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# Akt/GSK3 Signaling in the Action of Psychotropic Drugs

Jean-Martin Beaulieu,[1] Raul R. Gainetdinov,[2*] and Marc G. Caron[2]

[1]Department of Anatomy and Physiology, Université Laval/CRULRG, Québec, Canada; email: Martin.Beaulieu@CRULRG.ULAVAL.CA

[2]Department of Cell Biology, Duke University Medical Center, Durham, North Carolina 27710; email: m.caron@cellbio.duke.edu

[*]Department of Neuroscience and Brain Technologies, Italian Institute of Technologies, Genova, Italy; email: raul.gainetdinov@iit.it



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## Key Words

Monoamine, Serotonin, Dopamine, Signaling, Psychiatric disorders

## Abstract

Psychotropic drugs acting on monoamine neurotransmission are major pharmacological treatments for neuropsychiatric conditions such as schizophrenia, depression, bipolar disorder, Tourette syndrome, ADHD, and Alzheimer disease. Independent lines of research involving biochemical and behavioral approaches in normal and/or genetically modified mice provide converging evidence for an involvement of the signaling molecules Akt and glycogen synthase kinase-3 (GSK3) in the regulation of behavior by dopamine and serotonin (5-HT). These signaling molecules have also received attention for their role in the actions of psychoactive drugs such as antidepressants, antipsychotics, lithium, and other mood-stabilizers. Furthermore, investigations of the mechanism by which D2 dopamine receptors regulate Akt/GSK3 signaling strongly support the physiological relevance of a new modality of G protein–coupled receptor (GPCR) signaling involving the multifunctional scaffolding protein beta-arrestin 2. Elucidation of the contribution of multiple signaling pathways to the action of psychotropic drugs may provide a better biological understanding of psychiatric disorders and lead to more efficient therapeutics.

## INTRODUCTION

**Antipsychotics:** class of therapeutic agents that relieve symptoms of psychosis, also referred to as neuroleptics

**D2-class dopamine receptors:** GPCRs that bind and transmit the physiological actions of dopamine

Despite more than 50 years since the discovery and clinical use of psychotropic drugs, the molecular mechanisms by which many of them exert their therapeutic actions in schizophrenia, mood disorders, and other psychiatric disorders remain shrouded in mystery. The identification of receptors and transporters for the monoamine neurotransmitters dopamine, norepinephrine, and serotonin (5-HT) has provided the principal pharmacological paradigms to explain the action of these drugs (1–3). Most antidepressant drugs appear to exert their effects by blocking the 5-HT and/or the norepinephrine transporters, thereby increasing the extracellular availability of these two neurotransmitters (2, 4). Conversely, first (typical)- and second (atypical)-generation antipsychotics are antagonists of D2-class dopamine receptors (3, 5), whereas the latter are also antagonists of 5-HT2 receptors (6). Identification of the primary pharmacological targets of these psychoactive drugs has held the promise that specific ligands for these molecules would pave the way for the development of more efficient drugs with fewer unwanted side effects. However, that promise has yet to be fulfilled (7). Furthermore, the nature of the processes through which the activation or blockade of dopamine, norepinephrine, or 5-HT receptors affects the regulation of brain functions such as cognition and mood is still far from being understood.

Investigation of monoamine receptors revealed a complex picture of the mechanisms through which these receptors exert their action in the brain (**Figure 1**). Essentially all receptors for

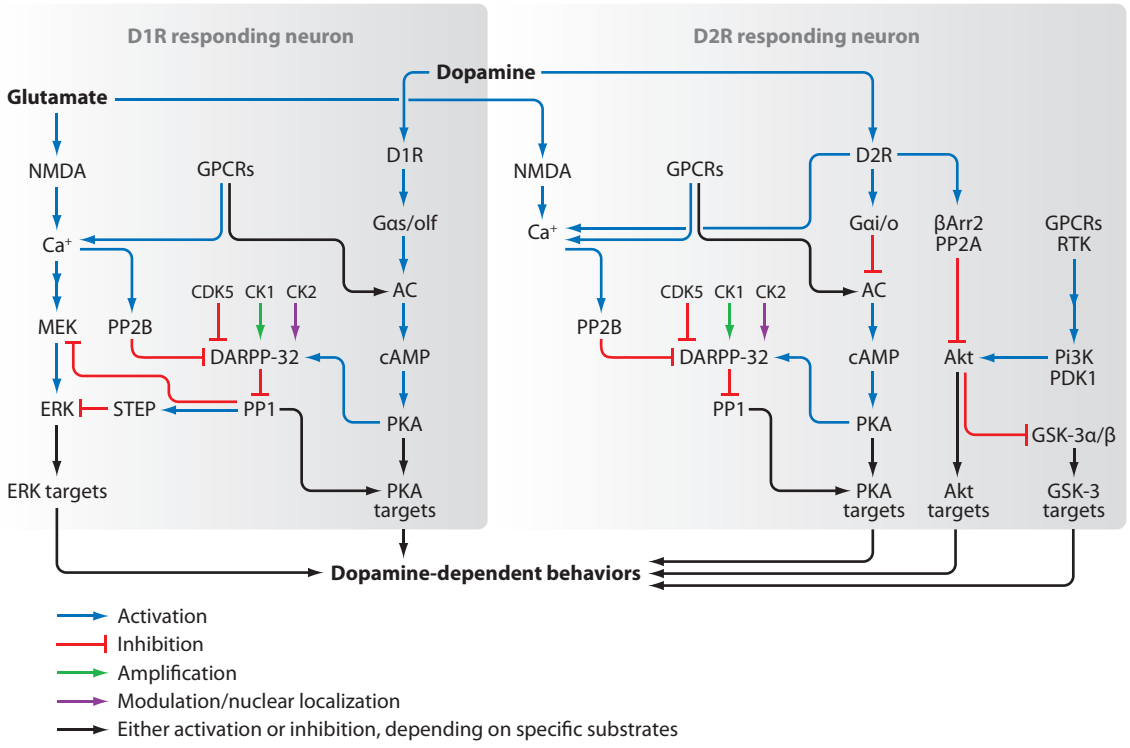


**Figure 1**

Complexity of signaling responses in vivo, signaling networks regulated by dopamine in D1 receptors (D1R) and D2 receptors (D2R) containing neurons in the mouse striatum. D2 dopamine receptors display G protein–dependent and βArr2- dependent responses. The actions of other neurotransmitters, growth factors, and neurotrophins have also been included to illustrate the role of many of these intermediates as signal integrators (8, 102, 141).

dopamine, norepinephrine, and 5-HT (with the exception of 5HT3 receptors) belong to the large family of G protein–coupled receptors (GPCRs) consisting of seven transmembrane–spanning domain proteins that couple to heterotrimeric guanine nucleotide binding proteins (G proteins). Multiple GPCRs have been shown to couple to more then one type of G protein and also have the ability to signal in a G protein–independent fashion (8–10). Furthermore, multiple mechanisms such as GPCR heterodimerization (11–13) or the integration of signal from different GPCRs by common downstream targets (14) provide several possibilities for receptor cross-talk, thereby making it difficult to predict therapeutically important biochemical responses to psychoactive drugs from in vitro studies of signaling responses or ligand specificity.

