DESCRIPTION FOR THE GENERAL PUBLIC

Some of the most important elements in the nervous system, often overlooked in favor of nerve cells, are microglia and astroglia. These cells form the blood brain barrier, assist in the nutrition the nerve cells, monitor the tissue microenvironment, make up glial scarring, and play an important role in the modulation of pain. Pain is usually a first symptom of disease, and the research indicate that one in five Europeans experienced chronic pain. Neuropathic pain results in a significant deterioration in quality of life, as patients often cannot perform basic activities on their own. These painful symptoms can lead to anxiety, depression, feelings of suffering and a general deterioration of living conditions. Therefore, many doctors and scientists are in search of an effective treatment, which would improve the quality of life of people suffering from neuropathic pain. Recent reports suggest that standard analgesics could be enhanced by the use of substances that modulate the activity of glial cells. One such substance that has been successfully applied in clinical practice in Krakow is pentoxifylline, which in our study showed enhanced analgesic properties in combination with opioids. Activation of glial cells leads to many changes in the cell, with the consequent release of agents mediating analgesic and algesic; however, in developing neuropathy, most factors released are pro-nociceptive.

Our project involves the examination of properties and mechanism of the signaling pathways inhibitors (minocycline, parthenolide) and antagonists of CCR5 and CXCR3 (maraviroc, NBI 74330). The minocycline is an antibiotic belonging to the semisynthetic tetracycline class. It is often used to treat acne and was shown in 2000 to have a protective effect on nerve cells and kidneys in patients with diabetes. Our research has been confirmed by other authors, who have shown that minocycline weakens the development of neuropathic pain by inhibiting microglial activity. However, its exact mechanism of action has not yet been defined and is thus one aim of our research. The second substance selected is maraviroc, which antagonize the CCR5 and is important for inflammatory processes. We hypothesize that it is highly relevant to the formation and maintenance of pain. Importantly, maraviroc is an antiviral drug used in the treatment of HIV-infected patients, although it has never been used for the treatment of neuropathic pain. Our preliminary results indicate that this is a promising drug with strong analgesic potential and beneficial properties modulating clinically used opioids. The aim of our project is to examine changes in the expression of selected GPCRs and factors important for the nociceptive transmission and produced by glial cells during the formation and duration of neuropathic pain and to assess the efficacy of therapeutically promising substances to restore the balance between pro- and analgesic agents, with the ultimate goal of alleviating patient ailment.

Implementation of this project is possible due to the combination of methods from different fields: behavioral biology (model of chronic pain), cell biology (primary cell cultures), and biochemical methods in order to investigate changes in gene expression level (qRT-PCR) and protein (Western blot, ELISA, protein microarray i/lub immunohistochemistry analyses). To assess the interaction of intracellular pathways as well as the influence of drugs and other substances on the morphology and physiology of the cells used in our study, we anticipate using cell cultures of microglia and astrocytes. Cell culture is an essential tool for research in the fields of molecular biology, genetics and immunology, and facilitates our understanding of the mechanisms underlying neuropathic pain, which is crucial for the development of effective therapies. The translational nature of our proposed research is innovative, mainly because of the novel approach to attenuation of neuropathic pain due to inhibition of glial activation using the signaling pathways inhibitors and chemokine receptor antagonists in both *in vitro* and *in vivo* studies. We hope to clarify the nature of the neuroimmune response that leads to the development of neuropathic pain.

In summary, the cells activation within the nervous system generates an immune response that leads to the development of neuropathic pain. An inflammatory response by microglia and astroglia leads to the release of pain-causing factors. The use of the compounds proposed in our project might change the activity of glial cells and restore the balance between pro-nociceptive and anti-nociceptive factors. Thanks to the introduction of combination therapy using standard analgesics and substances that modulate glial cells, we can achieve the alleviation of unpleasant symptoms associated with the sensation of pain. The results obtained in this project will extend our knowledge of the mechanisms of formation and maintenance of neuropathic pain and will aid in the development of new treatments.

***Everything that the human race has done and thought is concerned with the satisfaction of deeply felt needs and the assuagement of pain.* - Albert Einstein**