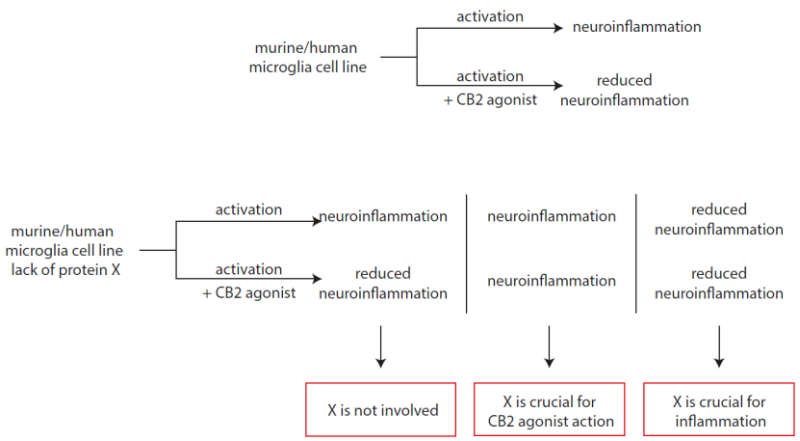
Project goal

One of the most striking features common to various neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, multiple sclerosis and chronic pain, is **microglia-derived neuroinflammation**. Microglia is a type of non-neuronal cell that plays the role of resident immune cells in central nervous system (CNS). Under normal conditions, microglia monitors the environment and interacts with physiological stimuli that perform various functions that contribute to the maintenance of CNS homeostasis, while during chronic activation microglia cells undergo **pyroptosis** (a form of regulated pro-inflammatory cell death), causing a widespread and prolonged inflammatory response. In our research, we will focus on the main pyroptosis-related complex - **NLRP3 inflammasome**, which is a potential target in the above-mentioned diseases, which currently lack effective treatment methods. Several promising strategies have been proposed for inhibiting microglia-derived neuroinflammation, one of which is based on the **pharmacological modulation of the cannabinoid type 2 receptor (CB2)**, which is known to be associated with both inflammation relief and neuroprotective properties. The mechanism and molecular pathway leading to the observed effects of CB2 receptor activation are still unclear. In our project, we postulate that the **neuroprotective function of stimulation of the CB2 receptor may be involved in suppressing the activation of the NLRP3 inflammasome in microglia-derived pyroptosis** in the CNS.

Research plan

Our studies will be conducted simultaneously in mouse and human microglia cells to compare the results in both species and provide data that will be more likely to be used in potential clinical treatment. To prove our hypothesis, we will prepare microglia cell lines that will not express the enzymes of the NLRP3 inflamasome pathway and check whether their absence affects the size of the immune response and whether they are necessary to lower the immune response after activation of the CB2 receptor. The outline of the study is shown in figure.



Awaited results

Although knowledge of the NLRP3 inflammasome pathway has been extensively studied in the last decade, the relationship between the components is still not fully understood, especially in microglia-derived neuroinflammation. Our research into microglia cell lines that lack expression of enzymes in this pathway will provide new details about the mechanisms operating in this cell path leading to pyroptosis.

In the present study we propose a new approach to pharmacological modulation of the NLRP3 inflammasome pathway in microglia cells. We believe that the anti-inflammatory effect of the CB2 receptor is directly / or indirectly dependent on the activity of the enzymes involved in pyroptosis mediated by the NLRP3 inflammasome. Our research, establishing these connections, will allow for the first time to determine the full molecular pathway of CB2 receptor anti-inflammatory activation in microglia.

The results of the proposed project may lead to the development of a completely new branch of pharmacological research combining the cannabinoid receptor system with the activity of pyroptotic enzymes in neurodegeneration derived from microglia.