Over the past few years, a series of studies involving a combination of biochemical and behavioral approaches in normal and genetically modified mice have provided converging evidence for an involvement of the signaling molecules Akt and glycogen synthase kinase-3 (GSK3) in the regulation of behaviors by dopamine and 5-HT as well as in the mechanism of action of certain psychoactive drugs. Furthermore, elucidation of the mechanism by which dopamine regulates Akt and GSK3 has provided support for the physiological relevance of new modalities of GPCR signaling that involve the multifunctional scaffolding protein β-arrestin 2 (βArr2) rather than G proteins. Here we present an overview of the recent findings on the mechanisms by which dopamine and 5-HT regulate Akt and GSK3, and we particularly focus on the involvement of these molecules in the mechanism of action of antipsychotics, lithium, and antidepressants.

## THE AKT/GSK3 SIGNALING PATHWAY

Akt, also termed protein kinase B (PKB), is a serine/threonine kinase regulated through phosphatidylinositol-mediated signaling. The activation of Akt (**Figure 2**) involves its recruitment to the plasma membrane by phosphorylated phosphatidylinositol (Ptdlns-3,4,5-P), phosphorylation on a regulatory threonine residue (threonine 308) by the phosphatidylinositol-dependent kinase 1 (PDK1), and further phosphorylation on another regulatory residue (serine 473) by PDK2/rictor-mTOR complex (15–18). GSK3α and GSK3β are two closely related serine/threonine kinases originally associated with the regulation of glycogen synthesis in response to insulin (19, 20). These kinases are constitutively active and can be inactivated through the phosphorylation of single serine residues, serine 21 (GSK3α) and serine 9 (GSK3β), of their respective regulatory amino-terminal domains (20). Akt has been shown to inhibit GSK3α and GSK3β (**Figure 2**) in response to multiple hormones and growth factors, including BDNF, IGF, and insulin (20–22).

## REGULATION OF BRAIN AKT/GSK3 SIGNALING BY D2-CLASS DOPAMINE RECEPTORS

Studies of altered cell signaling in response to persistently elevated extracellular dopamine levels identified a reduction of Akt phosphorylation/activity and a concomitant activation of both GSK3α and GSK3β in the striatum of mice lacking the dopamine transporter [dopamine transporter–knockout (DAT-KO) mice] (23, 24). Administration of amphetamine, methamphetamine, or the nonselective dopamine receptor agonist apomorphine to normal mice also resulted in an inhibition of Akt activity whereas striatal dopamine depletion had the opposite effect, thus firmly establishing the regulation of the Akt/GSK3 pathway by dopamine (23, 25–27). Further characterization of these signaling responses using (D1 and D2 dopamine receptor antagonists (SCH23390 and raclopride) in DAT-KO mice showed that Akt, GSK3α, and GSK3β are regulated by D2-class receptors in these mice (23). In other studies, the D2-class receptor antagonist and antipsychotic haloperidol

**Guanine nucleotide binding proteins (G proteins):** protein family that acts as a molecular switch to transmit the signal from cell surface receptors

**G protein–coupled receptor (GPCR):** a large family of seven transmembrane proteins that bind extracellular signaling molecules to activate intracellular signaling pathways

**Akt:** member of the serine/threonine-specific protein kinase family, or protein kinase B, involved in mammalian cellular signaling and activated by phosphorylation downstream of the phosphatidylinositol signaling cascade

**Glycogen synthase kinase (GSK3):** cellular serine/threonine protein kinase existing as two distinct gene products, α and β, both important substrates of Akt

**Antidepressants:** class of therapeutic drugs that relieve symptoms of depression

**Amphetamine:** A stimulant used clinically and illegally that produces its effect mainly by releasing dopamine from intracellular neuronal stores

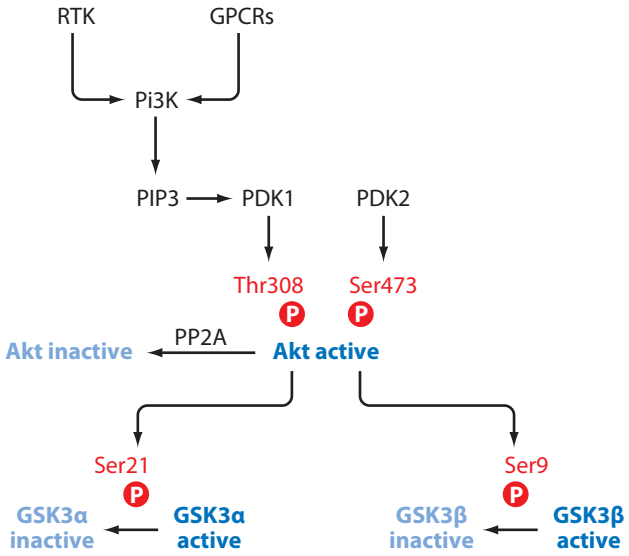


**Figure 2**

Schematic representation of Akt/GSK3 signaling. Akt is activated in response to (Pi3K)-mediated signaling. Production of Phosphatidylinositol (3,4,5)-trisphosphate (PIP3) as a result of Pi3K activity leads to the recruitment of Akt and its upstream kinase, PDK1, to the membrane, resulting in the phosphorylation of Akt by PDK1. Full activation of Akt is mediated by two kinases, PDK1 and PDK2/rictor-mTOR, that phosphorylate Thr 308 and Ser 473 of Akt1, respectively. Akt deactivation is mediated by phosphatases, including Protein phosphatase 2A (PP2A). Activated Akt inactivates both GSK3α and GSK3β by phosphorylating their amino-terminal regulatory domains on either Ser 21 (α) or Ser 9 (β). RTK: receptor tyrosine kinase, GPCR: G protein–coupled receptors.

has also been shown to enhance Akt phosphorylation thus inhibiting GSK3 in normal animals (28, 29). Finally, an investigation of dopamine-dependent regulation of Akt phosphorylation in mice lacking different subtypes of D2-class receptors showed that D2 receptors are essential for the inhibition of striatal Akt by these drugs (30). Mice lacking the dopamine D3 receptors showed a reduced sensitivity of Akt-mediated signaling to dopaminergic drugs but retained the action of these drugs on Akt at high dose regimens, suggesting that D3 receptors also participate the regulation of Akt/GSK3 signaling, potentially by enhancing D2 receptor responses (30).

