Title of the project: "Unlocking Synapses: Role of Astrocytic IGFBP2 in Synaptic Plasticity"

What is the problem?

Our brain contains billions of nerve cells called neurons, which communicate with each other through tiny connections called synapses. Think of a synapse as a small gap where one neuron sends a message to the next, allowing information to travel throughout the brain. Our brain's remarkable ability to learn new things, form memories, and adapt depends on a process called by scientists "synaptic plasticity", where the connections between neurons strengthen, weaken, or reorganize. This fundamental mechanism is obviously essential for everyday learning but when it malfunctions, it can lead to many neurological and psychiatric disorders, including Alzheimer's disease, schizophrenia, autism, depression, or epilepsy.

However, the brain is not just made of neurons. It contains almost as many cells called astrocytes, which look like tiny stars. Because astrocytes do not conduct electrical signals like neurons, they were long thought to be just "brain glue," hence their general name – glia. Yet, astrocytes surround neurons, feed them nutrients and clear away their waste. Crucially, small astrocytic protrusions also touch synapses and recent scientific advances have shown that these "quiet neighbours" of neurons has a lot to say!

Aim of the Project:

Our goal is to describe in detail the complex signals exchanged between astrocytes and neurons that control synaptic plasticity.

Proposed Research:

One important way, how astrocytes communicate with neurons is by releasing special proteins to the extracellular space which surrounds all cells. This space is filled with "extracellular matrix" proteins and complex sugars that supports and influence cells. One key protein released by astrocytes is called IGFBP2 (Insulin-like Growth Factor Binding Protein 2). During learning and memory recall, astrocytes produce more IGFBP2, which controls another molecule important for strengthening synapses, called IGF1 (Insulin-like Growth Factor). However, IGFBP2 holds onto IGF1 like a clam shell, keeping it inactive until the right moment.

Here's where an enzyme released by neurons, called MMP-9 (Matrix Metalloprotease 9), acts like a molecular switch. MMP-9 cuts IGFBP2, freeing IGF1 to activate neurons and strengthen their synaptic connections exactly when needed. This precise control helps the brain learn and remember effectively.

In the project, we will study how this system operates under normal conditions and how it may become disrupted in Alzheimer's disease models. Ultimately, understanding how astrocytes communicate with neurons through proteolytic control of growth factor signalling could reveal new therapeutic strategies to restore brain plasticity and cognitive function in neurodegenerative diseases and other brain disorders.

To study memory, we will use a method called fear conditioning. In this test, a mouse is placed in a box where it receives a very mild electric shock (the mouse is unharmed but finds it unpleasant). When the mouse is placed in the same box the next day, it "freezes" because it remembers the unpleasant experience. However, in conditions like Alzheimer's disease, mice often forget and do not freeze, revealing memory impairment.

Expected results:

By shining light on this "astrocyte-extracellular matrix-neuron" communication triad, we hope to unlock new insights into the brain's capacity to learn, remember, and heal itself.