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The Akt–GSK-3 signaling cascade in the actions of dopamine

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Drugs that act on dopamine neurotransmission are important tools for the management of multiple neuropsychiatric disorders. Classically, dopamine receptors have been shown to regulate cAMP–PKA (protein kinase A) and Ca^{2+} pathways through G-protein-mediated signaling. However, it has become apparent that, in addition to this canonical action, D_2-class dopamine receptors can function through a protein kinase B (Akt)–GSK-3 (glycogen synthase kinase 3) signaling cascade. This novel signaling mode involves the multifunctional scaffolding protein β-arrestin 2, which has a role in G-protein-coupled receptor (GPCR) desensitization. In this article, we provide an overview of how this dual function of components of the GPCR desensitization machinery relates to dopamine-receptor-mediated responses and we summarize recent insights into the relevance of the Akt–GSK-3 signaling cascade for the expression of dopamine-associated behaviors and the actions of dopaminergic drugs.

Introduction

Dopamine receptors are prototypic examples of G-protein-coupled receptors (GPCRs) mediating slow neurotransmission [1,2]. Dopamine has an important role in the modulation of fast glutamate- and GABA-mediated neurotransmission and is involved in crucial brain functions such as movement, emotion, reward and affect [2–4]. Consequently, drugs acting on dopamine neurotransmission have become widely used tools for the management of multiple neuropsychiatric disorders, including schizophrenia, mood disorders, Parkinson's disease, attention deficit hyperactivity disorder (ADHD) and Tourette syndrome [2–4]. A major dopamine-containing region of the brain, the nigrostriatal system, comprises dopamine-containing neurons that arise from the substantia nigra and the ventral tegmental area, which project to GABA-containing medium spiny neurons in the caudate putamen and nucleus accumbens (striatum) [5].

Classically, the functions of dopamine receptors have been associated with the regulation of cAMP–PKA (protein kinase A) through G-protein-mediated signaling [1,2]. Two classes of GPCR mediate dopamine functions. The D_1 class of receptors (D_1 and D_5 receptors) couple mostly to $G\alpha_s$ and stimulate the production of the second messenger cAMP and the activity of PKA. By contrast, the D_2 class of receptors (D_2, D_3 and D_4 receptors) couple to $G\alpha_{i/o}$ to regulate the production of cAMP negatively, thus resulting in a diminution of PKA activity [1] (Figure 1). D_2-class receptors also modulate intracellular Ca^{2+} levels by acting on ion channels or by triggering the release of intracellular Ca^{2+} stores [1,2]. Downstream from PKA, dopamine- and cAMP-regulated phosphoprotein with molecular weight 32 (DARPP-32) has important functions in regulating the efficacy of dopamine receptor signaling and its integration with other signaling modalities [2]. 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 [6–8].

Recent investigations have shown that, apart from their canonical actions on G-protein-mediated signaling and the regulation of the cAMP–PKA pathway, dopamine receptors exert their effects *in vivo* through cAMP-independent mechanisms. This new mode of dopamine receptor signaling involves proteins that have classically been implicated in GPCR desensitization [9,10]. Moreover, cAMP-independent dopamine receptor signaling displays different kinetic properties and might serve as an integrator of dopamine receptor signaling and signaling events that emanate from other neurotransmitter receptors.

In this article, we provide an overview of recent advances in the characterization of the dual functions of dopamine-receptor-desensitizing mechanisms that act at the same time as terminators and mediators of different modalities of dopamine receptor signaling. We also highlight the potential relevance of the novel signaling mechanism that involves the protein kinase B (Akt)–GSK-3 (glycogen synthase kinase 3) pathway (Box 1) for the expression of dopamine-associated behaviors and the action of dopaminergic drugs.