## β-ARRESTIN 2–MEDIATED D2 DOPAMINE RECEPTOR SIGNALING

The various functions of dopamine receptors have been primarily associated with the regulation of cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) via G protein–dependent signaling. The D1-class receptors are mostly coupled to $G_{\alpha}s$ and stimulate cAMP production and the activity of PKA. In contrast, D2-class receptors are coupled to $G_{\alpha}i/o$ to inhibit the production of cAMP and thus diminish PKA activity (31–34). However, in the mouse striatum, neither Akt nor GSK3 were affected by direct modulation of cAMP levels, indicating that this signaling pathway is not controlled by this second messenger (23). Instead, behavioral and biochemical evidence has revealed a role for βArr2, a multifunctional scaffolding molecule generally involved in GPCR desensitization, in the regulation of the Akt/GSK3 pathway by D2 receptors.

It is well established that following stimulation, G protein–mediated signaling is inactivated by mechanisms that result in receptor desensitization, internalization, and termination of

G protein–mediated signaling. GPCR activation induces the rapid polyphosphorylation of the receptors by members of a family of GPCR kinases (GRKs) (35–38). Phosphorylation of receptors by GRKs leads to their uncoupling from G proteins and to recruitment of scaffolding proteins termed arrestins (37–39). Most mammalian tissues, including brain, express two arrestins, β−arrestin 1 and βArr2, whereas two other proteins, the visual arrestins, are specifically expressed in retinal cones and rods (38). The interaction of arrestins with GPCR is followed by the recruitment of an endocytic complex, which results in an arrestin dependent internalization of receptors, mostly in clathrin-coated pits (38–41). However, the role of arrestins in GPCR functions is not limited exclusively to desensitization. It has become apparent that apart from their canonical action on G proteins, GPCRs can also elicit cellular responses mediated by the formation of signaling protein complexes (**Figure 3**) scaffolded by β-arrestins (42–44).

When administered to βArr2-KO mice, both amphetamine and apomorphine failed to reduce Akt phosphorylation as they do in wild-type (WT) animals (25). Similarly, mice lacking both

**Arrestins:** adaptor proteins that bind activated/phosphorylated GPCRs to block G protein activation, trigger for endocytosis, and scaffold signaling molecules

**βArr2-KO mice:** line of mutant mice in which the gene for one of the two nonvisual arrestins, β-arrestin 2, has been inactivated by genetic manipulation

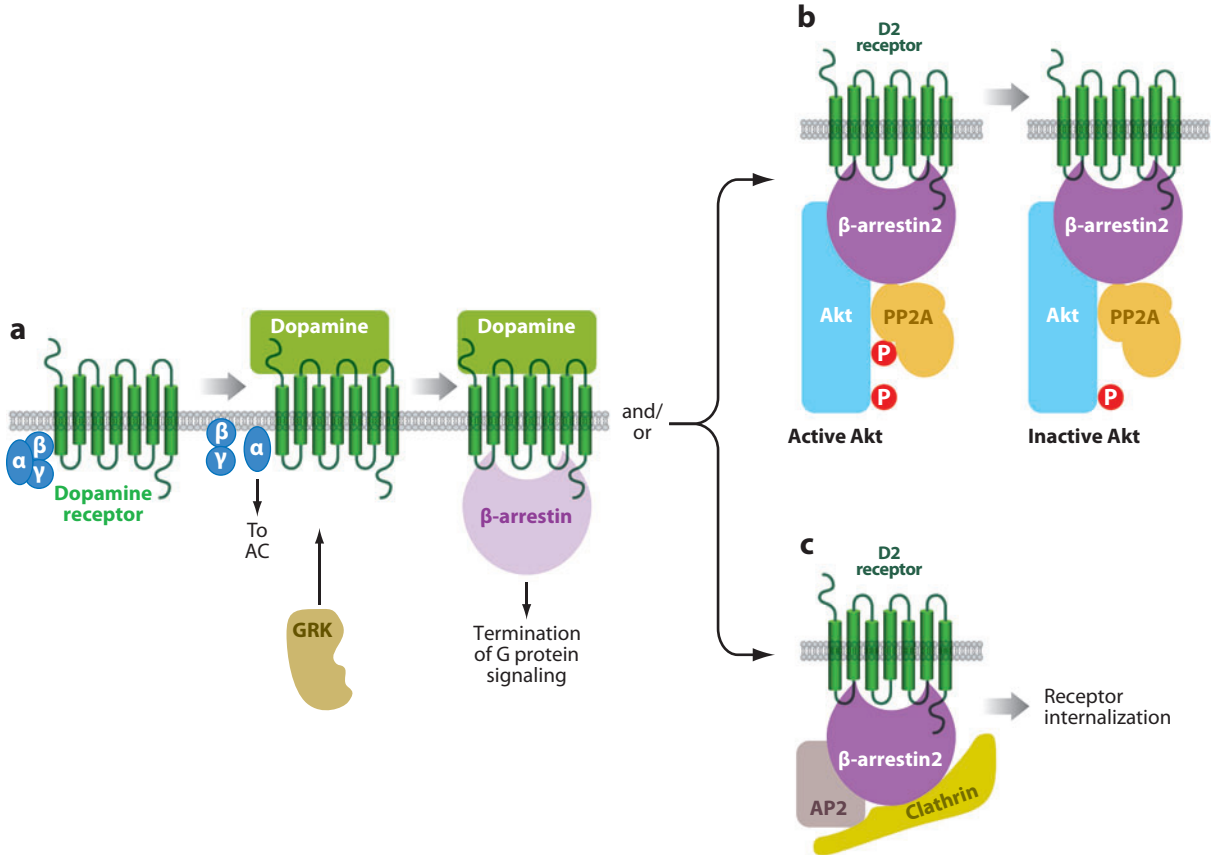


**Figure 3**

Dual role of β-arrestins (βArr 1,2) in GPCR signaling. (*a*) Stimulation of dopamine receptors (DAR) leads to receptor phosphorylation by GRKs and the recruitment of β-arrestins. (*b*) Activation of D2-Class receptors results in the formation of a signaling complex comprised of at least βArr2, PP2A, and Akt. Formation of this complex results in a deactivation of Akt by PP2A and subsequent stimulation of GSK3-mediated signaling. (*c*) Recruitment of β-arrestins to receptors also results in the formation of an internalization complex formed by β-Arr1 and/or βArr2, AP2, clathrin, and other intermediates. Formation of the internalization complex leads to a termination of G protein–mediated signaling and to receptor internalization.

