



Modulation of GSK-3 as a therapeutic strategy on tau pathologies

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Glycogen synthase kinase-3 (GSK-3) is ubiquitously expressed and unusually active in resting, non-stimulated cells. In mammals, at least three proteins (α , β 1, and β 2), generated from two different genes, *gsk-3 α* and *gsk-3 β* , are widely expressed at both the RNA and protein levels although some tissues show preferential expression of some of the three proteins. Control of GSK-3 activity occurs by complex mechanisms that depend on specific signaling pathways, often controlling the inhibition of the kinase activity. GSK-3 appears to integrate different signaling pathways from a wide selection of cellular stimuli. The unique position of GSK-3 in modulating the function of a diverse series of proteins and its association with a wide variety of human disorders has attracted significant attention as a therapeutic target and as a means to understand the molecular basis of brain disorders. Different neurodegenerative diseases including frontotemporal dementia, progressive supranuclear palsy, and Alzheimer's disease, present prominent tau pathology such as tau hyperphosphorylation and aggregation and are collectively referred to as tauopathies. GSK-3 has also been associated to different neuropsychiatric disorders, like schizophrenia and bipolar disorder. GSK-3 β is the major kinase to phosphorylate tau both *in vitro* and *in vivo* and has been proposed as a target for therapeutic intervention. The first therapeutic strategy to modulate GSK-3 activity was the direct inhibition of its kinase activity. This review will focus on the signaling pathways involved in the control of GSK-3 activity and its pathological deregulation. We will highlight different alternatives of GSK-3 modulation including the direct pharmacological inhibition as compared to the modulation by upstream regulators.

Keywords: GSK-3, kinases modulation, tau pathologies, Alzheimer

TAU HYPERPHOSPHORYLATION AS A COMMON MARKER IN TAU PATHOLOGIES

A number of neurodegenerative disorders present intraneuronal proteinaceous aggregates, denoted as neurofibrillary tangles (NFT), as common markers of disease. NFT are made up of hyperphosphorylated, aggregated tau. Thus, they are collectively referred as tauopathies, and include disorders such as frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), and Alzheimer's disease (AD), among others.

The mechanisms responsible for tau aggregation are still unknown. Therefore, understanding how tau is regulated may be essential to identify the origin of tau aggregate formation. The regulation of tau takes place predominantly through post-translational modifications where tau phosphorylation has been suggested to play a central role in tau aggregation. It is generally accepted that an increase in tau phosphorylation reduces its affinity for microtubules, resulting in neuronal cytoskeleton instability. Even though abnormal tau phosphorylation occurs in many of the tau pathologies mentioned above, tau phosphorylation appears not to be sufficient to induce tau aggregation (Buee et al., 2000; Hernandez et al., 2009). There are at least 85 putative phosphorylation sites in tau, 45 serines, and 35 threonines. It has

been shown that tau phosphorylation is regulated by many different kinases, including GSK-3 β , CDK5, MAPKs, PKA, PKB/Akt, PKC, PKN, and CaMKII (Hanger et al., 1992; Harr et al., 1996; Yu et al., 2009). The precise role of some of these kinases is still under investigation with particular interest on glycogen synthase kinase-3 (GSK-3). However, we do not discard the important role of other kinases such as CDK5, p38, etc. In fact, the role of CDK5 in tau phosphorylation and NFT formation has been clearly established in transgenic mice (Noble et al., 2003; Piedrahita et al., 2010).

Tau hyperphosphorylation could result from the inhibition of phosphatases. Indeed, earlier work indicates that phosphatase activity is decreased in AD brains (Gong et al., 1993; Rahman et al., 2005). In summary, a combination of kinases and phosphatases may be postulated to play a central role in tauopathies.

ROLE AND REGULATION OF GSK-3 ACTIVITY

Glycogen synthase kinase-3 is a serine/threonine protein kinase initially described to phosphorylate and inhibit glycogen synthase (Rylatt et al., 1980). GSK-3 has been evolutionary conserved and homolog genes have been identified in practically every eukaryotic genome examined including *Xenopus laevis*, *Drosophila*

melanogaster, and *Dictyostelium discoideum* (Ruel et al., 1993; Itoh et al., 1995; Kim et al., 1999).

