GABA<sub>A</sub> Receptor’s Role in Keeping the Brain Calm

Pius XI SMART Team: Steven Brzezinski, James Carian, Katie Eszes, Bilal Garner, Brittany Givens, Jenna Motz, Bernie Mulvey, Richa Rathore, Joseph Schwemmer, Kathryn Sulik, Stefan Thompson, Jordan Zawacki, Sydney Zettler

Teachers: Julie Fangmann, Mimi Verhoeven
Mentor: David Wagner, PhD, Marquette University

Abstract

Numerous neurological pathologies, such as anxiety disorders, epilepsy, and insomnia, are due to neurons in the brain malfunctioning by being overactive. Like a stop sign directing traffic, the activation of gamma-aminobutyric acid (GABA<sub>A</sub>) receptors reduces neural activity preventing neurons from firing excessively. When GABA binds to the GABA<sub>A</sub> receptor, negative chloride ions flow into the neuron. This inhibits neural activity because neurons need a net positive charge inside them to send messages. GABA<sub>A</sub> receptors are targets for depressants, including alcohol, benzodiazepines (such as Ambien™, Valium™, and Xanax™), and general anesthetics. These drugs bind to the GABA<sub>A</sub> receptor to increase inhibition of neural activity. The specific GABA binding site(s) on the GABA<sub>A</sub> receptor are unknown. Current research focuses on altering amino acids potentially involved in binding GABA. If one of these amino acids in the binding site is altered, GABA will unbind faster from this mutated GABA<sub>A</sub> receptor than it does from the wild type (normal) receptor. Finding the specific amino acids involved in binding GABA could lead to breakthroughs in GABA<sub>A</sub> receptor-related pathologies and allow for better design of new drugs.

Introduction

Seizures and insomnia are more common than most people realize. These pathologies occur when brain cell activity is not properly regulated. GABA, a chemical, slows brain cell activity when it binds to its receptor. If the GABA<sub>A</sub> receptor is misshapen, GABA cannot bind, making it less effective at inhibiting neural activity. If brain cells fire uncontrollably, then insomnia or seizures may occur. Drugs, such as alcohol, benzodiazepines (Ambien™) and general anesthetics, currently target GABA<sub>A</sub> receptors, but the exact GABA binding site is currently unknown.

I. Basic Function of Neurons

II. GABA and the GABA<sub>A</sub> Receptor

III. Neural Inhibition Due to GABA Binding

IV. Proposed GABA Binding Sites

The exact location of the binding site of GABA is unknown. Current research focuses on several amino acids (such as βArg207, βPhe200, αArg120, and αArg67) in the α-β interfaces of GABA<sub>A</sub> receptors. Dr. David A. Wagner mutates amino acids on the GABA<sub>A</sub> receptor to determine how it alters the rate at which GABA unbinds, thus indicating if it plays a role in GABA binding.

A mutation in one amino acid (Arg207) causes GABA to unbind much more quickly than GABA unbinds from the wild type (unmutated) GABA<sub>A</sub> receptor. In this case (βR207A), the 207<sup>th</sup> amino acid (an arginine) is mutated to alanine. These data suggest this particular amino acid is part of the GABA binding site.

Future Research and Drug Design

The exact GABA binding site on the GABA<sub>A</sub> receptor remains a mystery. As research continues to improve knowledge of the GABA<sub>A</sub> receptor, new drugs can be designed to specifically target the GABA<sub>A</sub> receptor’s GABA binding site. These drugs could then inhibit neural firing more effectively, offering better treatment of insomnia and epilepsy.