

Figure 1. Basic mechanisms of lithium function.

Arrows with triangular heads represent activations, arrows with oval heads represent inhibitions.

A) In the absence of lithium, myo-inositol (MI) and cytidine-diphosphate-diacylglycerol (CDP-DAG) are converted by phosphatidylinositol synthase (PI synthase) into phosphatidylinositol (PI). Phosphatidylinositol-kinase (PIK) converts it to phosphatidylinositol-phosphate (PIP), which is further phosphorylated by phosphatidylinositol-phosphate-kinase (PIP2K) to phosphatidylinositol-diphosphate (PIP₂). Phosphatidylinositol-diphosphate can be processed by two separate pathways.

The pathway of phospholipase C (PLC) splits it to produce inositol triphosphate (IP₃) and diacylglycerol (DAG). Inositol triphosphate can be recycled by inositol-phosphate phosphatase 5 (IPP5), which converts it to inositol diphosphate (IP₂). Inositol diphosphate can be subsequently dephosphorylated to inositol phosphate (IP), by inositol phosphate phosphatase (IPP): this is a magnesium-dependent and chain-limiting step, that may impair the whole inositol-phosphate cycle. Inositol phosphate can finally be dephosphorylated by inositol monophosphate phosphatase (IMP) to regenerate myo-inositol: this is also a magnesium-dependent chain-limiting step. Before being recycled, inositol triphosphate can bind to inositol triphosphate receptors (IP₃R) on the endoplasmic reticulum, to promote the liberation of calcium into the cytosol. This free calcium rapidly binds to several proteins, among which calmodulin can promote the activation of calcium-dependent kinases (CaMKs) and phosphatases (CaN); calcium can also bind and activate protein kinase C (PKC), together with diacylglycerol.

The pathway of phosphatidylinositol 3 kinase (PI3K) instead produces phosphatidylinositol-triphosphate, which can directly bind and activate protein kinase B (Akt).

These pathways converge, together with the contribution from G-protein coupled receptors (GPCR) which also comprise dopamine receptors (DR), to determine the activation status of the Akt/Glycogen synthase kinase 3 beta (GSK-3β) complex. GPCRs can recruit β-arrestin, which serves as a scaffold; phosphatidylinositol-triphosphate activates Akt; protein kinase C inhibits GSK-3β; the calcium-dependent phosphatase instead activates GSK-3β.

Therefore, in the absence of lithium: the inositol-phosphate cycle can be activated, calcium signals can be activated; the Akt/GSK-3β complex can be regulated.

B) lithium can enter the cell through sodium channels (Na⁺ chnl). With lithium, the magnesium-dependent and chain-limiting steps of the inositol-phosphate cycle are blocked, with the result of an accumulation of inositol-diphosphate and a depletion of all other intermediates. This causes a deactivation of both PI3K and PLC pathways, resulting in a dramatically decreased calcium signaling. Finally, the Akt/GSK-3β complex does not receive any more regulating phosphorylations or dephosphorylations; moreover, lithium can destabilize the complex.

Figure 2. Basic mechanisms of lithium effects on the Akt/GSK-3β complex.

Arrows with triangular heads represent activations, arrows with oval heads represent inhibitions.

A) In the absence of lithium, the activation of G-protein coupled receptors (GPCRs) ~~which also comprise dopamine receptors (DR), can lead to the activation of αq G-protein subunits that~~ stimulate an increase of cytosolic calcium levels and activate protein kinase C (PKC) and the calcium-dependent phosphatase (CaN). While protein kinase C can inhibit glycogen synthase kinase 3 beta (GSK-3β), the calcium-dependent phosphatase can inhibit protein kinase B (Akt) and activate GSK-3β. Magnesium has additional roles since it can stabilize the Akt/GSK-3β complex and it is a cofactor required for the activity of GSK-3β. Therefore, in the absence of lithium, the Akt/GSK-3β promotes the inactivation of Akt and the activation of GSK-3β.

B) with lithium, calcium signals are suppressed, leaving PKC and CaN inactive. Moreover the Akt/GSK-3β complex cannot be stabilized and GSK-3β is deprived of its required cofactor. This leaves Akt as the only active enzyme with the result of additional GSK-3β inhibition.

Figure 3. Relevant effects of Akt activation.

Boxes show proteins targeted by Akt. Arrows with triangular heads represent activations, arrows with oval heads represent inhibitions.

Figure 4. Relevant effects of GSK-3 β activation.

Boxes show proteins targeted by GSK-3 β . Arrows with triangular heads represent activations, arrows with oval heads represent inhibitions.