In mammals, GSK-3 is encoded by two genes known as *gsk-3 α* and *gsk-3 β* (Woodgett, 1990; Frame and Cohen, 2001; Grimes and Jope, 2001) that encode three different proteins, GSK-3 α and two GSK-3 β proteins (β 1 and β 2; Mukai et al., 2002; Schaffer et al., 2003). These isoforms are almost identical (98%) but differ in their N- and C-terminal domains (Woodgett, 1990). It has been extensively established that GSK-3 plays an important role in various essential physiological processes, including cell cycle or survival-apoptosis (Pap and Cooper, 1998; Lucas et al., 2001a; Ferkey and Kimelman, 2002). It is well known that GSK-3 has a plethora of substrates, identified in many cell types and in all cellular compartments; i.e., metabolic proteins (Alessi et al., 1996), cytoskeletal proteins (Hanger et al., 1992), as well as transduction (Cohen, 1999) and transcription factors (Hart et al., 1998).

Glycogen synthase kinase-3 is a kinase differentially regulated by tyrosine and serine/threonine phosphorylation (Wang et al., 1994). One of the main characteristics of GSK-3 is that its activity is relatively high in resting, non-stimulated cells. For many years, it was believed to be a constitutively active kinase. However, it has become apparent that the activity of GSK-3 may be regulated by a variety of signals (Sayas et al., 2002) and many extracellular signals may induce a rapid and reversible decrease in enzymatic activity. Moreover, the regulation of GSK-3 activity has turned out to be much more complex than originally thought (Medina and Wandosell, 2011). The regulatory mechanisms of GSK-3 activity may be classified as follows.

REGULATION BY PHOSPHORYLATION

Two general mechanisms are involved in the regulation of GSK-3 activity, Ser/Thr phosphorylation of GSK-3 specific residues by other kinases, and Tyr phosphorylation, through auto-phosphorylation (Frame and Cohen, 2001; Harwood, 2001). Different regions can be identified in the GSK-3 structure that can be modified by phosphorylation: the first one corresponds to the amino-terminal domain and contains a serine residue at positions 21 in GSK-3 α and 9 in GSK-3 β . It has been undoubtedly demonstrated that phosphorylation of serine 21 or 9, correlates with inhibition of the kinase activity (Sutherland et al., 1993; Stambolic and Woodgett, 1994; Frame et al., 2001). Many protein kinases including Akt, ILK, PKA, p90Rsk are competent at phosphorylating GSK-3 at residues 21 and 9 *in vitro* and *in vivo* (Cross et al., 1995; Delcommenne et al., 1998; Fang et al., 2000).

Two other regulatory sites have been described: threonine 43, only present in the GSK-3 β isoform, may be phosphorylated by Erk (Ding et al., 2005) whereas p38 MAPK phosphorylates serine 389 and threonine 390 present in GSK-3 β (Thornton et al., 2008). In both cases, the data suggests that these phosphorylations may facilitate the competence of serine 9 to be phosphorylated rather than support a direct GSK-3 inhibition.

Conversely, an increase in tyrosine phosphorylation at residues 216 (GSK-3 β) or 279 (GSK-3 α) is in clear correlation with an increase on GSK-3 activity in neuronal cells, following exposure to lysophosphatidic acid (LPA; Sayas et al., 1999) or after neurotoxic insults such as β -amyloid or PrP (Munoz-Montano et al., 1997; Takashima et al., 1998; Perez et al., 2003b). Different candidates

have been reported to phosphorylate GSK-3 on tyrosine 216/279 including Pyk-2 and Fyn kinases *in vitro* or MEK1/2 in fibroblasts (Lesort et al., 1999; Hartigan et al., 2001). These data are in contrast with those reported in *D. discoideum* where there is convincing evidence demonstrating that ZAK 1 (Kim et al., 1999, 2002) is the kinase responsible for this tyrosine phosphorylation of GSK-3. However, no homolog of ZAK1 has been found in mammals.

More recently, an alternative hypothesis has been proposed for the regulation of GSK-3 tyrosine phosphorylation. This hypothesis suggests that phosphotyrosine 279/216 in GSK-3 corresponds to an intra-molecular auto-phosphorylation event (Cole et al., 2004). However, this hypothesis still lacks a cellular demonstration. Data generated in our laboratory indicated that not all pharmacological inhibitors of GSK-3 decrease the level of phosphotyrosine (Simon et al., 2008). Thus, in view of the tantalizing autoregulatory system proposed and taken all data together, we hypothesize that some as-yet-unidentified tyrosine kinases and phosphatases may also regulate GSK-3 activity.

