β are regulated only by D_2-like receptors (Beaulieu et al., 2004). Finally, an investigation of DA-dependent regulation of Akt phosphorylation in mice lacking different subtypes of D_2-like receptors showed that D_2 receptors are essential for the inhibition of striatal Akt by these drugs (Beaulieu et al., 2007b; Li et al., 2009). The finding of cAMP-independent and DA D_2 receptor-mediated Akt/GSK3 activation in the behaviorally sensitized animals implies that a signal cascade downstream of D_2 receptors is a fundamental element of the addiction network (Chen et al., 2009; Miller et al., 2009; Perrine et al., 2008).

9. Akt and GSK-3 are involved in the actions of psychotropic drugs

DA D_2 receptor antagonism is a universal property of all antipsychotic drugs (Artigas, 2010; Conn et al., 2008; Laruelle et al., 2005; Seeman, 2002). However, the effecter molecules through which these medications exert their actions remain elusive. Typical antipsychotics such as haloperidol exert their actions by blocking D_2-like receptors, thus supporting a role for dysfunction of DA neurotransmission in the etiology of schizophrenia (Freyberg et al., 2009). Emerging evidence indicates that antipsychotic medications may treat symptoms of psychosis through modulating the activity of Akt/GSK-3 signaling. Recent genetic and postmortem studies have established a link between the deregulation of Akt/GSK-3 signaling and schizophrenia (Alimohamad et al., 2005a,b; Arguello and Gogos, 2008; Del'guidice and Beaulieu, 2008; Molteni et al., 2009; Seeman et al., 2006; Sutton et al., 2007; Tan et al., 2008). A major association of Akt1 haplotypes with schizophrenia (Emamian et al., 2004; Roh et al., 2007; Tan et al., 2008) and reduced Akt activity or expression levels (Emamian et al., 2004; Kozlovsky et al., 2000) have been reported in the brains of schizophrenic patients. However, results from some investigations were inconsistent about in the role of GSK-3β in schizophrenia (Bersudsky et al., 2008; Nadri et al., 2004). Therefore, further investigation of a greater number of brain samples is needed to clarify the possible role of this enzyme in the pathophysiology of schizophrenia.

In addition, the D_2-like receptor antagonist and antipsychotics have been shown to enhance Akt phosphorylation and thus to inhibit GSK-3 activity in normal animals (Alimohamad et al., 2005a,b; Beaulieu et al., 2009; Del'guidice and Beaulieu, 2008; Emamian et al., 2004; Molteni et al., 2009; Roh et al., 2007; Sutton et al., 2007), whereas activation of striatal D_2-like receptors by DA results in the inhibition of Akt. It is therefore possible that the reduced function of Akt results in an exacerbated response to increased D_2 receptor stimulation in schizophrenia, similar to results observed in Akt1-KO mice. Antipsychotics could regulate this imbalance by preventing further reductions in Akt activity through antagonizing D_2-like receptors (Beaulieu et al., 2007a).

It should be noted that many atypical antipsychotics display a strong affinity for 5-hydroxytryptamine $(5\text{-HT})_{2A}$ receptors (Kapur and Remington, 2001; Meltzer et al., 2003; Seeman, 2002). Acute or chronic *in vivo* administration of atypical antipsychotics results in the inhibition of GSK-3β in different regions of the brain (Alimohamad et al., 2005a; Koros and Dorner-Ciossek, 2007; Li et al., 2007; Roh et al., 2007). Interestingly, two 5-HT receptors seem to antagonistically regulate GSK-3β activity, with increased GSK-3β activation by stimulation of 5-HT_{2A} receptors and decreased GSK-3β by stimulation of 5-HT_{1A} receptors (Li et al., 2004, 2007). This action of atypical antipsychotics indicates that Akt and GSK-3 might function as signal integrators for both DA and 5-HT transmissions. However, further studies are needed to address the function of GSK-3 in the regulation of 5-HT function and the actions of 5-HT drugs (Beaulieu et al., 2009, 2008; Del'guidice and Beaulieu, 2008).