Receptor desensitization mechanisms

Following receptor stimulation, GPCR signaling is rapidly inactivated by a series of mechanisms that results in receptor desensitization, internalization and termination of signaling. GPCR activation leads to the rapid phosphorylation of the receptors by members of a family of GPCR kinases (GRKs) [11–14]. The phosphorylation of receptors by GRKs leads to the recruitment of scaffolding proteins termed arrestins, resulting in the uncoupling of the receptors from G proteins [13–15] (Figure 1a). Two arrestins, β-arrestin 1 and β-arrestin 2, are expressed in most mammalian tissues, including the brain, whereas two other proteins, the visual arrestins, are expressed specifically in retinal cones and rods [14]. The interaction of arrestins with GPCRs is followed by the recruitment of an endocytic complex, which

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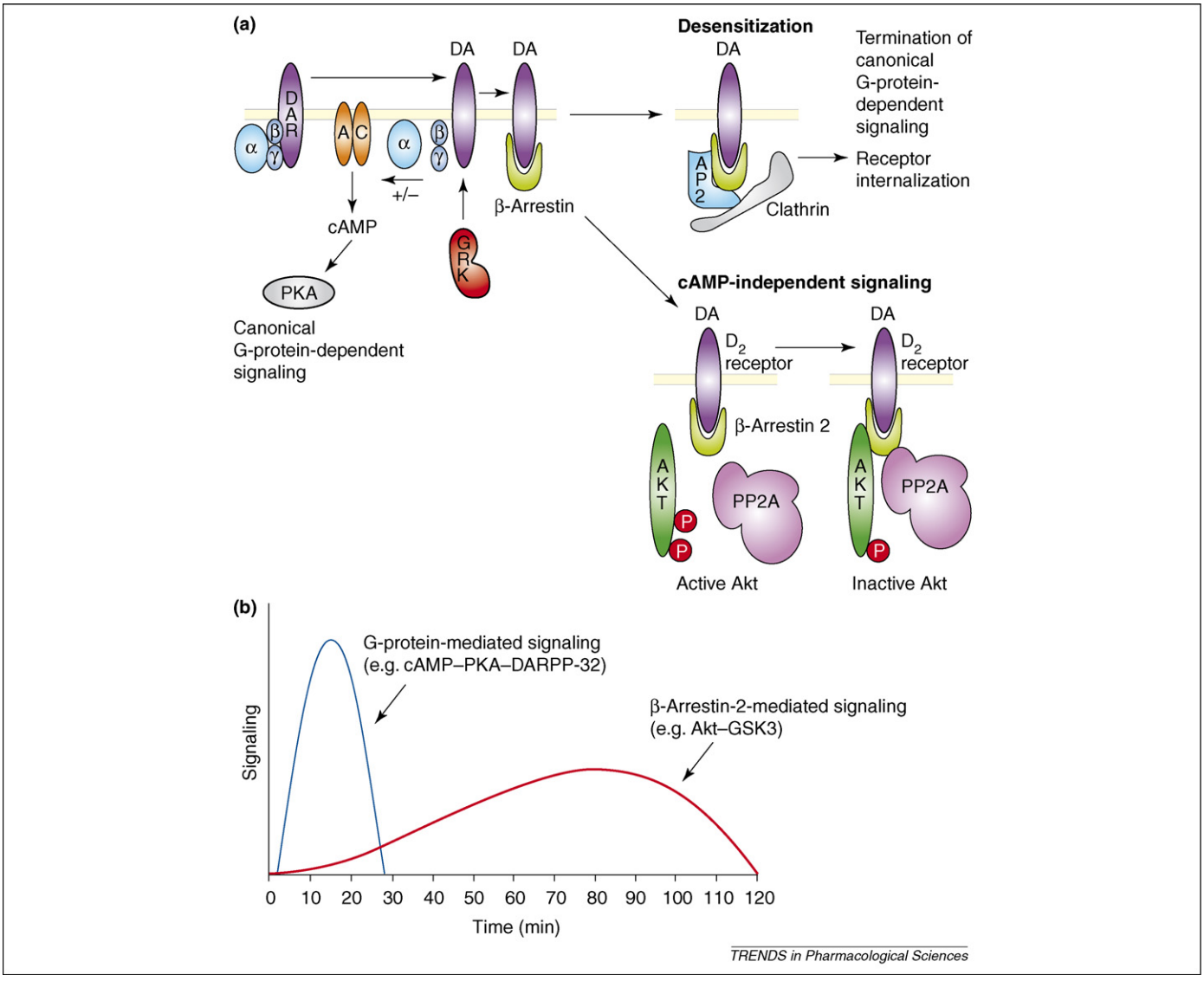