REGULATION BY PROTEIN COMPLEX ASSOCIATION

It is well known that GSK-3 forms part of a multiprotein complex formed by axin and adenomatous polyposis coli (APC) among others. This protein complex is the core of the canonical Wnt signaling (for review see Moon et al., 2004). In the absence of ligand, β -catenin is phosphorylated by GSK-3 in this multiprotein complex and targeted for proteasome degradation (Aberle et al., 1997). In addition, different GSK-3-binding proteins have been described.

The first GSK-3-binding protein was denoted as FRAT (Li et al., 1999; Fraser et al., 2002) and three different FRATs have been characterized since then. Surprisingly, FRAT1 appears to act as an inhibitory system, whereas FRAT2 appears to increase GSK-3 activity (Yost et al., 1998; Stoothoff et al., 2005). More recently, a GSK-3 interacting protein symbolized by GSKIP, has been cloned and characterized. GSKIP can block phosphorylation of different substrates and functions as a negative regulator of GSK-3 β (Chou et al., 2006).

REGULATION BY PRIMING/SUBSTRATE SPECIFICITY

As a general rule, the specificity of many kinases is governed by a consensus sequence of amino acids present in their substrates. However, the crystal structure of human GSK-3 β has provided a model for the binding of pre-phosphorylated substrates to the kinase (Dajani et al., 2001; ter Haar et al., 2001; Noble et al., 2005). It is now evident that some GSK-3 substrates require a previous (*primed*) phosphorylation by a *priming* kinase. This primed residue (Ser or Thr) is usually located four amino acids, C-terminal to the Ser or Thr residue to be modified by GSK-3 (Dajani et al., 2001; ter Haar et al., 2001). Several priming kinases have been identified, such as cdk-5, PAR-1, casein kinase I, PKC, or PKA (Sengupta et al., 1997; Amit et al., 2002; Liu et al., 2003; Noble et al., 2003; Nishimura et al., 2004; Alonso Adel et al., 2006). However, is not completely established whether a second set of “*non-primed*” substrates may define a different group of functions (Twomey and McCarthy, 2006). In addition, different GSK-3 isoforms appear to exhibit distinct substrate preferences in the brain (Soutar et al., 2010).

REGULATION BY SUBCELLULAR LOCALIZATION

The presence of GSK-3 appears to be developmentally regulated in the brain (Takahashi et al., 1994) and, in fact, the developmental profile of GSK-3 α and GSK-3 β is different and the putative differential role of each isoform has been explored (Garrido et al., 2007). It is important to indicate that a portion of GSK-3, mostly β , has been associated with the growth cone. This GSK-3 pool appears to respond rapidly, being modified by phosphorylation and/or re-located in the growth cone, by external signals such as semaphorins (Eickholt et al., 2002) or NGF (Zhou et al., 2004). The presence of GSK-3 α and β in primary neurons have been reported in different neuronal compartments, like in axon and dendrites, as well as in the cytoplasm, endoplasmic reticulum (ER; Meares et al., 2011), nucleus, and the mitochondria (Grimes and Jope, 2001; Watcharasil et al., 2002; Bijur and Jope, 2003). With respect to the nuclear localization, GSK-3 may be involved in phosphorylation of many transcription factors such as: Cyclin D1, β -catenin, HSF-1, NFAT, and cAMP-response element-binding protein, among others (for review see Cohen and Frame, 2001; Harwood, 2001; Xu et al., 2009). Moreover, the nuclear presence of GSK-3 in the nucleus may also play a role in alternative splicing (Avila et al., 2004).

REGULATION BY PROTEOLYTIC CLEAVAGE

A new mechanism of GSK-3 regulation has been recently proposed. This regulation involves the removal by calpain of a fragment from the N-terminal region of GSK-3, including the regulatory serines 9/21 (Goni-Oliver et al., 2007). Interestingly, GSK-3 β has also been recently shown to be cleaved at the N-terminus (and subsequently activated) by matrix metallo-proteinase 2 (MMP-2) in cardiomyoblasts (Kandasamy and Schulz, 2009).

