

The brain because of its complicated structure, is characterized with limited regenerative ability. For this reason the evolution equipped us with hard skull and spine, which role is to protect Central Nervous System from injuries. But there are more of defense tactics. The inner skull is padded with meninges in which there floats the Cerebral-Spinal-Fluid (CSF). Its role is to provide optimal conditions for the brain to work. Brain organ is so precious, that the nature made it immunologically privileged – it is protected from external factors with blood-brain barrier. This barrier is made by astrocytes – the cells that surrounds the blood vessels that penetrate the brain. This barrier won't let any pathogens or potentially trouble making factors to penetrate inside the brain - even the white blood cells! Fortunately, in the neural tissue there are residing specialized immune cells called microglia. Those cells protect the brain from pathogens that somehow slip through the blood-brain barrier, but they also take part in neural tissue remodeling and regeneration.

Unfortunately, all of those defense systems are helpless if the brain starts to fall ill from the inside. One of the reasons of neural tissue death, can be neurodegenerative diseases, like Alzheimer Disease, Parkinson Disease or Spinocerebellar Ataxia. As the result of those genetic pathologies the neural tissue undergo progressive loss, and the blood-brain barrier gets broken. The symptoms of neurodegenerative disorders are the problems in motor skills, dementia, and death. In the pathology, very often there is involved the microglia that underwent hyper activation. This results with inflammation, which in brain is very dangerous.

There is no effective therapy available for neurodegenerative disorders, so the medicine starts to consider other potential solutions. One of them could be the application of psychedelics – psychoactive compounds from some plants and fungi. According to Food and Drug Administration, psychedelics (in particular psilocybin – alkaloid from *Psilocybe* fungi) in recent years made a breakthrough therapy in psychiatry for Treatment Resistant Depression. Since past two years psychedelics are taken seriously as a prospect candidates to treat neural tissue damage. It appeared that the application of N,N – dimethyltryptamine (DMT) may be applicable to treat stroke. DMT administration in rats reduced stroke infarct and restored post-stroke motor functions. Those results inspired Algernon Pharmaceuticals Company to start Phase I clinical trial on the application of DMT as a first aid to the patients undergoing stroke. It is proposed that the therapeutic mechanism of psychedelic in neural tissue damage treatment, might be related to their ability to stimulate certain receptors on the brain cells. Activation of those receptors protect the tissue from damage by reducing the inflammation inside the neural tissue. The scientists also wonder – could psychedelics stimulate brain stem cells to regenerate this organ?

The aim of the NCN SONATINA 5 project is first preclinical study on application of psilocybin in Spinocerebellar Ataxia type 3 (SCA3). We will investigate how psilocybin affect the brain regeneration of mice that suffers from SCA3. We expect, that this psychedelic will reduce brain tissue inflammation and make hyper active microglia to acquire pro-regenerative character. We hypothesis that it will stop neural tissue loss, induce neural tissue regeneration and maintain blood-brain barrier integrity. As the result, the SCA3 mice will retrieve motor functions. We also plan to perform *in vitro* study, where we will investigate deeper the process of neurogenesis and mechanisms of shaping microglia immune character after LSD, DMT and psilocin induction. As SCA3 display similarities with other neurodegenerative disorders, the project will provide a lot of information about potential medical application of psychedelics in their treatment.