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Glycogen synthase kinase-3 inhibitors: Rescuers of cognitive impairments

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ABSTRACT

Impairment of cognitive processes is a devastating outcome of many diseases, injuries, and drugs affecting the central nervous system (CNS). Most often, very little can be done by available therapeutic interventions to improve cognitive functions. Here we review evidence that inhibition of glycogen synthase kinase-3 (GSK3) ameliorates cognitive deficits in a wide variety of animal models of CNS diseases, including Alzheimer's disease, Fragile X syndrome, Down syndrome, Parkinson's disease, spinocerebellar ataxia type 1, traumatic brain injury, and others. GSK3 inhibitors also improve cognition following impairments caused by therapeutic interventions, such as cranial irradiation for brain tumors. These findings demonstrate that GSK3 inhibitors are able to ameliorate cognitive impairments caused by a diverse array of diseases, injury, and treatments. The improvements in impaired cognition instilled by administration of GSK3 inhibitors appear to involve a variety of different mechanisms, such as supporting long-term potentiation and diminishing long-term depression, promotion of neurogenesis, reduction of inflammation, and increasing a number of neuroprotective mechanisms. The potential for GSK3 inhibitors to repair cognitive deficits associated with many conditions warrants further investigation of their potential for therapeutic interventions, particularly considering the current dearth of treatments available to reduce loss of cognitive functions.

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1. Introduction

Cognitive abilities define our species and our individual identities. Yet these functions are often threatened, as it seems that nearly every neurological and psychiatric disease includes a component of cognitive disability. This is particularly true of aging-associated diseases, which afflict an ever-increasing portion of the population. With the recognition of the importance of disease-associated cognitive disabilities, much effort, although perhaps insufficient, is being directed towards finding ways to protect and restore cognitive functions. Here we review the rapidly

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β peptide; APP, amyloid precursor protein; CNS, central nervous system; FX, Fragile X; GSK3, glycogen synthase kinase-3; LTD, long-term depression; LTP, long-term potentiation; MTPT, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SCA1, spinocerebellar ataxia type 1; TBI, traumatic brain injury.

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accumulating evidence that inhibitors of glycogen synthase kinase-3 (GSK3) represent one of the strongest candidate classes of agents for this purpose. Although most widely studied for their potential therapeutic actions in Alzheimer's disease (AD), in fact more than a dozen distinct conditions in rodent models involving cognitive impairments have been shown to be ameliorated by the administration of GSK3 inhibitors (Fig. 1). Thus, this substantial evidence suggests that GSK3 inhibitors should be more widely considered as interventions for protecting and restoring cognitive abilities that are jeopardized in many individuals with neurological and psychiatric diseases.

2. GSK3 and inhibitors

GSK3 refers to two paralogs, GSK3α and GSK3β, that are commonly referred to as isoforms because of their similar sequences and functions although they are derived from different genes and differential actions have been identified (Kaidanovich-Beilin & Woodgett, 2011). They are ubiquitously expressed, serine/threonine kinases that are involved in a large number of cellular functions (Jope & Johnson, 2004). The activity of GSK3 is most commonly regulated by phosphorylation on a regulatory serine, serine-21 in GSK3α and serine-9 in GSK3β. Phosphorylation of these regulatory serines inhibits the activity of GSK3. GSK3 can be phosphorylated on these serines by several kinases, such as Akt, protein kinase C, protein kinase A, and others. This provides a mechanism for many intracellular signaling pathways to control the activity of GSK3. However, it appears that this also provides a mechanism for disease-associated impairments in signal transduction pathways to result in failure to adequately inhibit GSK3. This failure can permit GSK3 to remain abnormally active, which appears to allow GSK3 to contribute to disease pathologies, including cognitive impairments, as discussed in later sections of this review.