PHYSIOLOGICAL AND PATHOLOGICAL REGULATION OF GSK-3

GSK-3 PHYSIOLOGY

In neuronal development, GSK-3 has been reported to control many different aspects of neuronal and glial physiology, like morphogenesis and axonal polarity (Shi et al., 2004; Garrido et al., 2007), synaptogenesis (Lucas and Salinas, 1997), and cell survival (Pap and Cooper, 1998; Lucas et al., 2001a). Some of these cellular activities of GSK-3 are regulated by signals orchestrated by a wide set of extracellular ligands including growth factors, neurotrophic factors, neurotransmitters, and hormones but also by cell-cell interactions. Most of these extracellular factors trigger signaling pathways which correlate with the inhibition, or transient inhibition, of GSK-3 activity. In the case of insulin/IGF1 (Cross et al., 1995; Delcommenne et al., 1998; Fang et al., 2000) and NGF (Zhou et al., 2004) the regulatory role of Akt and/or ILK has been reported to be responsible for the increased inhibitory serine phosphorylation. More recently, we and others have shown that estradiol may also inhibit GSK-3 by a pathway modulated by PI3K-Akt (Cardona-Gomez et al., 2004; Mendez et al., 2005; Varea et al., 2009).

An alternative system of GSK-3 regulation is represented by the Wnt signaling pathway in which, in the absence of ligand, GSK-3 β phosphorylates β -catenin, as a part of a degradation signal (for review see, i.e., Moon et al., 2004; Rosso et al., 2005). When Wnt (at least some Wnt's) binds the Wnt receptor frizzled (*fz*), disheveled

(*Dsh*) inhibits the activity of GSK-3 β in a manner that is not fully understood. This system appears to be specific to GSK-3 β as no counterpart has been described for GSK-3 α to date. Some recent data suggests that this complex may be specific for the GSK-3 β 2 isoform (Castaño et al., 2010).

In addition, Reelin and Netrin signaling have been shown to regulate GSK-3 activity even though the exact mechanism is far from being fully elucidated. The binding of Reelin appears to induce signals which may activate GSK-3 (Gonzalez-Billault et al., 2005). In this pathway, the function of GSK-3 appears to be associated with CDK5, however, the specific system that controls GSK-3 activity has yet to be defined (Gonzalez-Billault et al., 2005). Similarly, Netrin 1 regulates, both *in vivo* and *in vitro*, the phosphorylation of neuronal MAP's, in a signaling pathway that depends essentially on the kinases GSK-3 and CDK5 (Del Rio et al., 2004).

As mentioned, GSK-3 is regulated by a plethora of membrane receptors, some of which show a specific subcellular localization in neurons. Among these receptors, some purinergic ATP/ADP receptors, such as P2 \times 7, P2Y1, or P2Y13, show a localized subcellular expression in neurons (Diaz-Hernandez et al., 2008; del Puerto et al., 2011). Purinergic receptors are expressed in glial and neuronal cells in the central and peripheral nervous system and are activated by purines and pyrimidines. The ATP-gated P2 \times 7 ionotropic receptor is expressed in the distal region of the axon of hippocampal neurons during development (Diaz-Hernandez et al., 2008) and has been identified in presynaptic terminals in adult brain. Inhibition of P2 \times 7 with brilliant blue G (BBG) increases GSK-3 phosphorylation, reducing its activity, and favors axonal elongation and branching in cortical and hippocampal neurons (Diaz-Hernandez et al., 2008), similarly to activation of P2Y1-ADP receptors (del Puerto et al., 2011). Inhibition of GSK-3 decreases PHF-I levels (phosphorylated Tau) and increases Tau-1 levels (dephosphorylated Tau). Moreover, this effect is also produced by GSK-3 inhibition with AR-A014418 (Garrido et al., 2007), which can counteract the action of ATP activation of the P2 \times 7 receptor (Diaz-Hernandez et al., 2008).

Conversely, some ligands such as LPA may trigger GSK-3 kinase activity. LPA is a bioactive lipid that can act as a growth factor and binds to specific G-protein-coupled seven transmembrane domain receptors (GPCR; Chun et al., 2002). In neurons, LPA has been shown to promote growth cone collapse and neurite retraction (Tigyi et al., 1996; Sayas et al., 1999). We have demonstrated this LPA-induced GSK-3 activation event, not only inferred from hyperphosphorylation of tau, but also directly measured from neuronal cell extracts (Sayas et al., 2002). Similarly, semaphorin 3A (Sema 3A), a molecule that inhibits axonal growth or neurite retraction, activates GSK-3 at the leading edge of neuronal growth cones. The inhibition of GSK-3 activity can prevent the growth cone collapse response induced by Sema 3A, suggesting that GSK-3 activity might play a role in coupling Sema 3A signaling to changes in cell motility, axonal growth and/or maintenance of axonal extension (Eickholt et al., 2002).