βArr2 and DAT showed no inhibitory action of excessive dopamine on Akt phosphorylation, thus demonstrating that D2 receptors regulate Akt through βArr2 (25). Further investigations of the mechanism by which βArr2 regulates Akt in response to dopamine showed that stimulation of D2-class receptors causes the formation of a protein complex comprised of at least Akt, βArr2, and the heterotrimeric protein phosphatase 2A (PP2A), which facilitates the dephosphorylation/deactivation (45) of Akt by PP2A in response to dopamine (**Figure 2**) (23, 25).

**Prepulse inhibition (PPI):** a sensorimotor response to a weaker prestimulus inhibits the response to stronger stimulus, often dysregulated in psychiatric conditions and experimental animal models of psychosis

**SSRI:** selective serotonin reuptake inhibitor

## BEHAVIORAL CONSEQUENCES OF THE D2/β-ARRESTIN 2/AKT/GSK3 PATHWAY MODULATION

Multiple lines of evidence indicate a role of βArr2, Akt, and GSK3 in the regulation of behavior by dopamine. It has been shown that βArr2-KO mice display reduced apomorphine-induced climbing (25, 37). These mice also have a reduced responsiveness to the dopamine-dependent actions of amphetamine and morphine over a range of drug doses (25, 37, 46). Furthermore, mice lacking both βArr2 and DAT display a reduction of the typical novelty-induced locomotor hyperactivity phenotype characteristic of hyperdopaminergic DAT-KO mice (25).

Apart from the deficits in dopamine-associated behaviors found in βArr2-KO mice, several other observations also support the involvement of the βArr2/Akt/GSK3 pathway in the regulation of dopamine-related behaviors. Particularly, GSK3 inhibitors can reduce locomotor hyperactivity both in DAT-KO mice and in amphetamine-treated WT animals (23, 47). These pharmacological studies were further substantiated by the observations gained in genetically engineered animals. GSK3β-KO mice die during embryogenesis whereas GSK3β heterozygote mice develop normally without overt phenotypes (48). Evaluation of the behavioral effects of amphetamine revealed that GSK3β heterozygote mice are less responsive to this psychostimulant, thus further indicating the involvement of GSK3β in the expression of dopamine-associated behaviors (23). Conversely, transgenic mice expressing a GSK3β mutant lacking an inhibitory phosphorylation site, thus constitutively active GSK3β, develop a locomotor hyperactivity phenotype reminiscent of hyperdopaminergic DAT-KO mice (49). Finally, mice lacking the Akt isoform Akt1 also show enhanced disruption of sensorimotor gating in prepulse inhibition (PPI) tests by amphetamine, but not by the glutamate NMDA receptor blocker MK801 (28). Disruption of sensorimotor gating by amphetamine has been used classically as a behavioral paradigm to model psychosis in rodents, and this effect can be potently blocked by antipsychotics such as haloperidol (50). Because Akt1 is inhibited following the stimulation of D2-class receptors, the increased behavioral effect of amphetamine in Akt1-KO mice gives further support for the involvement of Akt inhibition in dopamine-related behavioral responses. Yet, dopamine regulates more than just locomotor activity and sensorimotor gating (51). Further detailed characterization of dopamine-related behaviors in various traditional or tissue-specific KO mice will be necessary to fully understand the functions of βArr2, Akt, and GSK3 in the expression of dopamine-related behaviors.

## REGULATION OF GSK3 BY 5-HT

In addition to its role in dopamine D2 receptor signaling, GSK3β has also been implicated in brain 5-HT functions. Drugs acting on 5-HT neurotransmission such as selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase (MAO) inhibitors, and tricyclic antidepressants have been shown to inhibit GSK3β by increasing its amino-terminal phosphorylation in many brain regions, including the frontal cortex, hippocampus, and striatum of normal mice (52–55). Furthermore, severe 5-HT deficiency in mice expressing a loss-of-function mutant form of the rate-limiting

enzyme for neuronal 5-HT synthesis, tryptophan hydroxylase 2 (tph2) (56–58), results in an about two fold increase in GSK3 activity in the frontal cortex (55).

Two serotonin receptors, the 5-HT1A and the 5-HT2A, appear to play antagonistic roles in regulating GSK3β activity (52, 53). Administration of the 5-HT1A agonist 8-OH-DPAT or of the 5-HT2A antagonist LY53857 to WT mice results in increased brain GSK3β phosphorylation (52). This suggests that 5-HT can inhibit GSK3β by acting through 5-HT1A receptors whereas activation of 5-HT2A receptors would result in GSK3β activation. However, it should be mentioned that the 5-HT2A agonist DOI and the 5-HT1A antagonist WAY100635 did not affect brain GSK3β activity (52), thus leaving the question of the relative contribution of different 5-HT receptors to the regulation of GSK3β only partially addressed. Furthermore, the mechanism by which 5-HT inactivates GSK3β appears to be independent from Akt as administration of SSRIs to WT or DAT-KO mice did not increase Akt activity in different brain regions (24, 53).

**5-HT1A and 5-HT2A receptors:** 2 of more than 14 different GPCRs that mediate the effects of 5-HT in the brain

**Anxiolytic:** a class of therapeutic agents that relieve anxiety

## BEHAVIORAL CONSEQUENCES OF 5-HT/GSK3β SIGNALING MODULATION

Recent evidence also supports a role for GSK3β in the regulation of behavior by 5-HT. In normal mice, GSK3 inhibitors, including lithium and AR-A014418, reduced immobility in the forced swim test, thus mimicking the action of antidepressants (47, 59). Similar behavior in this test was also observed (59, 60) in GSK3β haploinsufficient mice (48), which display a 50% reduction in the expression of this kinase. However, although immobility in the forced swim test is predictive of the antidepressant effects of SSRIs, multiple neurotransmitter systems, including norepinephrine and dopamine (61), can also provide complex control of behavior in this test.