Figure 1. Dual role of β-arrestins in GPCR-mediated slow synaptic transmission. **(a)** The stimulation of dopamine (DA) receptors (DARs) leads to an initial change in receptor conformation that mediates the activation of G proteins, leading to activation ($G\alpha_s$) or inhibition ($G\alpha_{i/o}$) of adenylyl cyclase and modulation of cAMP-dependent PKA (canonical G-protein-dependent signaling). Receptor phosphorylation by GRKs and the recruitment of β-arrestins then ensue. The recruitment of β-arrestins to receptors results in two distinct processes: the termination of G-protein-dependent signaling and the formation of an internalization complex comprising β-arrestin 1 and/or β-arrestin 2, adaptor protein 2 (AP2), clathrin and other intermediates. Formation of the internalization complex leads to receptor internalization through clathrin-mediated endocytosis. The recruitment of β-arrestin 2 following the activation of D_2-class receptors also results in the formation of a signaling complex that comprises at least β-arrestin 2, PP2A and Akt. The formation of this complex results in the deactivation of Akt by PP2A and the subsequent stimulation of GSK-3-mediated signaling. **(b)** The different kinetics of G-protein-mediated and β-arrestin-2-mediated dopamine receptor signaling following the administration of amphetamine. Shown are the two waves of signaling responses involved in slow dopamine synaptic transmission. In the first wave of responses, G-protein-mediated signaling induces a rapid and transient change in the phosphorylation of direct or indirect PKA targets such as DARPP-32, cAMP-response-element-binding protein (CREB) and ERK. In parallel to these events, a second wave of signaling, mediated by the Akt–β-arrestin-2–PP2A complex, results in a more progressive and longer-lasting response.

leads to the arrestin-dependent internalization of receptors, principally in clathrin-coated pits [14–17] (Figure 1a). Although arrestins were originally identified as key molecules that control GPCR desensitization, recent evidence indicates that arrestins and, potentially, GRKs also promote novel G-protein-independent signaling events that, in the case of dopamine receptors, do not involve a regulation of cAMP-mediated signaling [9,14,18–20].

Role of GRKs in the regulation of dopamine functions

Studies of dopamine receptor function in mice lacking different GRKs have, in most cases, supported a role for these kinases in both GPCR desensitization and signaling [13]. The seven GRKs in mammals (GRK1–GRK7) belong to three classes: GRK1-like, GRK2-like and GRK4-like [13]. Whereas GRK1 (rhodopsin kinase) and GRK7 (iodopsin kinase) are found primarily in the retina and are involved in the termination of phototransduction by opsins, GRK2, GRK3, GRK4, GRK5 and GRK6 are widely expressed in the body, including the brain. Thus, mice deficient in GRK3 (*Adrbk2*) [21], GRK4 (*Gprk21*) [13], GRK5 (*Gprk5*) [22] or GRK6 (*Gprk6*) [23] have been examined for their behavioral responses to dopaminergic drugs. Mice that lack GRKs are normal in most tests {with the exception of the embryonically lethal GRK2 (*Adrbk1*)-knockout mice [24]} until challenged with an appropriate agonist [13]. Because the GRK–β-arrestin system has dual roles, both suppressing G-protein-mediated signaling and

