Multiple recent lines of evidence have underscored the potential role of glycogen synthase kinase-3 (GSK3) as a common molecular signal integrator and therapeutic target for different classes of psychiatric drugs (Figure 1). GSK3α and GSK3β are two closely related serine/threonine kinases originally associated with the regulation of glycogen synthesis in response to insulin (Embi et al., 1980). These constitutively active kinases are regulated negatively through the phosphorylation of single serine residues, Ser21 (GSK3α) and Ser9 (GSK3β), of their regulatory amino-terminal domain (Frame and Cohen, 2001). The protein kinase Akt/PKB has been shown to inhibit both GSK3 isoforms in response to insulin and insulin growth factors (Cross et al., 1995). However, other protein kinases such as PKA and PKC can also regulate GSK3 in different cellular systems (Frame and Cohen, 2001). Apart from its function in glycogenesis, GSK3 plays a role in a host of physiological processes including neurodevelopment, cell proliferation and apoptosis. Moreover, dysregulation of GSK3 function is involved in tumour proliferation as well as in the formation of neurofibrillary tangles in Alzheimer’s disease (Woodgett, 2003).

The first suggestion of an involvement of GSK3 in the biological action of psychotropic drugs came from the identification of the mood stabilizer lithium as a direct GSK3 inhibitor (Klein and Melton, 1996). Interestingly, lithium can also inhibit GSK3 activity in cells through an indirect mechanism (Figure 1) involving Akt activation (Beaulieu et al., 2004; Chalecka-Franaszek and Chuang, 1999; Zhang et al., 2003). Acute and chronic administration of lithium has been shown to inhibit brain GSK3 activity in mice as revealed by enhanced regulatory amino-terminal domain phosphorylation (Beaulieu et al., 2004; De Sarno et al., 2002). Moreover, GSK3 inhibitors or reduction of GSK3β expression by genetic manipulation both reproduce some of the behavioural action of lithium in rodents indicating that inhibition of GSK3 may contribute to lithium’s psychopharmacological actions (Beaulieu et al., 2004; O’Brien et al., 2004).

Further investigation of the involvement of GSK3 in mood disorders has revealed that GSK3β can be regulated by antidepressants acting on serotonergic (5-HT) neurotransmission (Li et al., 2004). Administration of either specific serotonin reuptake inhibitors (SSRIs) or monoamine oxidase (MAO) inhibitors to mice results in a substantial increased phosphorylation (deactivation) of brain GSK3 (Figure 1). Moreover, GSK3 inhibitors have been shown to have some antidepressant-like effects in rodents (Gould et al., 2004) while electroconvulsive shock therapy, a common approach for the management of drug-resistant depression, may also affect GSK3 regulation (Roh et al., 2003). Interestingly, antidepressants are sometimes used in conjunction with lithium to increase their efficacy (De Montigny et al., 1981). Two 5-HT receptors appear to play important and antagonistic roles in regulating GSK3β, stimulation of 5-HT1A receptors leading to kinase inhibition while stimulation of 5-HT2A receptors has the opposite effect (Li et al., 2004).

Finally, recent evidence revealed a link between dysregulation of the Akt/GSK3 signalling pathways, schizophrenia and dopaminergic neurotransmission (Figure 1). Significant association of Akt1 haplotypes with schizophrenia has been reported following transmission disequilibrium tests while reduced Akt protein levels were shown in the brains of schizophrenic patients (Emamian et al., 2004). 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 aetiology of schizophrenia (Snyder, 1976). Importantly, prolonged stimulation of striatal D₂ class receptors by dopamine results in an inhibition of Akt leading to an activation of both GSK3 kinases (Beaulieu et al., 2004, 2005). The regulation of the Akt/GSK3 signalling pathway by dopamine is mediated by the formation of a signalling protein complex composed of Akt, βArrestin-2 and protein phosphatase 2A (Beaulieu et al., 2005). Administration of haloperidol or the selective D₂ class-receptor antagonist raclopride prevents the regulation of Akt by dopamine or enhanced Akt phosphorylation in animal models (Alimohamad et al., 2005; Emamian et al., 2004). Furthermore, genetic inactivation of Akt1 or GSK3β, uncoupling of Akt from dopamine receptors and administration of GSK3 inhibitors antagonizes dopamine-dependent changes in locomotor activity and sensory motor gating in mice (Beaulieu et al., 2004, 2005; Emamian et al., 2004; Gould et al., 2004).

