Localization of Ca^{2+} signals involved in gliotransmitter release

a) What is proposed project about?

We can essentially divide cell types found in the brain to: neurons, which actively pass information between each other, and glial cells which originally were considered as a "glue" which holds neurons together. Astrocytes – one of three main types of glial cells are the most abundant cells in the brain. Morphology of an astrocyte resembles a sponge with few main processes starting in a relatively small cell body. It was estimated that an astrocyte can contact over almost two million neuronal connection (synapses) in the human brain. For a long time neuroscientists considered glia as merely supportive cells in the brain which provide ion and water homeostasis, produce and remove neurotransmitters, and provide neurons with nutrients. However revolutionary discovery in 1994 that astrocytes respond to neurotransmitter with calcium waves which can spread across many astrocytes and can subsequently cause calcium signals in neurons lead to appreciation of their neuromodulatory function. These days we consider that releasing specific transmitters (called gliotransmitters) by glial cells is a main mechanism by which astrocytes influence neuronal transmission.

b) Why it is interesting?

The current state of knowledge paints a picture of astrocytes as an integral part of brain networks that not only regulate brain's environment but also process information in parallel with neurons. It seems that increase in astrocytes size and complexity was crucial for the brain evolution as human astrocytes have not only more morphological subclasses but are also over 16 fold larger in volume than those in rodents and are able to propagate 4 times faster calcium waves. Amazingly when human glial progenitors were engrafted into mice brain, they caused enhancement of learning and synaptic plasticity. Moreover reactive astrocytes are a hallmark of nearly all brain pathologies including traumatic brain injury, stroke, ischemia, infectious disease, neuroinflammatory and neurodegenerative disease, epilepsy, brain tumours, depression, schizophrenia and even addiction. It turns out that once activated astrocytes express much more dramatic intracellular calcium elevations and increased gliotransmission. Therefore grasping the link between calcium and gliotransmission is of great importance for our understanding of brain physiology and pathology.

c) Where is it going? What is the goal of the research?

Due to new genetic technologies as well as better microscopes which can image even single molecules we learned in recent years that calcium signalling is much more complicated than previously considered. It also turned out that we do not understand mechanisms of gliotransmission as well as we thought and that many laboratories obtained contrary results while studying influence of astrocytes on neuronal communication. We think that it is a good time to take a step back and instead of creating new even more complex live animal models to tackle certain mechanisms in cultured cells which can be observed with much more detail. We therefore proposed new research which should clarify what are the sources of calcium that lead to release of transmitters from astrocytes.

One of the proposed mechanisms how gliotransmitters are released from astrocytes is by fusion of small vesicles filled with transmitters with cell membrane. This process can occur in almost all cells but not always this process can happen as a reaction to definite stimulus. The goal of this project is to identify calcium signals which are necessary and/or sufficient for vesicular release of gliotransmitters from astrocytes. It will help us to understand glia – neuron communication and possibly design new tools to study this processes in live animals, what can potentially lead to new therapies for brain pathologies.