Box 1. Akt and GSK-3 signaling

Akt is a serine/threonine kinase that is regulated through phosphatidylinositol-3-kinase-mediated signaling [56]. The regulation of Akt has been associated with the action of insulin, insulin-related peptides [e.g. insulin-like growth factor (IGF)] and neurotrophins [e.g. nerve growth factor, brain-derived neurotrophic factor (BDNF) and neurotrophin 3], which exert their biological function by stimulating RTK [56,57] (see Figure 2 in the main text). The kinases GSK-3α and GSK-3β are constitutively active and can be inactivated through the phosphorylation of the single serine residues serine 21 (GSK-3α) and serine 9 (GSK-3β), which are located in their regulatory N-terminal domains, by Akt and other kinases [58]. Akt inhibits GSK-3α and GSK-3β in response to multiple hormones and growth factors, including insulin, IGF and BDNF [58].

promoting non-G-protein signaling (Figure 1), the loss of GRKs can have opposing effects on physiological function: either promoting unregulated (supersensitive) receptor responses because of deficient desensitization or decreasing responses because of a reduced activation of arrestin-mediated non-G-protein signaling pathways.

In mice that are heterozygous for GRK2 deletion, locomotor responses to the psychostimulants cocaine and amphetamine or to the direct dopamine receptor agonist apomorphine are essentially normal, although certain doses of cocaine induce slightly enhanced locomotor activation [13]. Thus, the impact of a partial loss of GRK2 on dopamine-receptor-mediated responses seems to be limited, although it is possible that a more pronounced level of GRK2 deficiency is necessary to reveal the potential involvement of this kinase in dopamine receptor regulation [13]. Further studies involving brain-specific GRK2-knockout mice will be necessary to address this issue.

GRK6 is the most prominent GRK in the striatum. In mice, GRK6 is expressed at high levels in the major striatal neuronal populations, including GABA-containing medium spiny neurons and acetylcholine-containing interneurons [23]. GRK6-knockout mice show significant supersensitivity to cocaine, amphetamine, morphine and the endogenous 'trace amine' β-phenylethylamine, which all induce psychomotor activation through the activation of dopamine neurotransmission [23]. Detailed investigations of these effects revealed that GRK6-knockout mice have an enhanced coupling of striatal D_2-like receptors to G proteins, an increased affinity of D_2, but not D_1, receptors and enhanced locomotor responses to direct dopamine receptor agonists [23]. Overall, these observations demonstrate that cAMP-mediated signaling by postsynaptic D_2-class receptors in the striatum is regulated by GRK6 and that D_2 receptor desensitization is reduced in the absence of GRK6.

Finally, locomotor responses to cocaine are not altered in GRK4-knockout mice, which is consistent with the limited expression of GRK4 in the brain [13]. Similarly, there are no differences in the effects of cocaine and apomorphine in GRK5-knockout mice, indicating that GRK5 is unlikely to be involved in the regulation of dopamine receptors [13]. However, GRK3-knockout mice have normal basal locomotor activity but demonstrate significantly reduced locomotor responses to cocaine, apomorphine and the D_1 receptor agonist SKF81297 [*R*-(+)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide] [13]. Thus, although it seems unlikely that GRK3 is directly involved in the desensitization of dopamine receptors, it is possible that this kinase is involved in G-protein-independent dopamine receptor signaling.

Role of β-arrestin 2 in cAMP-independent dopamine receptor signaling and function

Several lines of evidence indicate that, in addition to their canonical action on G proteins, GPCRs can also activate signaling through molecules that are classically involved in the regulation of GPCR desensitization [25] (Figure 1a). 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 [18,20,25]. However, the implication of β-arrestin-mediated signaling in biologically relevant processes such as slow synaptic transmission has remained largely unexplored. Interestingly, both β-arrestin 1 (*Arrb1*)-knockout and β-arrestin 2 (*Arrb2*)-knockout mice display reduced behavioral responses to the dopamine receptor agonist apomorphine [9,13]. Mice lacking β-arrestin 1 also have a reduced responsiveness to cocaine, whereas β-arrestin-2-knockout mice show blunted locomotor responses to the dopamine-dependent actions of amphetamine and morphine [9,13,26]. Furthermore, in mice lacking the dopamine transporter [DAT (*Slc6a3*)-knockout mice], the locomotor hyperactivity phenotype associated with enhanced dopaminergic tone can be antagonized by a concomitant lack of β-arrestin 2 [9]. These observations indicate that one or many different types of β-arrestin-containing protein complexes might mediate dopamine receptor signaling. We have recently identified one of these mechanisms and shown that β-arrestin 2 is a signaling intermediate implicated in the cAMP-independent regulation of Akt and GSK-3 by dopamine [8–10] (Figure 1a).

