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Role of DAG Signaling Pathway in Bipolar Disorder

Alagu Thiruvengadam*

Retired Scientist, 76-6331 Kololia Street, Kailua Kona, HI 96740 , USA.

***Correspondence:**
Alagu Thiruvengadam, Retired Scientist, 76-6331 Kololia Street, Kailua Kona, HI 96740, USA.

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ABSTRACT

Lithium is an effective mood stabilizer in 70-80 percent of bipolar disorder patients. It has been observed that the membrane potential is hyperpolarized in bipolar patients and lithium treatment depolarizes it. Hokin and his colleagues found that the lithium increases accumulation of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) in brain cortex slices in species ranging from mouse to monkey. DAG and IP3 activate the DAG signaling pathway depolarizing the membrane potential. The DAG signaling pathway regulates the calcium activated potassium (CAK) channels. The CAK channels in turn control the membrane potentials and excitabilities of neurons. The clinical observations that the membrane potential is hyperpolarized (lower) in bipolar disorder patients and lithium depolarizes (increases) are explained using the action of DAG signaling pathway. Lithium increases the concentration of DAG thereby increasing the activity of DAG signaling pathway which controls the potassium flow through the CAK channel. If this result is established through further independent corroboration it would greatly enhance our understanding of the mechanisms of bipolar disorder. Knowledge of this signaling pathway elucidates how lithium treats bipolar disorder.

Additionally, the mechanism of induced switching associated with certain antidepressants given to patients who are bipolar can also be explained by this pathway. Further analysis of this pathway would lead to the discovery of new drugs for this disease.

Keywords

Bipolar Disorder, Lithium Efficacy, Membrane Potentials, Diacylglycerol Signaling Pathway.

Abbreviations

BD: Bipolar Disorder; CAK: Calcium Activated Potassium Channel CaM: Calmodulin; cAMP: Cyclic adenosine 3',5'-monophosphate DAG: Diacylglycerol; DGK: Diacylglycerol Kinase EtOH: Ethyl Alcohol; GPCR: G-Protein Coupled Receptors; hSK: human Small Conductance Potassium Channel; IP3: Inositol Triphosphate; KCNN: Potassium Channel NN MP: Membrane Potential MPH: Methylphenidate; MPR: Membrane Potential Ratio PA: Phosphatidic Acid; PIP2: Phosphatidylinositol 4,5-bisphosphate ; KA: Protein Kinase A; PKC: Protein Kinase C; PMA: Phorbol 12-Myristate 13-Acetate.

Background

Calculations of the membrane potentials in neurons using Goldman-Hodgkin-Katz equation showed that they are hyperpolarized in bipolar patients and lithium treatment would depolarize them [1]. Analysis of the equivalent electrical circuits showed that the excitability of neurons would be lowered by lithium [2]. There were experimental and clinical results supporting these calculations. Laboratory experiments using red blood cells from bipolar patients were hyperpolarized. This led to the question of the common link between red blood cells and neurons. The answer led to the diacylglycerol (DAG) signaling pathway [3]. The calcium activated potassium (CAK) channels give rise to the

membrane potentials. The CAK channels are part of the DAG signaling pathway. There are four members of the family of CAK channels (SK1, SK2, SK3 and SK4). SK1, SK2 and SK3 are widely distributed in the brain including the limbic brain whereas SK4 is distributed in the peripheral cells. The selectivity filter of the SK family is directly responsible for the selective and rapid conductance of the potassium ions. This filter is highly conserved in all the family members. This reflects the connection between the RBCs and neurons [3].

The Calcium Activated K Channels are controlled by the DAG signaling pathway.

DAG Signaling Pathway

In one of the biological signaling pathways, diacylglycerol functions as a second messenger signaling lipid [4]. DAG is a product of the hydrolysis of the PIP2 (phosphatidyl inositol-bisphosphate) by the enzyme phospholipase C. It produces inositol triphosphate (IP3) through the same reaction. Although IP3 diffuses into the cytosol, diacylglycerol (DAG) remains within the plasma membrane due to its hydrophobic properties. The production of DAG in the membrane facilitates translocation of PKC from the cytosol to the plasma membrane [5].

Hence, both DAG and PKC play important roles in several signal transduction cascades. Calcium activated potassium channels (CAK channels of which hSK4 is a member) are activated by Calmodulin (CaM). CaM is a widespread and abundant transducer of calcium signaling in cells. It can bind to and regulate a number of different protein targets, thereby affecting many different cellular functions. Calcium gating is the primary mechanism controlling the potassium flow through the pores in the small conductance CAK channels. CaM is responsible for this calcium gating [6]. CaM, in turn, is modulated by the following two important signaling pathways in the cell. The cAMP pathway and the DAG pathway are activated by the G-protein coupled receptors (GPCR) which receive the signal from external stimuli by the ligands [7]. Promoters and inhibitors of the primary proteins were used to determine the pathway controlling the MPs in RBCs [3].

Lithium Activates the DAG Signaling Pathway

Hokin et al. [6] found that the lithium increases accumulation of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) in brain cortex slices in species ranging from mouse to monkey. However they could not connect their result directly to the illness since the relationship to the DAG signaling pathway was unknown then. If we consider the neuron as a radio transmitter the neurotransmitter activates the g-protein receptors. They activate the DAG signaling pathway which in turn controls the CAK channels. The membrane potentials generated by the CAK channels travel down the axon as action potentials and release the neurotransmitters. Now we know that the DAG signaling pathway controls the calcium activated potassium channels that control the MP and excitability of neurons. Thus the DAG signaling pathway connects the neurotransmitter signaling to the excitability of neurons in this disorder providing a holistic understanding of the mechanism of BD.

The Switching of Depression to Mania by Tricyclic Antidepressants

The switch-inducing potential of antidepressants is unclear, although tricyclic antidepressants, which confer higher risk of switching than other classes of antidepressants, are a possible exception [7]. “Despite the fact that it is a core aspect of the clinical presentation of bipolar disorder, the neurobiology of the switch process is still poorly understood [7]”. Tricyclic antidepressants are anti-cholinergic agents and they block DAG signaling pathway thus hyperpolarizing the membrane. This explains how the switching process works.

Concluding Remarks

The DAG signaling pathway plays a critical role in the cause of bipolar disorder. Lithium efficacy in bipolar disorder patients is explained by this pathway. The hyperpolarization and depolarization of membrane potentials are also explained by this pathway. The finding by Hokin and his colleagues that the lithium increases accumulation of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) in brain cortex slices in species ranging from mouse to monkey is explained by this pathway. DAG and IP3 activate the DAG signaling pathway depolarizing the membrane potential. The DAG signaling pathway regulates the calcium activated potassium (CAK) channels.

The CAK channels in turn control the membrane potentials and excitabilities of neurons. The clinical observations that the membrane potential is hyperpolarized (lower) in bipolar disorder patients and lithium depolarizes (increases) it are explained using the action of DAG signaling pathway. Lithium increases the concentration of DAG thereby increasing the activity of DAG signaling pathway which controls the potassium flow through the CAK channel. Additionally, the mechanism of induced switching associated with certain antidepressants given to patients who are bipolar can also be explained by this pathway. The decreased activity of the pathway sends the patient into a manic state. These observations indicate that the DAG signaling pathway controls the mood states. If these results are established through further independent corroboration it would greatly enhance our understanding of the mechanisms of bipolar disorder. Knowledge of this signaling pathway elucidates how lithium treats bipolar disorder. Further analysis of this pathway would lead to the discovery of new drugs for this disease. These clinical observations lead one to conclude that the malfunctioning of the DAG signaling pathway is the cause of bipolar disorder.

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