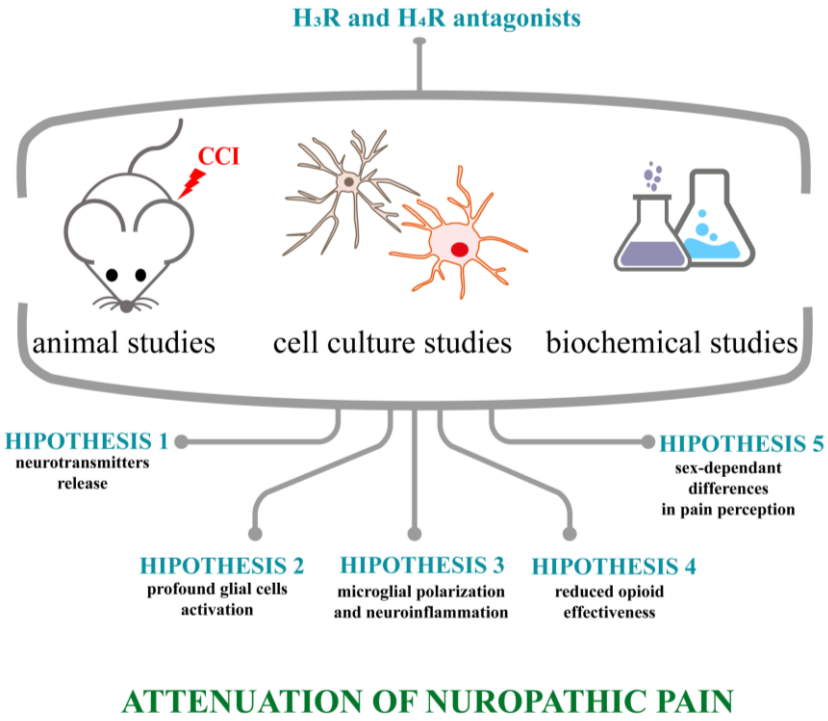
DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Neuropathic pain is a chronic pain condition, which can develop when the nerves of the somatosensory nervous system become injured in consequence of various diseases, including tumours, diabetes, multiple sclerosis, HIV infections, or after surgeries. It is estimated that this type of chronic pain affects 6.9-10% percent of the general population and its pathology is more frequent in women (8%) compared to men (5.7%). Epidemiological studies demonstrate a higher occurrence of pain-related disorders (including migraine, fibromyalgia, arthritis) in women, which is connected with a frequent use of analgesics. Moreover, neuropathic pain is relatively less responsive to opioids than other types of pain, which is possibly due to a disrupted opioid system partially caused by a profound glial cells activation and neuroinflammation. Chronicity of symptoms and not fully understood development mechanisms make neuropathic pain a burning problem for the worldwide healthcare and represent a significant, yet unmet medical need. The results of our recent studies suggest that pharmacological modulation of histamine receptors H_3 (H_3R) and H_4 (H_4R) is particularly interesting direction for research on novel therapeutic targets for the management of neuropathic pain.

In the frame of our project we are planning a series of studies designed to investigate the mechanism of H_3R and H_4R antagonists-induced analgesia during neuropathic pain. The project proposes an innovative and comprehensive series of experiments, including the use of novel H_3R and H_4R antagonists. Moreover, keeping in mind that increasing the efficacy of drugs is an important strategy for improving the management of chronic pain, the research tasks proposed in this project focus on the problem of the loss of opioids effectiveness in neuropathy. Our preliminary data show that H_3R and H_4R antagonists potentiate morphine analgesia. This important implication of opioid effectiveness raises great hopes for future pain therapy. Therefore, in the present project we are planning to combine clinically used drugs (such as buprenorphine, oxycodone) with H_3R and H_4R antagonists to improve opioids effectiveness and minimalize therapeutic doses. An important aspect of neuropathic pain is gender-related pain prevalence, which still remains an unexplored issue. Therefore, in the frame of our project we will investigate the mechanism underlying the differences in the perception of pain stimuli and analgesic response to H_3R and H_4R antagonists by males and females under neuropathic pain conditions. We believe that this direction of studies in the field of pain may help us to develop sex-specific treatments in future therapy. Additionally, an important element of the project is our interdisciplinary cooperation with chemists, which allows us to test new compounds with potential analgesic effects. The implementation of the project will be possible thanks to the combination of various experimental methods, such as behavioural tests (animal model of neuropathic pain), primary glial cell cultures (microglia and astrocytes) and a biochemical analysis (**Scheme**).

Moreover, the limited efficacy of drugs (such as opioids), high risk of side effects, and observed differences in pain perception between sexes prompt us to seek molecular mechanisms of these phenomena. Therefore, the objective of the project is to deepen our knowledge on the mechanism of H_3R and H_4R antagonists action in neuropathy and provide new perspectives, which may help to design effective therapy of this pathology. We believe that knowing the mechanisms of H_3R and H_4R antagonist analgesia will also allow us to understand their contribution to the intensification of opioid effects and gender- related differences in pain sensations



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