Investigations of cell signaling in response to persistently elevated extracellular dopamine levels identified a reduction of Akt phosphorylation and activity in the striatum of DAT-knockout mice [8,10]. The inactivation of Akt in these mice results in concomitant activation of the substrates GSK-3α and GSK-3β [10], which are inhibited by Akt (Box 1). Further characterization of these signaling responses using dopamine depletion [10,27] or dopamine receptor antagonists in DAT-knockout mice showed that Akt, GSK-3α and GSK-3β are regulated by D_2-class receptors [10] (Figure 2). Furthermore, the D_2-class receptor antagonist and antipsychotic haloperidol leads to enhanced Akt phosphorylation and to GSK-3 inhibition in non-transgenic animals [28]. Administration of amphetamine or the nonselective dopamine receptor agonist apomorphine to non-transgenic mice also results in an inhibition of Akt activity, thus confirming the regulation of the Akt–GSK-3 pathway by dopamine [9,10]. Interestingly, the regulation of this pathway by dopaminergic drugs shows different kinetics (Figure 1b) compared with those of canonical cAMP-mediated events (Box 2), and neither Akt nor GSK-3 is affected by direct modulation of cAMP levels in the striatum, indicating that the Akt–GSK-3 pathway is not controlled by this second messenger [10]. By contrast, when