Other membrane receptors that regulate GSK-3 function are only expressed in brain regions associated to specific brain diseases. For example, D2 dopamine receptors are mainly expressed in striatum and can also regulate the activity of GSK-3. Activation

of D2-like receptors inhibits the phosphorylation of Akt, leading to activation (dephosphorylation) of GSK-3 through a G protein-independent mechanism involving a complex of Akt:PP2A scaffolded by β -arrestin-2. Lithium inhibits the behavioral actions of dopamine via disruption of the D2 receptor-mediated complex of Akt: β Arr2:PP2A (Pawlak and Kerr, 2008). Similarly, other neuropeptide receptors, such as those of serotonin, regulate GSK-3 activity. Two serotonin receptors, 5-HT1A and 5-HT2A, appear to play antagonistic roles in regulating GSK-3 β activity. Administration of a 5-HT1A agonist or a 5-HT2A antagonist to mice results in increased brain GSK-3 β phosphorylation (Beaulieu et al., 2009). Moreover, drugs acting on 5-HT neurotransmission such as the selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase (MAO) inhibitors, and tricyclic antidepressants have been shown to inhibit GSK-3 β in many brain regions, including the frontal cortex, hippocampus, and striatum of normal mice.

The acetylcholinesterase inhibitor physostigmine, the muscarinic agonist pilocarpine, and the *N*-methyl-D-aspartate (NMDA) receptors antagonist memantine, also modulate the phosphorylation state of the two isoforms of GSK-3 in mouse hippocampus, cerebral cortex, and striatum (De Sarno et al., 2006). Metabotropic glutamate receptor 5 (mGluR5) can modulate the PI3K/Akt/GSK-3 pathway in the hippocampus, and that modulation of this signaling pathway can reverse β -amyloid-induced neuronal toxicity (Liu et al., 2005).

Glycogen synthase kinase-3 or GSK-3-upstream elements can be selectively regulated in specific neuronal domains, such as the pre- or post-synaptic domains or the axon initial segment (place of neuronal action potential generation), in order to maintain or generate changes in neuronal function. For example, prolonged stimulation of neurons by depolarization results in GSK-3 phosphorylation and inactivation. Thus, GSK-3 activity could be acutely regulated by action potential stimulation (Smillie and Cousin, 2011). In conclusion, it is of great interest to identify proteins specifically located in domains that can regulate GSK-3 activity and the generation of selective pharmacological inhibitors to control GSK-3 activity at the subcellular level. Dendritic spines express GSK-3 regulated through NMDA receptors by two different stimuli (LTP stimulus or LTD stimulus), that, in turn, can activate or inhibit GSK-3 activity (Peineau et al., 2007).

IS DEREGULATION OR DYSFUNCTION OF GSK-3 THE CAUSE NEURODEGENERATIVE DISEASES?

Aberrantly phosphorylated tau is a common factor in tauopathies but the pathological mechanisms responsible may be diverse (Trojanowski and Lee, 2005). The presence of a FTDP-17 mutation in tau may result in altered splicing or may correspond with missense mutations that modify the microtubule binding capacity and subsequently the phosphorylation/dephosphorylation kinetics (Ballatore et al., 2007; Hernandez and Avila, 2008). In fact, early tau-related deficits could be the result of synaptic abnormalities caused by the accumulation of hyperphosphorylated tau within intact dendritic spines (Hoover et al., 2010). Indeed, alterations in the expression and/or the activity of tau kinases (i.e., GSK-3 β ; Pei et al., 1997; Swatton et al., 2004; Hye et al., 2005) have been reported in affected brains, suggesting that one or several kinases could be involved in tau hyperphosphorylation (for

review see, i.e., Hernandez and Avila, 2008). In addition, in transgenic mice the over-expression of some kinases such as GSK-3 increase tau phosphorylation and neurodegeneration (Lucas et al., 2001b). Conversely, inhibition of GSK-3 β reduces tau phosphorylation and neurodegeneration and may block NFT formation (Nakashima et al., 2005; Noble et al., 2005; Engel et al., 2006b). Without excluding that more than one kinase may be important in the pathological phosphorylation of tau, these data suggests that inhibition of GSK-3 is probably an excellent therapeutic strategy for the treatment of tauopathies.