An article published in this issue of the International Journal of Neuropharmacology (Li et al., 2006) reports that apart from being similarly affected by lithium, MAO inhibitors, SSRIs and haloperidol, GSK3β is also negatively regulated by atypical antipsychotics (AAPs) in vivo and that the action of these drugs on GSK3 can be potentiated by antidepressants. The term atypical antipsychotic was originally coined to distinguish clozapine from older antipsychotics such as haloperidol and chlorpromazine (Kapur and Remington, 2001; Meltzer, 1991). Subsequently, the term AAPs has come to designate a whole class of antipsychotic drugs characterized by a reduced incidence of extrapyramidal side-effects, improvement of ‘negative-symptoms’ of schizophrenia and a preferential action on symptoms related to mood and cognition, a characteristic that has led to their use in the management not only of schizophrenia but also of mood disorders. Functionally, AAPs can be distinguished from typical antipsychotics by their reduced affinity and lesser specificity for dopamine D₂ receptors. Notably many AAPs display a strong affinity for 5-HT₁A receptors. However the exact nature of the main therapeutic target of AAPs remains controversial.

Previous investigations have shown that clozapine can act as an enhancer of Akt/GSK3 signalling in a cell culture system (Kang et al., 2004) and that sub-chronic administration of risperidone can increase GSK3β phosphorylation and expression in the rat prefrontal cortex (Alimohamad et al., 2005). Building from these observations and their previous work on the regulation of GSK3β by 5-HT (Li et al., 2004), Li and colleagues undertook to examine the impact of AAPs on GSK3 phosphorylation in different brain regions. In a first set of experiments the authors showed that acute administration of risperidone produced a rapid, transient and dose-dependent phosphorylation/inhibition of GSK3β in different regions of the mouse brain. They then extended their investigation to several other AAPs including olanzapine, clozapine, quetiapine as well as ziprasidone and showed that all these AAPs have a common inhibitory action on GSK3β. Finally, the authors used combined administration of antidepressants acting on 5-HT neurotransmission potentiated the effect of AAPs on GSK3β phosphorylation and extends the action of these drugs to GSK3α.

In their article, Li et al. (2006) left somewhat unresolved the question of the mechanism by which antidepressants and AAPs inhibit GSK3. From previous work on the regulation of GSK3 by 5-HT and dopamine (Beaulieu et al., 2004; Li et al., 2004) Li et al. (2006) postulate that blockade of 5-HT₁A and, to a lesser extent, of D₄ receptors by AAPs can contribute to the effect of these drugs while antidepressants would act on GSK3 by stimulating 5-HT₁B receptors following enhancement of 5-HT neurotransmission.
However, the authors do not explain why 5-HT appears to preferentially inhibit GSK3 while acting simultaneously on both 5-HT↦ and 5-HT↧ receptors. Li et al. also reported that AAPs do not enhance Akt phosphorylation thus suggesting that the mechanism by which AAPs regulate GSK3 may differ from the action of haloperidol and other D2 receptor antagonists which have been shown to enhance Akt activity (Beaulieu et al., 2004, 2005; Emamian et al., 2004).

Independently of the molecular mechanism by which it occurs, Li et al.’s observation of an action of AAPs on GSK3 activity in vivo brings further support for a function of GSK3 in the action of an ever-expanding number of psychoactive drugs. Moreover, the fact that GSK3 can be similarly affected by different drugs often used in combination for the management of mood disorders and schizophrenia suggests that dysregulation of brain GSK3-mediated signalling may be involved in the development of common endophenotypes (Gottesman and Gould, 2003) of these different psychiatric disorders.

Finally the study of the action of AAPs on GSK3 phosphorylation underlines the importance to examine psychotropic drug potency with regard to their actions on integrative signalling mechanisms in vivo. High throughput screening of psychotropic drugs with therapeutic action have shown that many of these, like AAPs, modulate more then one neurotransmitter systems while more specific drugs acting on single neurotransmitter/receptor systems display lesser therapeutic potential (Roth et al., 2004). One possibility is that many of these drugs, like AAPs, have the potential to exert a compound action on integrative signalling pathways by acting through different receptors. Moreover, as in the case of GSK3, some signalling molecules may be common effectors of different drugs acting on different receptors and neurotransmitter systems. In-vivo studies of signalling changes induced by different psychiatric drugs may help to discover unsuspected common effectors of these drugs that can become interesting new targets for the management of psychiatric disorders.

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Statement of Interest
None.

References


