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Lithium: A Novel Therapeutic Drug for Traumatic Brain Injury

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Tauopathy and β Amyloid: The Neuropathological Markers of TBI

Traumatic brain injury (TBI) has long been a major public health issue. Approximately 1.7 million individuals currently suffer from TBI [1]. A significant portion of individuals with TBI (up to 24%) suffer "sustained TBI" for many years [2]. A particular concern is that sustained TBI has a tendency to take a chronically deteriorating course as the acute neuropathology of TBI initiates progressive apoptotic cascades leading to chronic neurodegenerative disorders such chronic traumatic encephalopathy (CTE) [3].

A large body of evidence from clinical studies with individuals with TBI and preclinical studies using TBI animal models indicates that hyperphosphorylated tau aggregation (tauopathy) and beta amyloid (Aβ) accumulation are the key neuropathological markers of CTE [3]. Interestingly, there are many similarities between CTE and Alzheimer's disease (AD) [4] (Table 1). Tauopathy and Aβ deposits are the pathological hallmarks of both disorders. Hyperphosphorylated tau proteins in CTE are chemically similar to that observed in AD. For example, in CTE as well as AD, hyperphosphorylated tau protein contains all six isoforms and the amino acid sites of phosphorylation. In tau protein are the same between the two disorders [5]. Apolipoprotein E (ApoE) ε4 allele, a strong genetic factor for AD susceptibility and Aβ deposition [6], increases the risk of CTE [7]. Global cerebral atrophy suggesting progressive neuronal loss is also observed in both disorders [8]. Additionally, cognitive impairment is the key symptom of both disorders [9]. In fact, a number of individuals with TBI directly develop AD, suggesting that TBI is an important predisposing factor for AD [10].

Glycogen Synthase Kinase-3 Inhibition: A Novel Therapeutic Target for TBI

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase and is constitutively active, and keeps the large number of its substrates in inactive states [11]. GSK-3 has a strong tendency to block neuroprotection and neuronal survival and promote apoptosis by phosphorylating (thus, inactivating) its substrates involved in neuroprotection such as transcription factors and signaling molecules [12]. GSK-3 also exacerbates tauopathy and Aβ accumulation, the key neuropathological markers of both TBI and AD. Conversely, the inhibition of GSK-3β mitigates tauopathy and Aβ deposits and attenuates neurodegeneration in these disorders [13].

	CTE	AD
Axonal damage	+	+
Synaptic/neuronal loss	+	+
Neurite degenration	+	+
Microgliasis	+	+
Neurofibrially tangles	+	+
Aβ/APP	+	+
Risk of Aβ/APP in 3x Transgenic AD Model>normal mice after TBI		
Caspase-3 Induction	+	+
APOE4	Susceptible to CTE	Susceptible to AD

Table 1: Tauopathy, Aβ plaques, cognitive impairment in CTE and AD.

The receptor tyrosine kinase (RTK) and Wnt signaling pathways are the GSK-3 upstream signaling pathways that play important roles in neuroprotective, anti-apoptotic and neurotropic actions [14] (Figure 1). These neuroplastic actions are largely mediated by down-regulating GSK-3 activity. A large number of neuro-active molecules including transcription factors and signaling molecules are constitutively in inactive states as they are inactivated (phosphorylated) by GSK-3. Activation of these pathways down-regulates GSK-3 activity and thereby, releases these molecules from inhibition by the enzyme. These activated molecules lead to diverse neuroprotection and neurotrophic actions. Studies with TBI rodent models have shown that RTK and Wnt signaling pathways are naturally activated shortly after TBI induced, and activation of the pathways is associated with neuroprotective actions against TBI-induced neuropathology [15,16] (Figure 1). Although these pathways may be an innate neuroprotective process against TBI, activation of these pathways is transiently and is not strong enough to produce sustainable therapeutic actions against TBI [15-17].