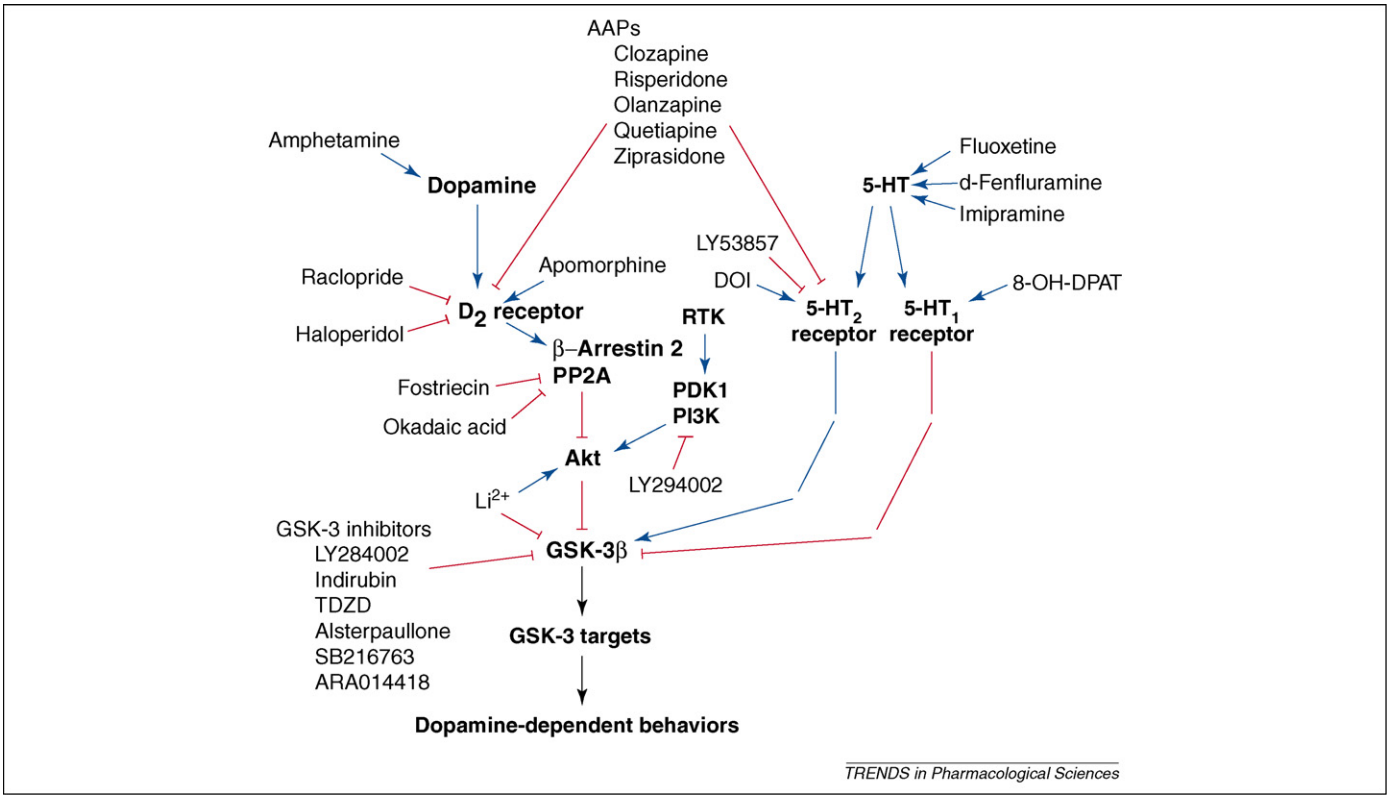

Figure 2. Regulation of Akt and GSK-3 by drugs affecting monoamine systems and related signaling events. Behavioral changes in dopaminergic responses have been reported in Akt1-knockout [28,32], β-arrestin-2-knockout [9,13] and GSK-3β heterozygote [10] mice. The GSK-3 inhibitors shown antagonize dopamine-dependent behaviors [10,29]. Lithium (Li^{2+}) both antagonizes dopamine-associated behaviors and enhances Akt phosphorylation [10]. All other drugs listed are included on the basis of their reported action on Akt or GSK-3 phosphorylation in the mouse striatum. Blue arrows denote activation, red arrows denote inhibition, black arrows denote effects that can be either activatory or inhibitory depending on specific substrates. Abbreviations: AAPs, atypical antipsychotics; RTK, receptor tyrosine kinase.

administered to β-arrestin-2-knockout mice, neither amphetamine nor apomorphine reduces Akt phosphorylation [9]. Furthermore, mice lacking both β-arrestin 2 and DAT show no inhibitory action of elevated levels of extracellular dopamine on Akt phosphorylation, demonstrating that dopamine receptors regulate Akt through β-arrestin 2 [9]. Further investigations of the mechanism by which β-arrestin 2 regulates Akt in response to dopamine showed that inhibitors of protein phosphatase 2A (PP2A) prevent the inhibition of Akt by dopamine, whereas the stimulation of D_2-class receptors causes the formation of a protein complex that comprises at least Akt, β-arrestin 2 and PP2A [9]. The formation of this complex facilitates the dephosphorylation and deactivation of Akt by PP2A in response to dopamine and results in the activation of GSK-3 [9,10] (Figures 1a,2).

In addition to the deficits observed in β-arrestin-2-knockout mice, multiple lines of evidence support the involvement of the β-arrestin-2–Akt–GSK-3 pathway in the regulation of dopamine-associated behaviors. For example, GSK-3 inhibitors can reduce locomotor hyperactivity both in DAT-knockout mice and in amphetamine-treated wild-type animals [10,29]. Confirmation of these pharmacological observations was also obtained using genetically engineered animals. GSK-3β (*Gsk3b*)-knockout mice die during embryogenesis, whereas GSK-3β heterozygote mice develop normally without overt phenotypes [30]. Evaluation of the behavioral actions caused by amphetamine revealed that GSK-3β heterozygote mice are less responsive to this drug over a range of doses, thus supporting the involvement of GSK-3β in the development of dopamine-associated behaviors [10]. Conversely, transgenic mice that express a 'constitutively active' GSK-3β mutant lacking an inhibitory phosphorylation site develop a locomotor hyperactivity phenotype that is reminiscent of DAT-knockout mice [31]. Finally,

Box 2. Two modalities of slow synaptic transmission

In cultured fibroblasts, β-arrestin-mediated signaling has a slower onset and a more prolonged duration than does GPCR signaling [59]. Likewise, the β-arrestin-2-dependent inhibition of Akt by dopamine in the mouse striatum displays a slower but more persistent effect than do signaling events that are regulated by the cAMP–PKA pathway [9,10] (see Figure 1 in the main text).