Interestingly, the P2 \times 7 receptor has also been related to Alzheimer's disease and β -amyloid production or involved in the regulation of a β -amyloid effect (Sanz et al., 2009). The purinergic receptor P2 \times 7 triggers α -secretase-dependent processing of the amyloid precursor protein (APP; Delarasse et al., 2010). BBG treatment is also able to reduce inflammation after spinal cord injury in rats, reduce neuronal death, and it is a promising drug for axonal regeneration (Wang et al., 2004).

As mentioned, blockade of the mGluR5-mediated pathways inhibits GSK-3. The NMDA receptor antagonist memantine confers neuroprotection to A β peptides (Liu et al., 2005). Moreover, memantine, physostigmine, or pilocarpine, have been used as therapeutic agents in AD due to their capacity to regulate GSK-3 activity (De Sarno et al., 2006). When using GSK-3 inhibitors, one may also need to consider the different cell types involved in GSK-3 associated diseases. In some tauopathies glial cells and/or neuronal cells are an essential component. Thus, inhibition of GSK-3 through cell specific receptors may help avoid alteration of GSK-3 in other cell types.

Besides its association with AD (Ishiguro et al., 1993; Lovestone et al., 1994) GSK-3 dysfunction has also been associated with different pathological conditions or brain damage; such as Ischemia (Bhat et al., 2000), prion neurotoxicity (Perez et al., 2003b), or with some psychiatric disorders such as schizophrenia (Beaulieu et al., 2009). In fact in Disrupted in schizophrenia 1 mutant (DISC1) neuronal progenitor proliferation is altered and the inhibition of GSK-3 restore this proliferation (Mao et al., 2009). Thus, GSK-3 is emerging as a promising therapeutic target in several neurologic disorders.

THERAPEUTIC APPROACHES: DIRECT INHIBITION VERSUS PHARMACOLOGICAL DOWN-REGULATION

As mentioned above, GSK-3 unique position in modulating the function of a diverse series of proteins in combination with its association with a wide variety of human disorders has attracted significant attention to the protein both as a therapeutic target and as a tool to understand the molecular bases of these disorders. Furthermore, GSK-3 appears to be a cellular nexus, integrating several signaling systems, including numerous second messengers and a wide selection of cellular stimulants.

If we consider GSK-3 as an example of a kinase associated with tauopathies, two different approaches would be considered as therapeutic strategies: direct inhibition of GSK-3 activity or a more generic modulation of GSK-3 acting upstream of the kinase. The first strategy, has been widely considered and indeed, some general inhibitors such as lithium have been tested in several AD animal models (Engel et al., 2008). A second approach

is the search for candidates taking into account that neurodegeneration may reflect “pleiotropic” neuronal cell dysfunction. Accordingly, we have considered here some of the pathways that may control neural morphogenesis and survival including the PI3K-Akt, PKA, and Wnt pathways and their implication in neurodegeneration. Also, we propose alternative and complementary “non-target-based” approaches, that may also be useful for the study of neurodegeneration (Simon et al., 2011). Using cellular based assays we may identify molecules that regardless of their ability to cross the cellular membrane may be identified by a cellular/neuronal modification downstream of a selected kinase, i.e., the tau phosphorylation level. Activation of serotonergic 5-HT₄ receptors have been shown to improve memory processes in preclinical cognition models, mainly through the stimulation of cholinergic neurotransmission (Lezoualc’h, 2007).

For many years, the mood stabilizing drug lithium has been considered as the reference GSK-3 inhibitor. Lithium ions directly inhibit GSK-3 (Klein and Melton, 1996), most likely by competing with magnesium but it also inhibits at least four phosphomonoesterases (including inositol monophosphatase; York et al., 1995), and phosphoglucomutase (Ray et al., 1978; Stambolic and Woodgett, 1994). Although the mechanism of action by which lithium exerts its therapeutic effects is unknown, GSK-3 is significantly inhibited at therapeutic lithium concentrations (Shalubina et al., 2001; Gould and Manji, 2002; Phiel et al., 2003). It has been generally assumed that a significant proportion of the therapeutic action of lithium in bipolar disorders results from the inhibition of GSK-3 (Li et al., 2002; Rowe et al., 2007).

Inhibition of GSK-3 by lithium prevents A β -induced neurodegeneration of cortical and hippocampal primary cultures (Alvarez et al., 1999). With regards to tau metabolism, lithium is able to prevent tau phosphorylation in several mouse models of tauopathies (Perez et al., 2003a; Nakashima et al., 2005; Noble et al., 2005; Engel et al., 2006a; Caccamo et al., 2007). In AD models, lithium has been shown to block the accumulation of A β peptides in mice that overproduce human APP (Phiel et al., 2003). Furthermore, it has been suggested that lithium could also be effective in a mouse model of FTDP-17 (Perez et al., 2003a).