A number of studies using TBI rodent models strongly suggest that GSK-3 inhibition is a novel therapeutic target for TBI. Among many GSK-3 inhibitors, lithium is known to be a prototype GSK-3 inhibitor, which directly inhibits the enzyme as well as inhibits the enzyme by phosphorylating it [18] (Figure 1). Studies using TBI rodent models have demonstrated that lithium reduces TBI-induced neuropathology, exerts neuroprotective actions, promotes cell survival and reduces tauopathy and Aβ accumulation (Table 2). These effects are correlated with the therapeutic effects of the drug such as improving TBI-induced cognitive impairment, abnormal locomotor coordination, depressive and anxiety-like behaviors (Table 2).

Lithium: Beyond GSK-3 Inhibition

Interestingly, SB-216763, a specific GSK-3 inhibitor, showed neither improvement in memory nor significant neuroprotection [17]. In contrast to SB-216763, lithium has neuroprotective actions beyond GSK-3 inhibition. Lithium inhibits GSK-3 activity by activating the RTK signaling pathway by stimulating phosphoinositide-3 kinase (PI_3 kinase) in the pathway [32] (Figure 1). Lithium also blocks protein kinase C activity by inhibiting inositol monophosphatase and stimulates cyclic AMP signaling pathways, leading to activation of transcription factors involved in neuroprotective and neurotrophic actions such as

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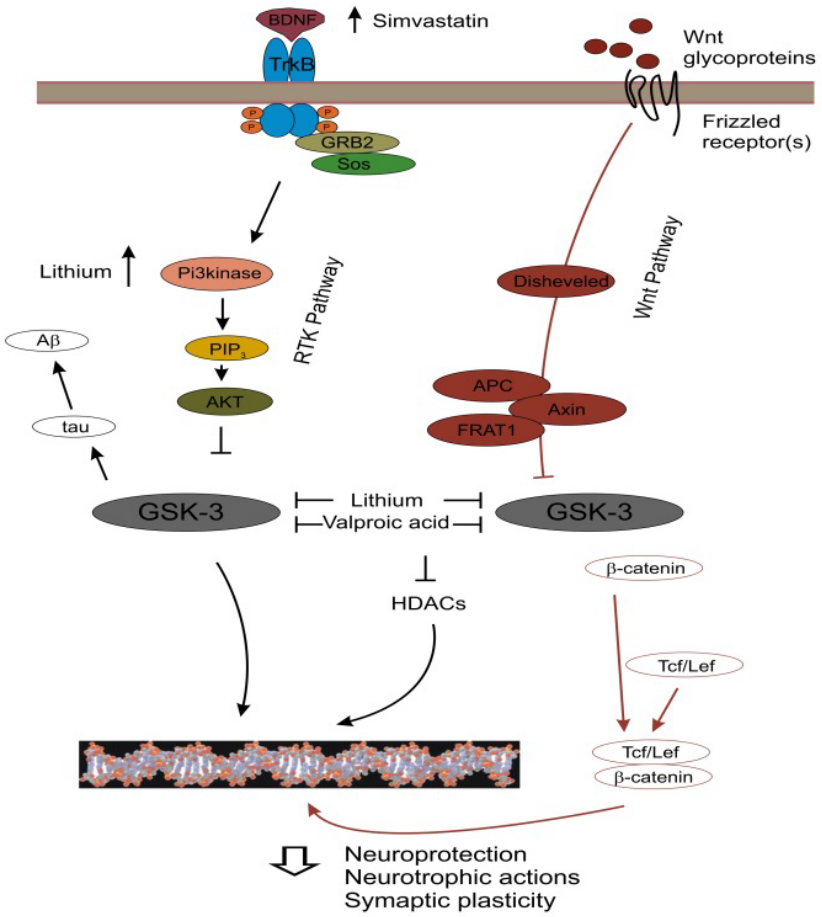

Figure 1: Therapeutic targets in GSK-3-mediated signaling pathways in the treatment of TBI.
Lithium activates the RTK and Wnt signaling pathways by inhibiting GSK-3. Lithium also inhibits GSK-3 indirectly by activating phosphoinositide-3 kinase (PI_3 kinase) in the RTK signaling pathway. Consequently, neuroactive molecules such as transcription factors such as p53, cyclic AMP response element binding protein (CREB), heat shock factor-1, c-Jun, Bax and Tcf/Lef are released from enzymatic inhibition of GSK-3 and lead diverse neuroprotection and neurotrophic actions.

