Research assumptions:

Migraine is a common condition associated with severe, disabling headaches. It is estimated that over a billion people suffer from migraines worldwide, making migraine one of the most common conditions. As a result, it is estimated that migraine is one of the most socially costly neurological disorders It is estimated that migraine generates nearly EUR 30 billion in annual costs in the EU alone. The frequency of migraine in the Polish population is estimated at about 8%, of which over 70% are women. The pathogenesis of migraine is not fully clear, there are indications for both neurological, neurovascular and genetic causes. Drugs most often used for migraine headaches, from the triptan group, are unfortunately poorly tolerated by some patients or even ineffective.

The mechanisms of migraine formation and the study of their treatment strategies are possible thanks to studies on model systems in which symptoms are induced by the administration of nitroglycerin (NTG).The measurable symptoms include: (1) hypersensitivity to pain (allodynia), (2) photosensitivity (photophobia), (3) aversive behavior associated with avoiding sites associated with administration of NTG, (4) impairment of social functions associated with migraine. Thus, we can study the so-called affective component of pain, which is the emotional component, associated with unpleasant feelings experienced during the course of migraine pain.

The nociceptin receptor (NOP) is a protein in the family of opioid receptors that regulates the activities of the nervous system related to, among other things, pain and emotions. Studies in recent years have shown the significant potential of this receptor in the analgesic effect. Contrary to the classic opioid receptors, drugs that act on NOP do not show any addictive tendencies. Our recently published results and preliminary studies showed that NOP activating compounds were effective in relieving acute symptoms of migraine, including allodynia and photophobia. So far, there is insufficient information to explain whether NOP receptor activation is associated with the alleviation of negative affective experiences in migraine pain associated with social disorders.

The aim of the research is to identify areas of the brain and individual neurons activated in migraine pain and to verify the hypothesis that the NOP system regulates affective migraine pain as well as photophobia and impairment of social functions accompanying migraine using pharmacological in conjunction with genetic engineering.

An innovative aspect of the project is the identification for the first time (using transgenic and chemogenetic tools) of individual neurons responsible for transmitting pain signals in migraine.

Description of the planned research:

We know from our preliminary research and literature data that NTG administration induces migraine symptoms. However, it is not entirely clear which areas of the brain and which populations of neurons are involved in the development of these symptoms. The use of a unique, transgenic strain of mice will allow us to trace the contribution of individual neurons to the formation of affective migraine pain. Genetically modified animals exhibit fluorescence in in neurons activated by pain stimuli in induced migraine. Microscopic examination will be used to identify active brain regions and specific neurons, where we will also be able to verify the coexistence of NOP receptors.

The identification of these activated areas will allow for the assessment of their importance using the chemogenetics method. The experimental model used here will be modified to enable the activation of selected populations of neurons by administering a suitably designed chemical compound. Thus, it will be possible to determine whether the activation of the previously identified population of neurons is sufficient to induce the symptoms of migraine. In addition, by using appropriate NOP receptor ligands, we will explain whether the activation of these receptors is associated with the alleviation of negative affective symptoms of migraine headache, including photophobia and social disorders.

Expected results: The proposed research will provide us with a better understanding of the mechanisms of migraine formation and the methods of its pharmacology. This is especially true of the hitherto unexplained negative affective symptoms of migraine headache, photophobia and social disorders. This information can lead to the identification of new therapeutic targets for more effective and safer treatments for headache, including migraine pain.