A recent study conducted on mice expressing a loss-of-function tph2 mutant has provided direct evidence of an involvement of GSK3β in the behavioral functions controlled by brain 5-HT (55). These mice express a R439H mutant of the mouse tph2 that is similar to a human mutation (R441H) identified in a small cohort of treatment-resistant depressive patients (62). Mice with the R439H mutant display ~80% reduction in brain 5-HT synthesis when this mutation is present in a homozygous state. Furthermore, 5-HT deficiency in tph2 mutant mice leads to behavioral abnormalities in tests assessing 5-HT-mediated emotional states such as anxiety and aggression. Interestingly, reduced 5-HT synthesis is accompanied by a concomitant activation of GSK3β in the frontal cortex of these mice, thus providing a good experimental system to examine the contribution of GSK3 to behavioral abnormalities resulting from 5-HT deficiency. Administration of the selective GSK3β inhibitor TDZD-8 to these mice resulted in a reversal of 5-HT-associated behavioral phenotypes in tests evaluating 5-HT-associated antidepressant (63–65) and anxiolytic (66, 67) drug effects. Breeding of tph2 knockin to GSK3β haploinsufficient mice resulted in a complete rescue of behavioral phenotypes associated with 5-HT deficiency in mice lacking one allele of the *gsk3b* gene. Taken together, these data strongly support a role of GSK3-mediated signaling in the behavioral effects of 5-HT.

## AKT, GSK3, AND THE EFFECTS OF ANTIDEPRESSANTS AND ANTIPSYCHOTICS

The action of SSRIs and other 5-HT-associated antidepressants on GSK3β as well as the apparent antidepressant-like action of GSK3 inhibitors in behavioral tests are strongly suggestive of an involvement of this kinase in the effects of antidepressants (47, 52, 55). However, more investigations are needed to firmly establish this possibility. It would be of interest to examine whether antidepressants acting on neurotransmitter systems other than 5-HT can also exert an inhibitory

effect on GSK3. Furthermore, a closer examination of the effects of SSRIs in mice lacking both GSK3 isoforms in brain would be needed to establish whether GSK3 is essential for the behavioral action of these drugs.

**Extrapyramidal side effects:** various movement disorders associated with the use of certain antipsychotic (neuroleptic) drugs

**Negative symptoms:** A loss or absence of normal traits or ability to experience emotions associated with a form of schizophrenia

**Wnt (named for Wg[wingless] and Int genes):** Morphogen that binds to Frizzled to mediate various developmental responses such as body axis specification, neural tube formation, and cancer

Typical antipsychotics such as haloperidol are thought to exert most of their action by blocking D2-class dopamine receptors, thus supporting a role for dopaminergic neurotransmission in the etiology of schizophrenia (68). It is thus possible that regulation of the Akt/GSK3 signaling pathway by D2 receptors could be critical for the action of typical antipsychotics (23, 28, 30). In addition, so-called atypical antipsychotics have been shown to either activate Akt or to mimic Akt activity by increasing the phosphorylation of its substrates GSK3$\alpha$ and $\beta$. The term atypical antipsychotic designates a class of structurally unrelated antipsychotic compounds characterized by reduced incidence of extrapyramidal side effects, improvement of negative-symptoms of schizophrenia, and a preferential action on symptoms related to cognition and mood (6). Atypical antipsychotics can be also distinguished functionally from typical antipsychotics by their reduced affinity and lower selectivity for dopamine D2-class receptors. Many atypical antipsychotics display, simultaneously, a strong affinity for 5-HT2A receptors (69). However, the precise nature of their therapeutic target is still a subject of debate.

The atypical antipsychotic clozapine has been shown to act as an enhancer of Akt/GSK3 signaling in cell culture systems (70). In vivo, acute or subchronic administration of several atypical antipsychotics, including olanzapine, risperidone, quetiapine, clozapine, and ziprasidone, results in an inhibition of GSK3$\beta$ that reproduces the action of Akt in different brain regions (53, 71). Because both dopamine and 5-HT affect the activity of GSK3 it is critical to establish whether any or both of these neurotransmitters are responsible for the regulation of GSK3 by atypical antipsychotics. Alternatively, it is possible that other signal transduction systems may also be involved. Notably, investigation conducted in pheochromocytoma (PC12) and neuroblastoma (SH-SY5Y) cells have pointed toward a contribution of components of the Wnt signal transduction pathway in the regulation of GSK3 by antipsychotics (72).

The fact that the Akt/GSK3 signaling pathway is a downstream target of two classes of antipsychotics that have overlapping therapeutic action but different profiles of side effects is intriguing. It is tempting to speculate that this pathway may play a pivotal role in the therapeutic action of antipsychotics and that other biochemical responses to these different types of antipsychotics may determine their divergent side effect potential (8). However, as in the case of antidepressants, further detailed studies are needed to firmly establish this possibility.

## AKT/GSK SIGNALING AND THE EFFECTS OF LITHIUM

Lithium is one of the most commonly prescribed drugs for the treatment of bipolar disorders (73). This agent is also occasionally used for other psychiatric conditions as combination therapy along with drugs targeting central monoaminergic transmission (74–76).

Multiple direct and indirect molecular targets of lithium have been identified over the years (75, 77–79). However, the mechanism or mechanisms by which lithium salts exert their therapeutic effects in mental disorders are still not well understood (75). Among other actions, lithium has been shown to directly inhibit GSK3 isoforms (77, 78), possibly by competing with magnesium for its association with these kinases (80–82). However, the therapeutic relevance of this finding has been unclear mostly because of the high $K_i$ of lithium for GSK3$\alpha/\beta$ (75, 83). In neuronal cells, lithium can also affect both isoforms of GSK3 indirectly by activating Akt, thus resulting in increased phosphorylation/inactivation of these kinases by Akt (84). Importantly, Akt activation and indirect inhibition of GSK3 by lithium has been shown to occur in brain following acute

administration (23, 85) or chronic treatment resulting in therapeutically relevant serum lithium concentrations in rodents (85, 86).

There is also evidence for an involvement of the Akt/GSK3 signaling cascade in the behavioral actions of lithium in experimental animals. When given acutely, lithium antagonizes the development of dopamine-dependent locomotor behaviors in rodents by interfering with regulation of the βArr2/Akt/GSK3 signaling pathway by D2 receptors (23, 87, 88). Furthermore, pharmacological or genetic inhibition of GSK3β in rodents recapitulates many behavioral effects of lithium (23, 47, 59), whereas overexpression of an activated GSK3β in mice reproduces behavioral correlates of hyperactivity and mania (49).