Animals, drug administration	TBI lesion	Neuron loss	β-catenin	P-tau	Aβ	Anxiety/depression	Cognitive function
Rat, posttraumatic for 5 days [26]	↓	↓	↑				↑
Mice, posttraumatic for 2 weeks [27]	↓	↓				↓	
Mice, posttraumatic for 3 weeks [28]				↓	↓		↑
Mice, pre-traumatic a single injection [29]			↑			↓	
Mice, pre-traumatic for 2 weeks,Post-traumatic for 4 weeks [30]	↓	↓					↑
Mice, post-traumatic for 3 weeks, subclinical doses of lithium/valproate [31]	↓	↓				↓	

Table 2: Effects of lithium on the neuropathology and symptoms of TBI in TBI rodent models.

cyclic AMP responsive element (CREB) [19]. Furthermore, lithium has stabilizing properties of the inositol triphosphate-dependent receptor (IP_3R) calcium channel localized to the membrane of the endoplasmic reticulum (ER), which is the primary storage of calcium as well as the major regulator of calcium concentration within the cell, by depleting IR_3 supply to the IP_3R [20,21]. Excessive activation of this channel triggers a wide array of neuropathological processes including apoptosis, impairments in synaptic plasticity and memory encoding, inflammatory responses and the formation of tauopathy and Aβ accumulation [22-24] (Figure 2). Our recent study shows that lithium reduces excessive calcium release from ER in 3xTg AD rodent models [25]. This finding suggests that lithium can reduce neuropathological processes triggered by excessive calcium release from ER such as tauopathy and Ab deposit. Thus, in addition to the blockade of GSK-3 activity, diverse mechanisms for neuroprotection may be needed to produce robust therapeutic actions against TBI. In this context, lithium is a drug of particular interest for complex pathological conditions such as TBI or AD since the drug targets multiple pathogenic processes simultaneously (Figure 3).

The molecular mechanism underlying tauopathy and Aβ accumulation is poorly understood. A number of studies have shown that tau protein is excessively hyperphosphorylated, and Aβ accumulates shortly after TBI produced. These neuropatholgical events contribute to the conversion of acute TBI to chronic neurodegeneration [4]. The molecular mechanism that triggers tauopathy and Aβ accumulation

