Title of the project: Role of astrocytes in chronic stress resilience

What is the problem?

Major Depressive Disorder or depression is a chronic, recurrent, and debilitating mental illness affecting over 25 million people per year world-wide. Although the neurobiology of depression has been intensely studied for several decades, its underlying cause is still not fully understood, and nearly 30% of patients with depression don't get better, even after multiple treatment attempts. Modern stressful life is the environmental trigger for depression, yet many individuals do not exhibit depressive or anxiety symptoms after exposure to traumatic events or chronic stress.

Recent reports indicate that resilience in humans represents an active, adaptive process rather than simply the absence of pathological responses observed in individuals more susceptible to stress.

Since the 1950s when pharmacotherapy of depression was first introduced, the prevailing theory of depression was that it decreases neurotransmitter – serotonin in the neuronal connections – synapses. This early "neuron-centric" view of depression is slowly changing mainly because existing theories cannot fully explain pathological mechanisms of depression and additionally, recent discoveries proved that we might not exactly know how antidepressants really work. It turned out that they also directly stimulate the other type of cells present in the brain – astrocytes (a type of glial cells).

This glial cells for a long time has been considered only as a "brain glue", hence their name – glia. However recent technical advances show that those "quiet neighbours" of neurons has a lot to say! Particularly in depression, it turned out that morphology of astrocytes changes and probably is a cause of later neuronal loss as the disorder progresses.

Aim of the Project

The aim of the project is to test if astrocytes can actually be the cells which are responsible for stress resilience.

Proposed Research

Astrocytes produce a cytoskeletal protein – GFAP which levels are almost always increased when something bad happens to the brain, like stroke, or epilepsy, however in patients with depression this protein is downregulated. We want to test if mice which do not have the gene encoding GFAP, would be less resilient to stress. Since GFAP has many functions in astrocytes, it might help us to know what it is exactly.

Additionally, we will use new sequencing techniques and transgenic animals, which (only in astrocytes) have a green fluorescent protein tagged to ribosomes – small cellular factories which produce all proteins in the cell. Brains of those mice actually glow green if illuminated with blue light. Ribosomes need the instruction for protein production and this instruction is mRNA – similar to that which was used in anti-COVID-19 vaccine. Not only ribosomes can read the instruction written in mRNA, we can do this too, and this information can tell us exactly which proteins are produced in the cell at the moment. So now, we can takeout brain from the mice, homogenize it and fish-out only those ribosomes which are tagged to GFP. To do this we will use magnetic beads with antibodies which recognize this green protein. Next thing is easy. We wash the beads from all the things which didn't bind to the antibody, and later isolate mRNA. Later we can read information in mRNA thanks to new "magical" machines, which only a handful of people can operate. So having this method, we can stress a group of mice (yes, it's not very nice) and later see which are resilient and which are anhedonic (they drink less sweet water). Later we can link the information from mRNA with the behaviour we observe, and voilà! We have an answer to the problem of depression. If only it was that easy.

Expected results:

As mentioned before, for a very long time astrocytes was not considered to be very interesting, as they are "silent" in comparison to neurons. However now, as we know more about them, we just don't want to stop, and we want to know even more. I believe, that once we read information written in mRNA of astrocytes, we will be able to point to some new exciting proteins and potential therapeutic targets. We probably don't even know what they might be. Depression is still such a big health problem, and recent times of global pandemic shows us just how badly we need new solutions.