## LITHIUM INTERFERES WITH THE REGULATION OF GSK3 BY AKT AND βARR2

A recent study by our laboratories has provided more direct evidence of an involvement of Akt/GSK3 signaling in the effects lithium (85). When administered acutely or chronically to βArr2-KO mice, lithium fails to activate Akt and indirectly inhibit GSK3 as it does in the striatum of WT animals. βArr2-KO mice also lose responsiveness to both acute and chronic lithium in various behavioral tests.

The nonresponsiveness of βArr2-KO to lithium is correlated with a biochemical effect of lithium on the formation of the Akt:βArr2:PP2A signaling complex. Series of coimmunoprecipitation experiments indicated that therapeutically relevant lithium concentrations (0.5–1 mM) are sufficient to destabilize the Akt:βArr2:PP2A both in vitro and in the brain of living mice. This could potentially explain the lack of effect of lithium in βArr2-KO mice because this complex cannot be formed in these mutants (25, 85). The exact mechanism through which lithium interferes with the formation of the Akt:βArr2:PP2A signaling complex needs further investigation. However, preliminary observations suggest that this complex is dependent on magnesium for its stability, and that a competition between lithium and magnesium for binding to at least one of the complex's components may contribute to the action of lithium (80, 85).

Taken together, these findings provide direct in vivo evidence that lithium exerts some of its biochemical and behavioral effects by interfering with a β-arrestin signaling complex involved in the regulation of Akt and GSK3β. Akt activity in vivo is regulated by signaling modalities associated with its phosphorylation/activation or with its dephosphorylation/inactivation (**Figure 2**, **3**). By disrupting the formation of the Akt:βArr2:PP2A signaling complex that normally promotes Akt dephosphorylation (25), lithium would thus increase Akt activity, thereby resulting in more pronounced phosphorylation/deactivation of GSK3 (85). This biochemical mechanism reconciles the effect of therapeutically effective lithium concentrations with its action on Akt/GSK3 signaling. However, it is unlikely that lithium has a single mechanism of action, and it is possible that other mechanisms such as the inhibition of inositol monophosphatase (79) also contributes to the pleiotropic effects of this pharmacological agent on behavior. Nevertheless, the identification of this novel mechanism of action for lithium may provide new insight into mechanisms of mood regulation and thus lead to unexplored research avenues to understand devastating human disorders such as major depression and bipolar disorder.

## EVIDENCE FOR A ROLE OF AKT AND GSK3 IN THE EFFECTS OF OTHER MOOD STABILIZERS

Apart from lithium, a handful of unrelated mood stabilizers are also currently prescribed for mood disorders (73). There is actually evidence for an action of two of these, valproate and lamotrigine, on

the regulation of the Akt/GSK3 signaling pathway. Several groups have reported that valproate inhibits GSK3 in vitro (89, 90). However, others have not been able to replicate this finding, or found significant inhibition only at concentrations above therapeutic levels (90). Although its direct effects on GSK3 are controversial, valproate exerts effects consistent with inhibition of GSK3 in cell culture. As with lithium, valproate treatment of SH-SY5Y cells or WT animals at therapeutically relevant concentrations results in activation of Akt and an increase in GSK3 inhibitory phosphorylation (91). Alternatively, valproate also potentiates the phosphorylation of both GSK3 isoforms in response to lithium in primary embryonic cortical neuron cultures (92). Furthermore, both valproate and lamotrigine have been shown to cause decreased phosphorylation of GSK3 substrates in several cell culture systems (90, 91), thus suggesting that these two mood stabilizers may potentially affect GSK3 activity and behavior by acting on upstream signaling molecules such as Akt.

**β-catenin:** intracellular signaling molecule downstream of the Wnt signaling pathway, which is a substrate of GSK3

## AKT AND GSK3 TARGETS IN THE REGULATION OF BEHAVIOR

Although there is extensive literature on the regulation of Akt and GSK3 by monoamines, the identity of the downstream targets of Akt/GSK3 signaling involved in the regulation of dopamine- and 5-HT-mediated behaviors has remained elusive. Both Akt and GSK3 have multiple substrates, including proteins involved in cellular processes as diverse as metabolism, cell survival/death, cytoskeletal organization, and regulation of gene expression (17, 20, 93, 94). Here we provide a brief overview of the possible involvement of a few of these targets that have recently been investigated in the context of psychotropic drug effects.

### β-Catenin

β-catenin is a multifunction protein that can act both as a transcription factor and as a scaffolding molecule in the formation of adherens junctions. In this latter function, β-catenin interacts with cadherins and α-catenin to anchor the junctional complex with the actin cytoskeleton. Formation of such complexes may play a role in synaptic plasticity because β-catenin is recruited to dendritic spines following depolarization (95). Moreover, it has been shown that a reduction in the cytoplasmic levels of β-catenin and other members of the catenin/cadherin complex can reduce dendritic arborization in cultured hippocampal neurons (96). In the Wnt signaling cascade, phosphorylation of unassembled cytoplasmic β-catenin by GSK3 leads to its ubiquitination and subsequent degradation by the ubiquitin/proteosome system (97). Thus it is possible that a modulation of GSK3 by monoamines and psychotropic drugs may lead to changes in β-catenin levels that may affect synapse morphology and gene expression. Chronic lithium treatment has been shown to increase β-catenin levels or the expression of a reporter for β-catenin-dependent gene expression in different regions of the mouse brain (59, 85, 98). Overexpression of β-catenin in transgenic mice has been shown to phenocopy the effects of lithium on dopamine-dependent locomotor hyperactivity and in tests used to evaluate antidepressant drug effects in rodents (98). However, a tissue-specific knockout of β-catenin in the adult mouse forebrain had little behavioral effect (99), thus suggesting that β-catenin may be important for the action of psychotropic drugs whereas it plays a relatively minor role in regulation of normal behavior by monoamine neurotransmitters.

