Lithium: A Novel Therapeutic Drug for Traumatic Brain Injury

Seong S Shim*
Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta VA Medical Center, USA

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 due to ApoE ε4 is one of the earliest changes observed in AD and CTE [8]. Consequently, a number of studies have demonstrated that lithium reduces TBI-induced neuropathology, 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).

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 [9]. GSK-3 has a strong tendency to activate and is constitutively active, and keeps the large number of its substrates in inactive states [9]. 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 with 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 (PI3 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 RTK and Wnt signaling pathways.

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

| Marker                          | CTE | AD |
|--------------------------------|-----|----|
| Axonal damage                  | ✦   | ✦  |
| Synaptic/neuronal loss         | ✦   | ✦  |
| Neurite degeneration           | ✦   | ✦  |
| Microgliosis                   | ✦   | ✦  |
| Neurofibrillary 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.

*Corresponding author: Seong S Shim, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta VA Medical Center, 1670 Clairmont Road, Decatur, GA 30033, USA, Tel: 404 321-6111; E-mail: seong.shim@va.gov

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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 (PI3 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, R) 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, supply to the IP, R [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 Aβ 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 neuropathological 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 IP₃-R-gated calcium channel in the treatment of TBI. Excessive calcium release from ER triggers multiple neuropathological processes including excessive phosphorylated tau accumulation and Aβ deposit. Lithium blocks the synthesis of inositol-1,4,5-triphosphate (IP₃) by inhibiting IMPase (inositol monophosphate phosphatase) as well as IPPase (inositol polyphosphate phosphatase) in the phosphatidyl inositol cycle. By blocking IP₃ production, lithium reduces excessive calcium release from ER via IP₃-dependent receptor-gated calcium channel via deleting IP₃ supply to the channel. Since excessive calcium release from the ER leads to neuropathological 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_3_K 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 IP₃ to the IP₃ 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 IP₃-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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