

The overlap between cannabinoid and nociceptin signaling and its role in intestinal inflammation

Inflammatory bowel diseases (IBD) is a group of non-infectious diseases which comprises mainly Crohn's disease and ulcerative colitis. Generally, the development of these diseases in human body is widely accepted to be multifactorial. Among others environmental and genetic factors are considered to play role. IBD are the most common in highly developed countries and by the "westernization" of central European countries the increase in IBD incidence is observed in this region. IBD are bound with times of remission when the disease produces no symptoms and flares, with symptoms such as abdominal pain, bloody diarrhea for up to 20 stools per day. Although knowledge of IBD development increases, still no cure is found and the treatment relies on extinguishing the flares. However, present drugs often produce adverse effects and sometimes fail to induce remission. Not to mention a necessity of surgery in some patients which is often debilitating and is not equivalent to an end of the disease. All these features lead to the impairment of quality of life in patients suffering from IBD. Adding the fact that IBD usually develops in young adults which are professionally and socially active, it further worsens their well-being. IBD are also a significant burden to the local health care system due to repeated hospitalization and the need therapy intensification. Therefore, new treatment options are needed.

Because of the multifactorial cause of IBD, a wide variety of fields are being examined, such as the endogenous cannabinoid system (ECS) and the opioid system. ECS consists of endogenous ligands, cannabinoid receptors 1 and 2 (CB1, CB2) and enzymes that synthesize and degrade the ligands. Nociceptin receptor (NOP) is a "non-classical" receptor of opioid receptor family which resembles other opioid receptors only in structure. Both ECS and NOP were already proved to be connected to intestinal inflammation and activation of both produce anti-inflammatory effects in laboratory models of IBD. The direct use of ECS is limited due to effects on central nervous system such as drowsiness, sleepiness, dizziness and even depression, paranoia and hallucination. However, ECS is complex because ligands other than cannabinoids were found to activate CB1 and CB2; moreover, cannabinoids activate receptors other than CB1 and CB2.

The cross-talk is evident for ECS and NOP, but it was not yet studied in intestinal inflammation. Our project will try to shed a light on this phenomenon. To achieve this the use of several methods is planned to carry in animal and human material. In case of the former, the model of chemically induced intestinal inflammation will be conducted with an administration of selective antagonists of CB1 and CB2 and agonist of NOP either alone or simultaneously. At the end of the experiment the material from large bowel will be taken for further examinations. The degree of inflammation will be assessed macro-and microscopically using specifically designed scales. Also, the myeloperoxidase activity will be measured which is the sensitive indicator of infiltration by neutrophils, the main acute-phase inflammatory cells. The level of pro-inflammatory cytokines will be assessed using molecular biology methods. Next, the Western blot analysis will be used to apprise the changes in the level of various secondary messengers in the cells of collected tissues. During the project the human material will be gathered: colonic biopsies from patients with IBD and patients with no pathology revealed at colonoscopy and midoperative material from patients with IBD and patients with no inflammatory disease in history undergoing surgery. Both animal and human material will be used to: (i) determine the co-localization of cannabinoid receptors and NOP in tissues using histological methods, (ii) measure the expression of these receptors in regard with disease activity, (iii) examine the ligands of both receptors in tissue.

Our project aims at explaining the molecular bases of cross-talk between ECS and NOP. Also, long-term objective is to help develop future drug candidates for IBD based on results of our proposal.