

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder with several underlying factors disrupting gut and systemic homeostasis, whose symptoms can be attenuated principally by pharmacological treatment and/or carefully adjusted diet. Typical IBS symptoms: abdominal pain and dysregulation of GI motility and defecation patterns negatively affect subject's work performance and quality of social interactions. IBS has no fully identified trigger and pathways involved in its development making it difficult to diagnose and to treat. It has been observed that changes in lifestyle and diet, or so called "Westernization of a lifestyle" may contribute to IBS.

Free fatty acids (FFAs), defined as carboxylic acids with an aliphatic tail can be classified depending on their chain length into: short chain fatty acids (SCFAs), containing 1-6 carbon atoms, medium chain fatty acids (MCFAs), with 7-12 carbon atoms, and long chain fatty acids (LCFAs), with more than 12 carbon atoms. FFAs are physiological ligands for specific G protein-coupled receptors (GPCRs), called Free Fatty Acid receptors (FFARs). Four types of FFARs are located on intestinal epithelial cells, endocrine L cells and immune cells present in the GI tract. Current literature shows that FFARs are involved in the pathophysiology of the GI tract disorders for example, they may exacerbate rectal hypersensitivity in IBS patients.

Here we hypothesize that FFAR ligands, that have been only merely studied in view of IBS and LGS, and their interactions with specific FFARs may be crucial for pathophysiology of those disorders. Therefore, the main aim of the project is to evaluate the therapeutic effects of synthetic FFAR ligands in in vitro and in vivo models of intestinal motility, hyperpermeability and abdominal pain. Which molecule/target could be used for IBS and LGS treatment (synthetic ligand of a specific type of FFAR, agonist or antagonist?) remains to be specified during the course of the project.

With the current knowledge on IBS pathogenesis, its treatment is only symptomatic and is based on alleviation of pain and regulation of GI motility disturbances. Anti-IBS drugs include opioids, 5-HT<sub>3</sub> antagonists (e.g. ramosetron) or laxatives (e.g. lubiprostone). However, none of these treatments proved fully effective, and exacerbation periods in the treated patients are very common. Realization of this project will increase the knowledge about the role of FFARs in the pathological states of the gut. Evaluation of the effects of FFAR selective agonists/antagonists may bring additional opportunities to develop novel therapeutics for IBS and LGS. The incidence and prevalence of IBS are high and still increasing. Epidemiology of IBS worldwide is worrisome. It has been estimated that up to 20% (!) of the entire human population has been affected and that IBS is the second – after flu and cold-like symptoms – cause for work absenteeism.