The increasing evidence that GSK3 contributes to the pathology of several prevalent diseases, perhaps most notably AD and mood disorders, has generated much interest in applying GSK3 inhibitors therapeutically. Lithium was the first GSK3 inhibitor to be identified (Klein & Melton, 1996; Stambolic et al., 1996), and lithium remains the most widely used experimentally and clinically. Lithium directly binds and inhibits GSK3 (Klein & Melton, 1996; Stambolic et al., 1996), and lithium administration also increases the inhibitory serine-phosphorylation of GSK3 (Jope, 2003). Lithium is widely used therapeutically as a mood stabilizer in patients with mood disorders, and much evidence indicates that inhibition of GSK3 makes an important contribution to its mood stabilizing therapeutic effect (Jope, 2011). In human patients, therapeutic levels of lithium are in the range of 0.5–1.2 mM lithium in the serum, and this serum concentration of lithium is often achieved in rodents by administration of food pellets containing 0.2–0.4% lithium (Jope, 2011). Many actions of lithium have been shown to be due to inhibition of GSK3, but lithium also has other actions, such as inhibition of inositol monophosphatase, that should not be discounted unless the effects of lithium have been verified to be due to inhibition of GSK3 using other selective inhibitors of GSK3 or molecular manipulations of GSK3 (Phiel & Klein, 2001). The utility of lithium and therapeutic promise of GSK3 inhibitors led to the development of many selective inhibitors of GSK3 during the last decade that are beginning to be more widely used (Eldar-Finkelman & Martinez, 2011). Many of these are ATP-competitive inhibitors of GSK3, but particularly promising are GSK3 inhibitors that are not ATP-competitive, since ATP-competitive inhibitors tend to also inhibit other kinases and may prove to be more toxic. Among the frequently used ATP-competitive GSK3 inhibitors are indirubin derivatives (Leclerc et al., 2001), paullone derivatives (Leost et al., 2000), SB415286 and SB216763, although care must be taken concerning their solubilities as originally described (Coghlan et al., 2000), and AR-A014418 (Bhat et al., 2003), although the reports of behavioral effects of AR-A014418 are mitigated by other studies indicating that it does not significantly enter the CNS (Vasdev et al., 2005; Selenica et al., 2007; Hicks et al., 2010). Reports of the kinase specificities of several GSK3 inhibitors are particularly valuable (Davies et al., 2000; Murray et al., 2004; Bain et al., 2007), enabling investigators to choose multiple GSK3 inhibitors with different off-target actions. Other GSK3 inhibitors that are not competitive with the ATP binding site in GSK3 are particularly promising (Eldar-Finkelman & Martinez, 2011). L803-mts is a cell-permeable, 11 residue peptide that is a substrate-competitive specific inhibitor of GSK3 (Plotkin et al., 2003; Kaidanovich-Beilin et al., 2004; Licht-Murava et al., 2011). TDZD-8 is a highly selective ATP non-competitive inhibitor of GSK3 (Martinez et al., 2002). VP0.7 is an allosteric (not competitive with ATP or substrate) selective GSK3 inhibitor that binds to the C-terminal lobe of the enzyme (Palomo et al., 2011). Here we review the evidence for cognitive effects involving GSK3. Studies of potential actions of GSK3 in cognition have primarily utilized lithium, in part because it is the GSK3 inhibitor that has been available the longest, so reports of lithium's effects predominate in this review, but newer GSK3 inhibitors and molecular modifications of GSK3 have also been studied.

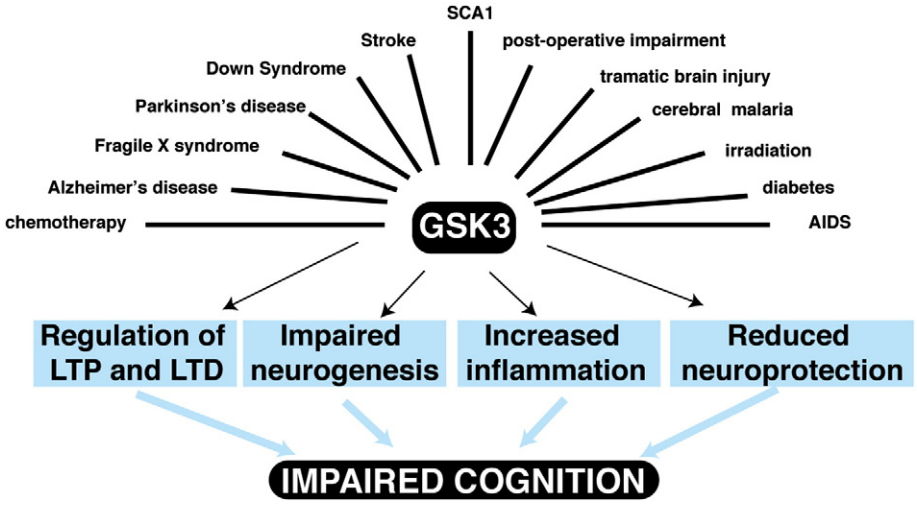

Fig. 1. GSK3 inhibitors improve impaired cognition in multiple conditions. Schematic representation of conditions in which inhibition of GSK3 improves impairments in cognitive processes. The improvements in impaired cognition following administration of GSK3 inhibitors likely involve a variety of different mechanisms, such as supporting long-term potentiation and diminishing long-term depression, promotion of neurogenesis, reduction of inflammation, and increasing a number of neuroprotective mechanisms.