Novel Molecules for the Treatment of Disorders that Benefit from Lithium Treatment (BGN)

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Inositol monophosphatase (IMPase) is a key enzyme in regulating the phosphatidylinositol (PI) signaling system. It catalyzes the dephosphorylation of myo-inositol monophosphates to free myo-inositol. Lithium salts (Li), the drug of choice for the treatment of bipolar disorder (manic-depressive illness), inhibit IMPase activity at therapeutically-relevant concentrations but has well-recognized limitations. Recently, it has been shown that calbindin D28k (calbindin) is an activator of IMPase and has been suggested that it attaches to residues 55-66 of IMPase, enhancing its activity. Calbindin could thus be a key endogenous regulator of the PI signaling cycle. Inhibitor(s) of IMPase could replace lithium salts in the treatment of disorders that benefit from Lithium treatment.

The Technology

Based on the structure of Calbindin D28k several peptides were designed which may serve as competitive inhibitors for the interaction between IMPase and calbindin D28k. The effect of several such peptides are demonstrated in the Figure bellow.
The activity of mouse brain crude homogenate IMPase is significantly increased (1.7 fold) in the presence of 20 M calbindin D28k. When peptide 1 is added to the reaction mixture the effect of calbindin D28k is abolished, while peptide 2 does not interfere with the enhancement of IMPase activity by calbindin D28k. This suggests that peptide 1 but not peptide 2 competes with calbindin D28k. Peptides 3 to 6 are mutated peptides decreasing or having no effect on IMPase activity in the presence of of calbindin D28k's.

Advantages

Lithium is far from being a satisfactory drug due to disturbing side effects and a narrow therapeutic window above which the drug is cytotoxic. The suggested peptides will serve as lead compounds for safer and more efficient drugs for the treatment of bipolar and other disorders that benefit from Lithium treatment.

Patent Status

Patent pending

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