Description for the general public

Stroke is a medical condition in which poor blood supply to the brain results in cells death. Stroke was the second, after heart disease and before cancer, reason of death worldwide in 2017 affecting in total 6.2 million individuals. The dysfunction of the brain vary widely depending on the size and location of the lesion, but usually corresponds to the area of injury. So far, no effective therapies or devices have been approved to prevent cell death and to promote regeneration of damaged neurons. Despite intensive research, it is still unclear why neurons die when the brain tissue suffers ischemia, and why they lose the ability to regenerate even if the blood flow is restored. The neuroscientists agree that the most plausible reason of this phenomenon is deprivation of neurons and supportive cells from essential blood-supplied trophic factors or losing the responsiveness to the external stimulation. This initiates ischemic cascades making neurons to execute programmed cell death. However, the hope comes with new discoveries showing pro-survival and pro-regenerative effect of cyclic AMP (cAMP), the ubiquitous second messenger in the cells. Enhanced cyclic AMP signaling was able to rescue deficient neuronal transmission through activation of downstream signaling pathways. Every neuron possesses special nodes by which these signals can be properly distributed throughout the cell. It is thought that these highly specialized centers called AKAPs (A-kinase anchoring proteins) could serve as potential sites for targeted enhancement of cAMP signaling allowing neurons to survive and maintain their functionality after injury. In our study, we want to test this hypothesis. Using retinal ganglion cells as in vitro model system, we plan to apply small interfering RNA and FRET-based live cell imaging to identify how generation of cAMP fluxes by different upstream enzymes may contribute to axon outgrowth and what is the role of AKAP located at the nuclear envelope. Then, we will selectively inhibit the players in cAMP signaling cascades to see what their role in neuronal outgrowth is. Based on the in vitro data we further plan to extend our research to animal model of white matter stroke and use virus-based gene therapy vectors to enhance survival and regenerative potential of neurons. We have constructed an adeno-associated virus selectively affecting cells that are frequency damaged in a white-matter stroke of the optic nerve. The virus carrying a message to protect cAMP degradation in the perinuclear compartment turned out to be very promising to enhance axon regeneration and gave a hope to restore vision after stroke. By using these novel gene therapy viruses, we anticipate discovering how to enhance trophic responsiveness and survival of neurons. This would be the significant step forward in the understanding of molecular mechanisms of stroke neuropathology and should reveal a pre-clinical potential of cAMP signaling modulators in developing a new treatment strategy.