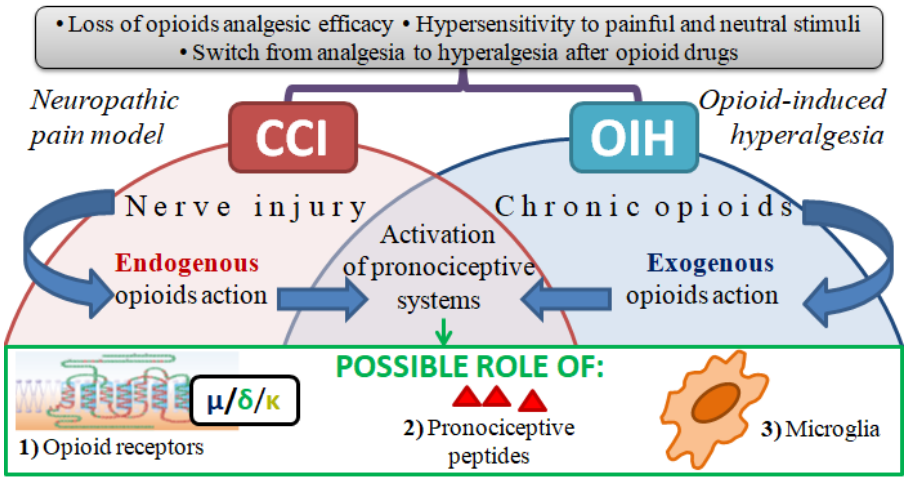
The need to find an effective therapy for chronic pain is still a very vital task of modern medicine. Chronic pain carries plenty of negative consequences for patients, such as the decreased quality of their life and the enforced change of their lifestyle, and for the society as a whole, for instance the growing needs of social care and high costs of medical care. The most important reasons for the lack of an effective therapy for such pain include the chronicity of diseases, which entails the need for the long-term use of medications, and the increased risk of side effects. Difficulties in such therapy are also caused by the weakening of the analgesic effects of opioid drugs in neuropathic pain. Current knowledge does not allow for indicating the sources of changes in the effectiveness of opioid drugs in this type of pain. The resolution of this issue is therefore delayed. In the light of the above, an effective and safe therapy is of utmost importance to the aging societies of the modern world and the quality of their life.

The project represents the outcome of many years of the manager's research on the mechanisms of endogenous opioid systems and their role in a nociception process. The project will investigate the changes underlying a decrease in the potency of opioid drugs in neuropathic pain and a parallel decline in hypersensitivity to sensory stimuli, hindering patients' daily routines. The research will also take a closer look at the mechanism of hypersensitivity development referred to as opioid-induced hyperalgesia (OIH) after repeated administrations of opioid drugs. OIH, with its unknown mechanism, is the cause of numerous therapeutic problems. According to our hypothesis, these two phenomena share common mechanisms. They both involve the activation of factors triggering pronociceptive systems (as a part of maintaining homeostasis) in response to the elevated activity of analgesic opioids induced by a tissue damage. In these two examined models, analgesic stimulation is caused by either endogenous opioid receptors ligands (neuropathic pain model, CCI) or multiple administrations of an opioid drug (OIH). Pronociceptive peptides, which become activated in response to this stimulation, come from various sources, e.g. opioid precursors, neuropeptide systems and/or activated microglial cells. Microglia are activated in response to a tissue damage. They constitute an important component of changes in chronic pain and have a documented impact on the effectiveness of opioid drugs. Their role in the investigated events, especially pronociceptive cytokines of microglial origin, requires further clarification in *in vivo* and *in vitro* tests. The differences in the activation of an opioid receptor by particular ligands may also be of great importance for activating the pronociceptive systems. The processes following the binding of a ligand with a receptor, such as the internalization of a receptor and the cascade of secondary messengers, affect the condition of such receptor, its availability and may be the cause of the development of tolerance to analgesic effects. Our previous studies indicate differences in opioids effectiveness depending on their affinity for a mu or delta opioid receptor, but the significance of these differences for the investigated problem requires a new and broader methodological approach.

The implementation of the project will be possible by means of combined methods from various areas: peptide biology (proteomics), cell biology (glial cells cultures), behavioral models (chronic pain model, CCI model, and OIH – opioid hypersensitivity model), genetics (gene expression) and interdisciplinary cooperation with chemists synthesizing hybrid chemical compounds – potential new analgesics. The solution to this issue requires a comprehensive experimental approach based on the latest knowledge of medical biology.

The project will, on the one hand, determine the mechanisms of the occurrence of undesired effects after the administrations of selective opioids and opioid drugs, and on the other hand, it will look for new targets for preventing adverse side effects which weaken pain therapy. The civilizational progress of the world's population also includes the effective treatment of chronic pain. Achieving this goal is not possible without comprehending the processes hidden behind its development. Their understanding and use in designing new therapies is the main aim of our project.



EXPECTED BENEFITS RESULTING FROM THE RESEARCH:

Multidimensional approach *based on research results (innovative hybrid compounds) might help* ***alleviate hypersensitivity more efficiently*** *than a standard monotherapy*