Of Mice and MAGL (Monoacylglycerol Lipase)

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Abstract

About 18.8 million American adults suffer depressive disorders that may occur with anxiety and substance abuse. Tetrahydrocannabinol (THC), a compound in marijuana, is a cannabinoid chemical that binds to and activates cannabinoid receptors (CB1) in the pre-synaptic cell membrane as part of neuron-to-neuron transmission in the endocannabinoid system (ECS). Glutamate in the pre-synaptic cell is released and binds to the post-synaptic cell triggering the synthesis and release of 2-arachidonoylglycerol (2-AG). 2-AG returns to the pre-synaptic cell binding to and activating CB1 receptors. THC mimics 2-AG action, and is used to study the ECS retrograde signaling system and its effect on appetite and mood. A protein from the pre-synaptic cell, monoacylglycerol lipase (MAGL), hydrolyzes 2-AG into arachidonic acid (AA) and glycerol controlling 2-AG levels. When MAGL is hyperactive, too much 2-AG degrades, causing 2-AG shortage, prompting depression, anxiety, and other neurodegenerative diseases. Hypoactive MAGL activity creates an excess of 2-AG, causing obesity, diabetes, and addictive behaviors. The Brown Deer Students Modeling a Research Topic Team, in alliance with MSOE, built a MAGL model using a 3D printer. Study of MAGL hydrolysis sites may provide the key to regulating MAGL’s enzymatic activity leading to therapies that will prevent neurodegenerative disorders.

Introduction

Approximately 80% of the 18.8 million American adults suffering from the serious neurological disorder known as depression are not receiving any treatment. Elucidation of neural signaling mechanisms in the brain may lead to more effective treatments. Specific brain cells called neurons transmit messages from pre-synaptic neurons to post-synaptic neurons across a gap called the synapse using neurotransmitter chemicals. One potential target of drug treatment is the regulation of the enzyme monoacylglycerol lipase (MAGL), found in the endocannabinoid system, shown in Figure 2. MAGL is an enzyme found in the pre-synaptic cell that hydrolyzes 2-AG:

- Increase in MAGL activity decreases 2-AG concentrations resulting in depression and anxiety.
- Decrease in MAGL activity increases 2-AG concentrations producing anti-depressant effects.

Inhibition of MAGL will increase 2-AG, therefore making MAGL a good target for drug therapy of depression.


Research has been conducted using mice to study their marble burying behavior. Mice normally demonstrate anxious behavior when foreign objects are placed in their cage. When marbles were introduced the mice responded by frantically trying to bury them. The y-axis demonstrates the number of marbles buried with a vehicle and increasing concentrations of JZL184. The vehicle includes the experimental protocol used to inject the mice. The data shown in Figure 5 illustrates that injection of JZL184 reduces the anxious behavior of the mice causing them to bury fewer marbles.

Biological Significance

JZL184 has an inhibitory effect on MAGL activity. Regulation of MAGL activity could effectively treat anxiety and depression disorders in human.