The cAMP-dependent phosphorylation of ERK2 and DARPP-32 peaks and subsides within the first 30 min after the administration of dopaminergic drugs such as amphetamine and cocaine [7,60,61]. By contrast, the inhibition of Akt by amphetamine develops progressively during the first 30–60 min of drug action and persists over the duration of the drug behavioral effect [9,10,62].

This indicates that the regulation and maintenance of certain dopamine-associated behaviors, in addition to the action of some dopaminergic drugs, might depend on two complementary waves of GPCR signaling responses: a first wave of cAMP-mediated responses with a rapid onset and a relatively short duration, and a second wave of responses characterized by slower onsets and longer durations, which are dependent on β-arrestin signaling functions. Moreover, the reduced behavioral responsiveness to dopaminergic drugs acting on either D_1- or D_2-class receptors observed in β-arrestin-1-knockout and β-arrestin-2-knockout mice [9,13] indicates that multiple β-arrestin signaling complexes might also mediate dopamine receptor signaling and, potentially, the action of other GPCRs implicated in slow synaptic transmission.

mice lacking the Akt isoform Akt1 also show enhanced disruption of sensory motor gating (pre-pulse inhibition) by amphetamine but not by glutamate NMDA receptor antagonists [28]. The disruption of sensory motor gating by amphetamine, which has been used as a behavioral paradigm to model psychosis in rodents, is efficiently blocked by antipsychotics such as haloperidol that act on D_2-class receptors. Furthermore, Akt1-knockout mice also show a more pronounced deficit in response to D_2-class, but not D_1-class, receptor agonists in cognitive tests associated with prefrontal cortex functions [32]. Therefore, because Akt1 is inhibited following the stimulation of D_2-class receptors [10], the altered behavioral effects caused by amphetamine and D_2-class receptor agonists in Akt1-knockout mice further support the involvement of Akt inhibition in dopamine-mediated behavioral responses.

Involvement of Akt and GSK-3 in the action of psychotropic drugs

Typical antipsychotics such as haloperidol are thought to exert most of their actions by blocking D_2-class receptors, thus supporting a role for dopamine neurotransmission in the etiology of schizophrenia. Recent genetic association studies have established a link between a deregulation of Akt signaling and schizophrenia. Following transmission–disequilibrium tests, a major association of Akt1 haplotypes with schizophrenia has been reported in several independent cohorts of schizophrenic patients [28,33–35]. Furthermore, reduced Akt activity or expression levels were also shown in the brains of schizophrenic patients [28,36].

Thus, because stimulation of striatal D_2-class receptors by dopamine results in an inhibition of Akt [9,10], it is possible that a partial loss of function of Akt1 in schizophrenia results in exacerbated responses to D_2 receptor stimulation that are similar to those observed in Akt1-knockout mice. In the same way, classical antipsychotics could correct this imbalance by preventing further reductions of Akt activity by D_2-class receptors (Figure 2).