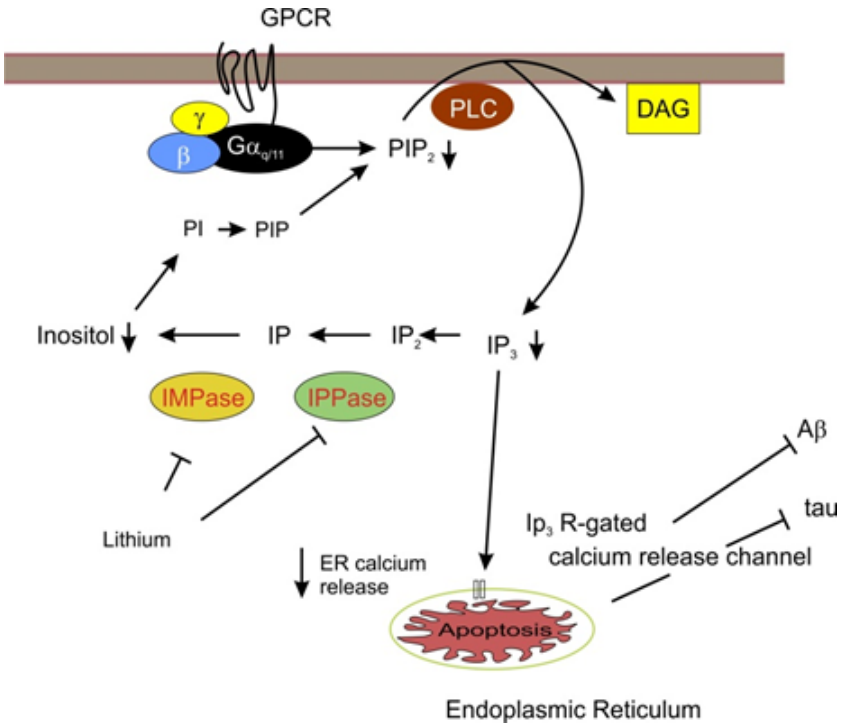

Figure 2: Therapeutic targets in ER IP_3R-gated calcium channel in the treatment of TBI.
Excessive calcium release from ER triggers multiple neuropatholgical processes including excessive phosphorylated tau accumulation and Aβ deposit. Lithium blocks the synthesis of inositol-1,4,5-triphosphate (IP_3) by inhibiting IMPase (inositol monophosphate phosphatase) as well as IPPase (inositol polyphosphate phosphatase) in the phosphatidyl inositol cycle. By blocking IP_3 production, lithium reduces excessive calcium release from ER via IP_3 dependent, receptor-gated calcium channel via deleting IP_3 supply to the channel. Since excessive calcium release from the ER leads to neuropatholgical processes including hyperphosphorylated tau aggregation and Aβ deposit, the restoration of normal ER calcium release could block tauopathy and Aβ deposit.

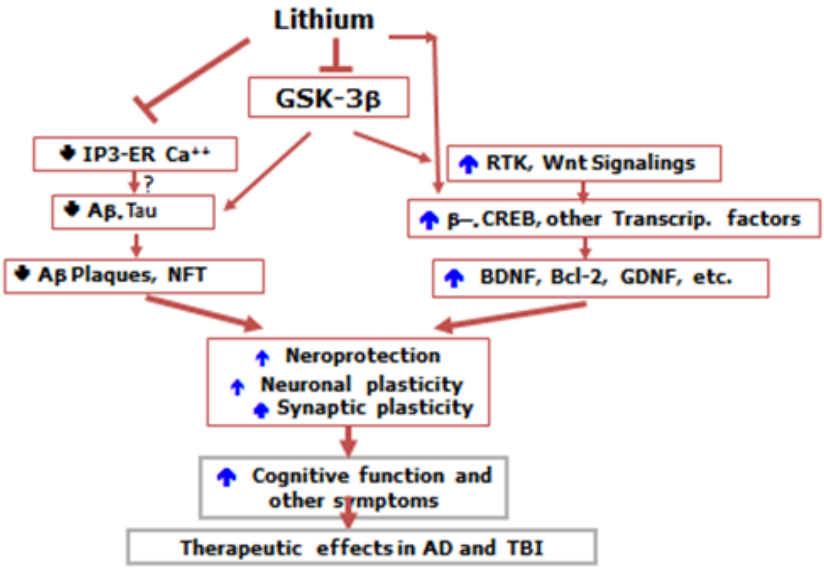

Figure 3: Therapeutic mechanism of action of lithium for TBI.
Lithium exerts neuroprotective and neurotrophic actions against TBI in diverse ways. Lithium activates the RTK and Wnt signaling cascades by inhibiting GSK-3 activity directly as well as stimulating the RTK signaling cascade by acting on PI_3K in the RTK pathway. Lithium stimulates the cAMP-dependent cascade and thus activates transcription factors such as CREB. Lithium also blocks excessive calcium release from ER by reducing the supply of IP_3 to the IP_3 receptor dependent calcium channel at ER, and this action can reduce tauopathy and Aβ deposit. However, whether lithium actually reduces tauopathy and Aβ deposit by blocking excessive calcium release from ER via IP_3-dependent calcium channels remains to be investigated.

following TBI is unknown. Understanding of that mechanism may lead to developing a novel therapeutic strategy in treating TBI and AD at the very early stages of the disorders.

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