Only a few observational studies have attempted to address the clinical effect of lithium in patients with AD. A retrospective study with a large sample of patients with dementia resulted in an increased risk of AD in patients who had been treated with lithium within 4 years prior to diagnosis (Ayuso-Mateos et al., 2001). This effect might be partially accounted for by the increased occurrence of depression associated with AD. Moreover, a single case study reported in a dementia patient showed that lithium treatment alleviated symptoms of aggression and agitation, while cognition persisted after 1.5 years of treatment (Havens and Cole, 1982). Furthermore, a significantly increased global cognitive ability, as measured by MMSE in non-demented patients, appears to be associated with lithium intake (Terao et al., 2006). However, the study design and low sample size precludes drawing any causative conclusion from these studies.

In addition, some pilot studies have been carried out to directly address the effect of lithium treatment in AD patients. An open label feasibility and tolerability study with a small cohort of 22 subjects receiving a low dose of lithium was carried out in the

UK and reported a high discontinuation rate despite few, relatively mild, and reversible side effects (Macdonald et al., 2008). A second randomized, single-blind, placebo-controlled, parallel group, multicenter 10-week study was carried out in Germany as a proof-of-principle (Hampel et al., 2009). A total of 71 patients with mild AD (MMSE scores between 21 and 26) were treated with lithium or placebo for 10 weeks after which neuropsychological and neuropsychiatric assessment was performed together with some biomarker determinations in plasma (A β 1-42), lymphocytes (GSK-3 activity), and CSF (total tau, phospho-tau, and A β 1-42). In spite of the fact that lithium plasma levels were within the therapeutic range, no treatment effect was observed in any of the cognition assessment scales or the selected biomarkers used. Given the short time of treatment of this study, the possibility that lithium has long-term effects on cognition or any other biomarker in AD remains to be tested.

Very recently, a randomized, double-blind, placebo-controlled study on 45 people with amnesic mild cognitive impairment (aMCI) treated with lithium for 12 months was reported (Forleza et al., 2011). Lithium treatment was associated with a significant decrease in CSF concentrations of pTau and with a better performance in cognitive tasks, strongly suggesting that lithium (most likely through GSK-3 inhibition) might have disease-modifying properties in AD and perhaps other tauopathies.

Use of lithium in clinical practice is problematic since it has a narrow therapeutic window (blood serum levels 0.6–1.2 mM) above which side effects are intolerable requiring titration. An overdose can lead to severe neurological dysfunction and in some cases death. Non-CNS side effects of lithium (common within therapeutic levels) include tremor, polyuria, polydipsia, nausea, and weight gain. Moreover, lithium can have adverse reactions with other drug classes including diuretics, NSAIDs, and other drugs that alter kidney function (Gould and Manji, 2006).

The unique position of GSK-3 as a pivotal and central player in the pathogenesis of both sporadic and familial forms of AD has attracted significant attention to this enzyme as a therapeutic target and has led to the synthesis of a high number of GSK-3 inhibitors, some of which are currently being tested in phase II proof-of-concept clinical trials (Mangialasche et al., 2010; Medina and Avila, 2010). Inhibition of GSK-3 with small-molecules would be expected to slow down progression of neurodegeneration in AD and perhaps other tauopathies as well.

A number of novel potent and relatively selective small-molecule inhibitors of GSK-3 activity from different chemical families have been recently described, including hymenialdisine, indirubins, paullones, maleimides, amino pyrazoles, thiazoles, and 2,4-disubstituted thiadiazolidinones (TDZD; reviewed in Medina and Castro, 2008). Most of them are ATP-competitive inhibitors, although more recently, new small-molecule derivatives that exhibit substrate competitive inhibition activity toward GSK-3 have been shown. Since different GSK-3 isoforms display a high degree of homology within the ATP-binding site, inhibitors are unable to exhibit isoform selectivity, as they all show similar potencies toward purified GSK-3 α and GSK-3 β . Thus, the development of isoform-specific inhibitors or the inhibition of

Table 1 | Selected GSK-3 kinase inhibitor drugs in clinical development for the treatment of tauopathies.