In addition, so-called atypical antipsychotics have recently been shown to either activate Akt [37] or mimic Akt activity by increasing the phosphorylation of its substrates GSK-3α and GSK-3β [38]. Atypical antipsychotics can be distinguished functionally from typical antipsychotics by their reduced affinity and lower specificity for D_2 receptors. Many atypical antipsychotics display a strong affinity for 5-hydroxytryptamine $(5\text{-HT})_{2A}$ receptors [39]. The atypical antipsychotic clozapine enhances Akt–GSK-3 signaling in cell culture systems [37]. Acute or chronic *in vivo* administration of multiple atypical antipsychotics – including risperidone, olanzapine, clozapine, quetiapine and ziprasidone – results in an inhibition of GSK-3β in different brain regions [38,40]. Furthermore, drugs that affect 5-HT neurotransmission, such as selective 5-HT-reuptake inhibitors, monoamine oxidase inhibitors and tricyclic antidepressants, amplify the action of atypical antipsychotics on GSK-3β [38]. Interestingly, increases in GSK-3 activity were recently reported in the prefrontal cortex of depressed suicide victims [41]. Two 5-HT receptors seem to have antagonistic roles in regulating GSK-3β: stimulation of 5-HT_{2A} receptors leads to kinase activation, whereas stimulation of 5-HT_{1A} receptors has the opposite effect [38,42] (Figure 2). This action of atypical antipsychotics and 5-HT drugs indicates that Akt and GSK-3 might function as signal integrators for dopamine and 5-HT transmission, and contribute to the action of drugs on these neurotransmitter systems [43]. However, in the absence of extensive behavioral studies addressing the function of GSK-3 in the regulation of 5-HT function and the action of 5-HT drugs, this integrative function remains hypothetical.

Akt and GSK-3 have been associated with the action of the mood stabilizer lithium. Lithium is a direct inhibitor of GSK-3 that can also inhibit the activity of this kinase in cells through an indirect mechanism (Figure 2) involving Akt activation [10,43–48]. Acute and chronic administration of lithium inhibits brain GSK-3 activity in mice, as revealed by enhanced regulatory N-terminal domain phosphorylation [10,48]. Moreover, GSK-3 inhibitors and reduced GSK-3β expression both reproduce some of the behavioral actions of lithium in rodents, including its inhibitory action on dopamine-dependent locomotor hyperactivity [10,29,49]. Although the mechanism by which lithium regulates Akt and GSK-3 activity is unclear, these observations indicate that a direct or indirect inhibition of GSK-3 might contribute to the psychopharmacological actions of lithium, at least in part, by inhibiting dopamine responses.

Future perspectives

The characterization of the mechanisms by which β-arrestins and GRKs contribute to dopamine receptor signaling is at an early stage and it would be naïve to believe that the complete palette of molecular responses associated with these molecules has been identified. Of particular interest, the further characterization of GRKs and other modulators of β-arrestins in the dopamine system might enable researchers to determine the functions of these molecules in regulating the positive and negative actions of β-arrestins on dopamine receptor signaling. Also of interest, the D_2-receptor-interacting protein spinophilin [50] has been shown to interfere with β-arrestin functions by competing with GRK2 for GPCR binding [51], and GRK2 has been shown to regulate Akt in non-neuronal cells [52], indicating a potential role of these molecules in the regulation of β-arrestin-mediated D_2-class receptor signaling. Furthermore, although behavioral studies indicate that β-arrestin 1 also has signaling functions in dopamine neurotransmission [13], the molecular mechanism(s) of these functions has yet to be identified. Interestingly, β-arrestin 1 has recently been shown to function as a nuclear signaling molecule that regulates chromatin structure and gene expression in cultured fibroblasts [19,53]. Such changes in chromatin organization have also been suggested to participate in the development of long-term adaptation and addiction to dopaminergic drugs such as cocaine [54], thus raising the possibility that β-arrestin 1 has a role in this phenomenon. Finally, the identification of a cAMP-independent (β-arrestin-dependent) modality of dopamine receptor signaling that involves the Akt–GSK-3 cascade indicates that dopamine receptor functions are mediated by multiple mechanisms that collaborate to

fine-tune the expression of dopaminergic responses under different physiological and environmental conditions. These mechanisms could be crucial for regulating the expression of distinct dopamine-associated behaviors and/or for ensuring the robustness [55] of important physiological outcomes. Understanding the complexity of this interplay between these modalities of dopamine receptor signaling could enable the development of novel pharmacological treatments with improved therapeutic actions while avoiding undesired side-effects.

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