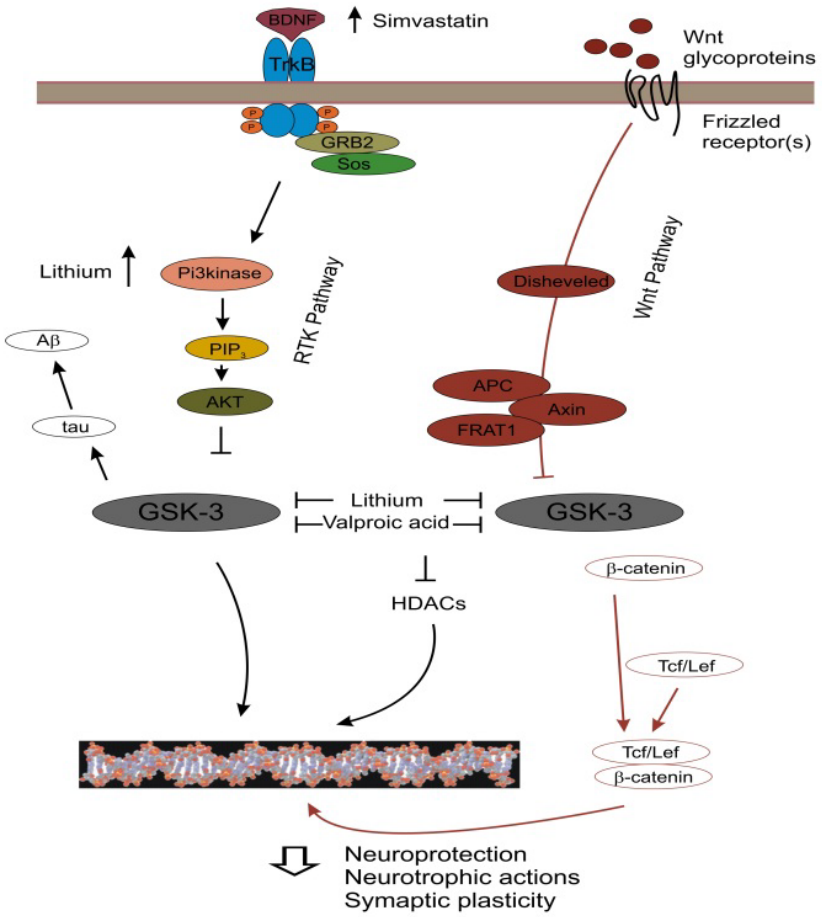

Figure 1: Therapeutic targets in GSK-3-mediated signaling pathways in the treatment of TBI.
Lithium activates the RTK and Wnt signaling pathways by inhibiting GSK-3. Lithium also inhibits GSK-3 indirectly by activating phosphoinositide-3 kinase (PI_3 kinase) in the RTK signaling pathway. Consequently, 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

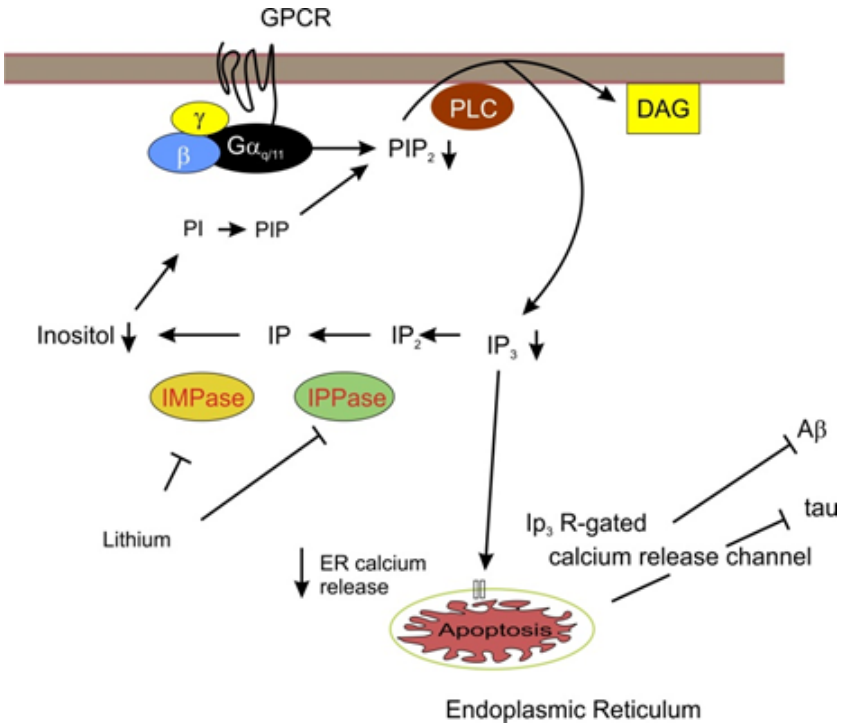

Figure 2: Therapeutic targets in ER IP_3R-gated calcium channel in the treatment of TBI.
Excessive calcium release from ER triggers multiple neuropatholgical processes including excessive phosphorylated tau accumulation and Aβ deposit. Lithium blocks the synthesis of inositol-1,4,5-triphosphate (IP_3) 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.

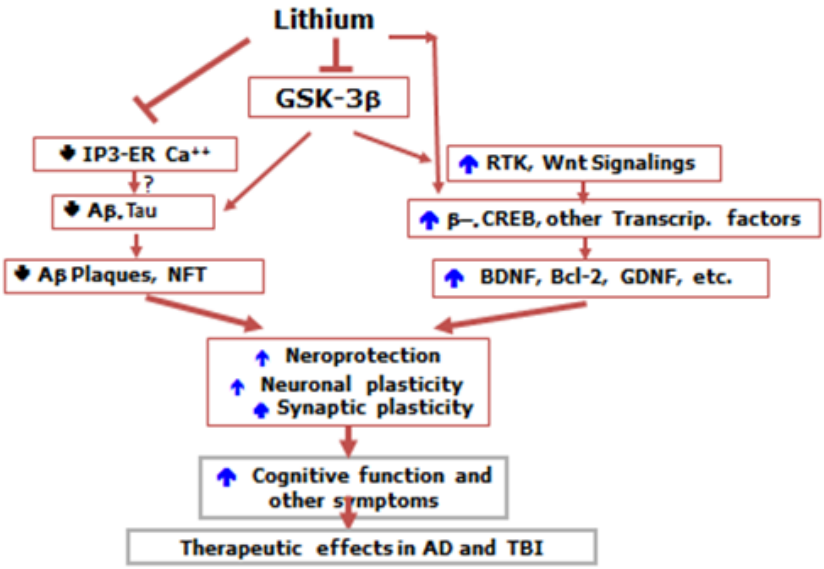

Figure 3: Therapeutic mechanism of action of lithium for TBI.
Lithium exerts neuroprotective and neurotrophic actions against TBI in diverse ways. Lithium activates the RTK and Wnt signaling cascades by inhibiting GSK-3 activity directly as well as stimulating the RTK signaling cascade by acting on PI_3K 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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