Drug	Company	Mechanism of action	Development phase	Indication
Tideglusib (NP-12)	Noscira	GSK-3 inhibitor	Phase II	Alzheimer's disease, PSP
Lithium	University of Sao Paulo	GSK-3 inhibitor	Phase II	Alzheimer's disease
Valproic acid	Nantes University Hospital	GSK-3 inhibitor	Phase II	PSP
AZD-1080	AstraZeneca	GSK-3 inhibitor	Discontinued	Alzheimer's disease

signaling pathways specific for one of the isoforms is necessary to selectively target the different substrates involved in different neurodegenerative diseases. Although ATP-competitive inhibitors occupy the general area of the highly conserved ATP-binding site, they also explore other available nearby space, depending on their structure. Thus, it may be possible to identify selective inhibitors by taking advantage of the small differences in primary sequence that exist between the different kinases. The crystal structures of GSK-3 β complexed with a variety of ligands (ter Haar, 2006), together with molecular modeling approaches (Gadakar et al., 2007), provide the necessary clues for enhancing selectivity toward GSK-3 (ter Haar et al., 2001; Patel et al., 2007).

Besides small-molecule inhibitors, some physiological peptides act as GSK-3 inhibitors, including GBP, a maternal *Xenopus* GSK-3-binding protein homologous to a mammalian T cell proto-oncogene (Yost et al., 1998) and p24, a heat resistant GSK-3-binding protein (Martin et al., 2002). That finding led to a synthetic strategy to develop new inhibitors, such as L803-mts, a peptidic inhibitor that binds to the substrate site (Plotkin et al., 2003). L803-mts has been more recently used to examine the impact of long-term *in vivo* inhibition of GSK-3 and its effects in specific tissues (Kaidanovich-Beilin and Eldar-Finkelman, 2006).

The last few years have seen the synthesis of quite a number of relatively selective, potent GSK-3 inhibitors with relative efficacy *in vivo* in a diverse array of animal models of human diseases, including AD. Despite the challenges faced by this approach with respect to safety and specificity, a number of efforts are underway to develop kinase inhibitors and, in fact, Noscira's tideglusib (NP-12; see Table 1), is already in phase II clinical trials for the treatment of both AD and PSP, a tauopathy (Medina and Castro, 2008).

In summary, there is a significant effort being made to validate a number of tau-related targets and to develop novel alternatives for the treatment of tauopathies such as AD or PSP (reviewed in Medina and Wandosell, 2011) including GSK-3 inhibition. We hope that future clinical trials will reveal the safety and efficacy of potential treatment strategies that are being tested in translational laboratories across the world.

CONCLUSION

Three decades after its discovery as a protein kinase involved in glycogen metabolism, GSK-3 has revealed itself as a common link, integrating several signaling systems, including second messengers and a wide selection of cellular stimulants. Modulation of its activity has also turned out to be much more complex than originally thought, as GSK-3 regulation occurs by complex mechanisms that are dependent on specific signaling pathways, including

post-translational modifications, protein complex formation, and subcellular localization. Although there seems to be a good degree of functional overlapping between different isoforms, some tissue- and isoform-specific functions and substrates are beginning to emerge. Thus, new data will open the possibility to design better and more specific inhibitors.

Deregulation or abnormal GSK-3 activity appears to be associated with various relevant pathologies, including AD and other tauopathies, as the enzyme is uniquely positioned as central player in AD pathogenesis. GSK-3 plays a critical role in key events such as tau phosphorylation, A β formation, and neurotoxicity, microtubule dynamics, synaptic plasticity, neuritic dystrophy, cognition, neuronal survival, and neurodegeneration.

In the last two decades, drug discovery and development efforts for AD have primarily focused on targets defined by the amyloid cascade hypothesis with disappointing results, underscoring the need for novel therapeutic targets. In contrast, tau-based approaches have received little attention until recently, despite the fact that tau pathology is paramount in all tauopathies including AD (Medina and Wandosell, 2011). A significant effort has been made in the last few years to synthesize a high number of relatively selective and potent GSK-3 inhibitors, while some of them have shown *in vivo* efficacy in various animal models of AD. Some of the known drug discovery and development challenges should be met, including: lack of good predictive animal models, the need for validated biomarkers of disease progression, appropriate clinical trial design, early diagnosis, and treatment, definition of target populations, difficulties in demonstrating disease-modifying effects, etc. Despite the challenges faced by this approach with respect to safety and specificity, a number of efforts are underway to develop GSK-3 inhibitors as potential drugs for the treatment of AD. Some agents have already reached phase II clinical trials and some proof-of-concept studies are currently ongoing or planned.

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