### Glutamate Receptors

There is also evidence for a possible role of the Akt/GSK3 signaling pathway in the regulation of synaptic plasticity and ionotropic glutamate receptor functions. These receptors and glutamate neurotransmission in general are strongly implicated in the etiology of psychiatric disorders such

as schizophrenia (1, 100–102). The AMPA and NMDA ionotropic glutamate receptors are heteromultimeric ion channels whose trafficking and expression are closely regulated by complex networks of signaling molecules and scaffolding proteins (103). The monoamine neurotransmitters dopamine and 5-HT have been shown to affect synaptic plasticity by regulating the expression, phosphorylation, and trafficking of ionotropic glutamate receptors and associated proteins in neurons (104–106). Independent studies showed that activation of GSK3 inhibits the development of long-term potentiation (LTP) (107) whereas its inhibition prevents the development of long-term depression (LTD) in rat hippocampal slices (108, 109). Furthermore, GSK3 also appears to affect the trafficking and reduce cell surface expression of the NMDA receptor subunits NR2A/B both in hippocampal slices and cultured cortical neurons (107, 110). However, whether these actions of GSK3 are relevant for the role of this kinase in monoamine receptor signaling and the action of psychotropic drugs still has to be established.

**Long-term potentiation or depression (LTP, LTD):** two states of AMPA-NMDA ionotropic glutamate receptor transmission resulting in enhanced or depressed communication between two neurons

## Regulation of Circadian Rhythms

The regulation of the fly GSK3 ortholog shaggy by 5-HT has been shown to modulate circadian entrainment in *drosophila* (111). It has been proposed that disruption of circadian rhythm plays a role in diverse human mental illnesses such as seasonal depression (112). A recent genetic study conducted on two separate cohorts has suggested an association between circadian genes and bipolar disorders (113). At the cell biology level, both lithium and D2 receptors, which regulate the activity of GSK3, affect either circadian rhythm–regulated gene expression (114, 115) or behavior (116), whereas GSK3β has been shown to regulate mammalian circadian protein functions in cultured cells (117). Thus, molecules involved in circadian regulation might also represent downstream targets of Akt/GSK3 signaling involved in the regulation of behavior by monoamines and psychotropic drugs.

## AKT, GSK3, ARRESTIN, AND THE ETHIOLOGY OF PSYCHIATRIC DISORDERS

The involvement of Akt, GSK3, and βArr2 in behavioral responses to dopamine and/or 5-HT and their possible involvement in the action of psychotropic drugs raises the possibility that these molecules may also contribute to the development of several psychiatric conditions such as schizophrenia, bipolar disorders, and major depression.

Multiple independent studies have revealed a link between a deregulation of Akt signaling and schizophrenia. Akt1 and Akt3 are the principal Akt isoforms expressed in the brain (118). These proteins show strong homology, but are encoded by different genes. A significant association of Akt1 haplotypes with schizophrenia has been reported in several independent cohorts of schizophrenic patients from different origins following transmission-disequilibrium tests (28, 119–123). Furthermore, a reduction in Akt protein levels has been observed in the brain of schizophrenic patients (28). Because stimulation of D2-class receptors by dopamine results in an inhibition of Akt (23, 25), it is possible that a partial loss-of-function of Akt1 in schizophrenia may cause exacerbated responses to D2 receptor stimulation, thus contributing to the development of the pathology. Alternatively, it is possible that mutations in other susceptibility genes for schizophrenia may also exacerbate Akt-mediated D2-receptor signaling by inhibiting Akt. In line with this, products of two schizophrenia susceptibility genes, Disrupted-In-Schizophrenia 1 (DISC1) and Neuregulin 1 (NRG1), have been shown to affect Akt phosphorylation in different cell culture systems (124–126), thus suggesting that the Akt/GSK3 signaling pathway also contributes to the complex set of pathological events induced by these mutant gene products in schizophrenia.

**G protein–coupled receptor kinase 3 (GRK3):** one of five nonvisual GPCR kinases that recognize and phosphorylate activated GPCRs and promote arrestin binding

There is presently no known association between the genetic locus encoding GSK3α and psychiatric disorders. However, some evidence points toward an involvement of GSK3β in depression, psychosis and responsiveness to lithium therapy. Reduced GSK3β phosphorylation, which results in kinase activation, in the prefrontal cortex has been associated with major depressive disorders in a cohort of suicide victims (127). Several studies have also reported an association between a -50T/C polymorphism in the GSK3β gene promoter and responsiveness to lithium therapy or the occurrence of psychotic symptoms in patients with mood disorders (128–130).

The identification of a βArr2 signaling complex as a target of D2 dopamine receptor, antipsychotics, and lithium raises the possibility that deregulation of β-arrestin functions may be involved in the development of psychiatric disorders. There are currently no known associations between the gene encoding βArr2 and any psychiatric conditions. However, a region of chromosome 22q12 containing the G protein–coupled receptor kinase 3 (GRK3) gene, a kinase that phosphorylates GPCR to promote β-arrestin recruitment, has been identified as a susceptibility locus for bipolar disorder (131). Transmission disequilibrium analyses indicate that two 5′-UTR/GRK3 promoter polymorphisms may be associated with bipolar disorder (131), and different mood stabilizers have been reported to affect the subcellular localization of GRK3 in the rat frontal cortex (132). In light of these observations, it is possible that a perturbation of GRK3 function may enhance βArr2 mediated signaling in bipolar disorder and that lithium can antagonize these changes by disrupting the Akt:βArr2:PP2A-signaling complex.

## CONCLUSION AND FUTURE PERSPECTIVES

Characterization of a role for the Akt/GSK3 signaling pathway in responses to dopamine, 5-HT, and psychotropic drugs in vivo has resulted in identification and validation of the diverse signaling molecules of this pathway as important modulators of behavior (**Figure 4**). Regulation of this pathway by at least two monoamine neurotransmitters (dopamine and 5-HT) and three classes of psychotropic drugs (antipsychotics, mood stabilizers, and antidepressants) suggests that Akt and GSK3 can act as signal integrators, allowing the precise coordination and cooperation of 5-HT and dopamine receptors signaling responses, with each other or with those related to other neurotransmitters, hormones, and growth factors (**Figure 4**). Inhibition of GSK3β may also provide a rationale for the mutual augmenting effects of lithium, antidepressants, and antipsychotics, which are often used as combination therapies for various psychiatric conditions (76, 133).

Although the Akt/GSK3 signaling pathway is important for the regulation of behavior, it would be presumptive to assume that this is the only cell signaling mechanism targeted by the psychotropic drugs 5-HT and dopamine. Multiple other signaling pathways are also modulated, albeit not necessarily in a synchronous fashion, by these drugs and neurotransmitters. However, none of these signaling intermediates appears to be an obligatory converging point for all actions of dopamine, 5-HT, or a given pharmacological agent. For example, mice lacking DARPP-32 or βArr2 show deficits in dopamine responses, but do not exhibit behavioral phenotypes comparable to those observed in mice totally deficient for dopamine (25, 134–137). This suggests that the biological effects of monoamines and psychotropic drugs are supported by complex signaling networks that regulate multiple molecular pathways in parallel.