10. Two modalities of slow synaptic transmission in hyperdopaminergic actions: cAMP/PKA/DARPP32 and Akt/GSK-3

DA-dependent behavioral changes have been reported in Akt1-KO (Emamian et al., 2004; Lai et al., 2006), β-arrestin-2-KO (Beaulieu et al., 2005) and GSK-3β heterozygotic mice (Beaulieu et al., 2004). The GSK-3 inhibitors antagonize DA-dependent behaviors, and administration of amphetamine to normal mice results in an inhibition of Akt activity, confirming the involvement of the Akt/GSK-3 pathway in DA-dependent behaviors (Beaulieu et al., 2004, 2005; Gould et al., 2004). In addition, βArr2 regulates Akt in response to DA and inhibitors of PP2A prevent the inhibition of Akt by DA, whereas activation of D_2 receptors causes the formation of a protein complex containing Akt, βArr2, and PP2A (Beaulieu et al., 2005). The Akt/βArr2/PP2A complex facilitates the dephosphorylation and deactivation of Akt in response to DA and results in the activation of GSK-3 (Beaulieu et al., 2004, 2005). The most intriguing phenomenon is that the regulation of this pathway by dopaminergic drugs shows distinctly different kinetics compared with those of the canonical cAMP-PKA-DARPP-32 pathway, and neither Akt nor GSK-3 is affected by direct modulation of cAMP levels, indicating that the Akt/GSK-3 pathway is not controlled by this second messenger (Beaulieu et al., 2007a, 2004). Beaulieu and colleagues reported that the β-arrestin-2-dependent inhibition of Akt by DA in the mouse striatum displays a slower but more persistent effect than do signaling events that are regulated by the cAMP–PKA pathway (Beaulieu et al., 2007a, 2004, 2005). The cAMP-dependent phosphorylation of DARPP-32 appears to peak and subside within the first 30 min after the administration of dopaminergic drugs such as amphetamine and cocaine (Svenningsson et al., 2003; Valjent et al., 2000, 2005). By contrast, amphetamine progressively inhibits Akt activity during the first 30 min and this effect peaks at 30–60 min and persists over the duration of the drug's behavioral effects (Beaulieu et al., 2007a,b, 2009, 2004, 2005). This finding indicates that the regulation of DA-dependent behaviors and the action of some dopaminergic drugs might depend on two complementary

GPCR signaling responses, i.e., a rapid and short cAMP-mediated response, followed by a slow and long response that is dependent on D_2/β-arrestin/Akt/GSK-3β signaling. The characterization of this intriguing cAMP-independent but β-arrestin-dependent D_2/Akt/GSK-3β signaling cascade indicates that DA receptor functions are mediated by multiple mechanisms that jointly fine-tune the DA actions under different physiological and pathological conditions (see Fig. 1). However, it remains unclear how these two modalities of slow transmission work together to regulate the distinct DA-dependent behaviors. Understanding the interactions of these complementary DA receptor signaling pathways would certainly enable the development of novel pharmacological treatments with improved therapeutic actions.

11. Summary and future perspectives

Characterization of the role of the Akt/GSK-3β signaling pathway in responses to DA, psychostimulants, and psychotropic drugs *in vivo* has identified and validated both Akt and GSK-3β as important signal integrators for DA-dependent responses, particularly for D_2 receptor-mediated hyperdopaminergic behaviors. These molecules allow the precise coordination and cooperation of DA receptor signaling responses. After years of study, the following issues seem to be clear about the role of the Akt/GSK-3β pathway in DA-dependent actions and we summarize here. (1) The actions of DA can be mediated through both cAMP-dependent and independent mechanisms. (2) The cAMP-independent D_2/Akt/GSK-3β pathway is a mediator of DA actions under acute and chronic hyperdopaminergic conditions and the study of this intriguing pathway has progressively increased our understanding of aberrant DA-associated behaviors. (3) The Akt/GSK-3β pathway is found to be dysregulated in various psychiatric disorders such as Alzheimer's disease, schizophrenia, bipolar disorder, and drug addictions. Indeed, inhibition of GSK-3β provides a rationale for the mutual augmenting effects of psychostimulants and psychotropic drugs, which are often used as combination therapies for various psychiatric conditions. GSK-3β has recently been proposed as a possible therapeutic target for the treatment of several neuropsychiatric disorders, including schizophrenia and Alzheimer's disease (Gould et al., 2006; Sereno et al., 2009). However, a number of issues need to be considered regarding therapeutic utility of GSK-3β inhibitors, and further studies are needed to explore whether GSK-3β inhibitors can yield desirable therapeutic effects and at the same time avoid undesired side effects (Koros and Dorner-Ciossek, 2007). In fact, many unanswered questions are associated with this novel signaling pathway and its role in DA-dependent behaviors. For example, what is the mechanism by which D_2-like receptors modulate Akt phosphorylation? What are the downstream target substrates of Akt and/or GSK-3β that contribute to the actions of DA and DA-associated psychostimulants and antipsychotics? What is the exact role of the Akt/GSK-3β pathway in manifestations of hyperdopaminergic functions such as sensorimotor gating, reward, or other DA-related behaviors? Are the cAMP-dependent and -independent pathways involved in differential behavioral aspects of DA actions? Is the role of the Akt/GSK-3β signaling cascade in mediating behavioral outcomes and actions of DA, psychostimulants and psychotropic drugs confined to certain areas of the brain? What is the role of the Akt/GSK-3β signaling pathway in the action of other neurotransmitters? Do 5-HT receptors regulate the Akt/GSK-3β pathway by the same G protein-independent mechanism as D_2 receptors? What is the relative contribution of the Akt/GSK-3β signaling pathway to various psychiatric disorders such as Alzheimer's disease, schizophrenia, bipolar disorder, and drug addictions? Are the effects of GSK-3β inhibitors in regulating the DA-dependent behaviors age-, dose-, and stage-dependent? What are the side effects and long-lasting aftereffects of GSK-3β inhibitors in the treatment of schizophrenia and other neurological disorders? Finding answers to these questions would certainly enhance drug development for the treatment of many of the DA-related neurological and psychiatric disorders.

Conflict of interest

The authors claim no conflict of interest.

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