It has recently become apparent that different drugs acting on a given GPCR may elicit a wide range of signaling responses (8–10). Evidence from cell culture systems has shown that mutated peptidic ligands for the angiotensin II type 1A or the parathyroid hormone receptor (PTH1R) can preferentially activate β-arrestin-mediated signaling mechanisms while exerting minimal activation of canonical G protein–mediated signaling (138, 139). In the same way, different ligands of the 5-HT2 receptors also appear to elicit pathway-selective signaling responses in the mouse frontal

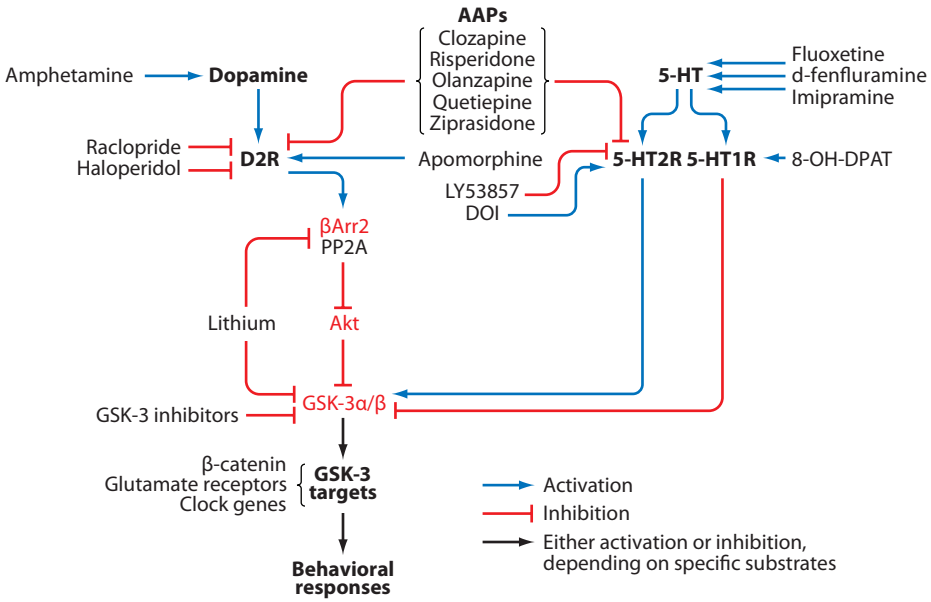


**Figure 4**

Regulation of Akt/GSK3 signaling by drugs affecting dopamine and 5-HT neurotransmitter systems and related signaling events in the brain. Putative downstream target of Akt/GSK3 signaling implicated in behavioral regulation are indicated. Behavioral changes in dopaminergic or 5-HT responses have been reported in Akt1- and βArr2-KO mice and in GSK3β-HET mice (*orange*). APPs: Atypical antipsychotics.

cortex (140). Because the Akt/GSK3 signaling pathway may be regulated by different neurotransmitters through both G protein–dependent and βArr2-dependent mechanisms, it is possible that drugs acting on dopamine D2-class or 5-HT receptors may have different effects on Akt/GSK3 signaling although binding to the same receptor. Intriguingly, a recent study using bioluminescence resonance energy transfer (BRET) indicates that several typical and atypical antipsychotics are antagonists for agonist-induced recruitment of βArr2 to the D2 receptor while having divergent pharmacological effects (antagonist, partial agonists, inverse agonists) on the regulation of cAMP by this same receptor (141). In light of these recent observations, it is tempting to speculate that antipsychotics may exert their shared therapeutic effects by blocking βArr2-mediated D2 signaling while inducing some of their divergent side effects through modulation of other signaling pathways. Far from a problem for drug development; understanding the complexity of signaling networks and pathway selective responses in relevant brain regions could thus allow the development of new drugs that might attain desired therapeutic actions while avoiding undesired side effects.

## SUMMARY POINTS

1. The brain monoaminergic systems play an important role not only in regulating a host of behaviors but also as targets of the most common therapeutic interventions for psychiatric disorders.
2. Monoamines mediate their physiological effects through action on GPCRs that can signal through both the activation of conventional G proteins and the recruitment of β-arrestin to scaffold signaling complexes.

3. In vivo, the Akt/GSK3 signaling pathway is potently modulated by changes in monoamine homeostasis.
4. Activation of D2-like receptors inhibits the phosphorylation of Akt, leading to an activation (dephosphorylation) of GSK3 through a G protein–independent mechanism involving a complex of Akt:PP2A scaffolded by β-arrestin 2.
5. Lithium inhibits the behavioral actions of dopamine via disruption of the D2 receptor–mediated complex of Akt:βArr2:PP2A.
6. Pharmacological manipulations that enhance brain 5-HT levels inhibit GSK3 whereas genetic impairment of 5-HT synthesis leads to increased GSK3 activity and pharmacological or genetic inhibition of GSK3 reverses the behavioral deficits resulting from low brain 5-HT.
7. The Akt/GSK3 signaling pathway appears to be an important target of psychotropic drugs such as antidepressants, antipsychotics, and mood stabilizers.
8. Evidence indicates that the Akt/GSK3 pathway may be deregulated in various psychiatric disorders such as schizophrenia and bipolar disorder.

### FUTURE ISSUES

1. Downstream targets of Akt and/or GSK3 in the action of psychotropic drugs need to be identified and investigated.
2. Whether the role of the Akt/GSK3 signaling cascade in mediating behavioral outcomes and actions of psychotropic drugs is confined to certain brain areas is of interest to explore.
3. The role of the Akt/GSK3 signaling pathway in the action of other neurotransmitters should be investigated.
4. Examination of whether 5-HT receptors regulate the Akt/GSK3 pathway by the same G protein–independent mechanism as D2 dopamine receptors is a question of interest.
5. Given that GPCRs can signal through distinct mechanisms, the contribution of different signaling modalities for specific cellular and behavioral responses should be determined.
6. The apparent selectivity of the action of lithium on D2 receptor engagement of the Akt/GSK3 pathway raises the possibility that other psychotropic drugs may also show functional signaling pathway selectivity.
7. The contribution of Akt, GSK3, and related molecules to psychiatric disorders need to be examined further.

## DISCLOSURE STATEMENT

M.G.C. serves on the Scientific Council of NARSAD and on the Scientific Advisory Board of Acadia Pharmaceutical.

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