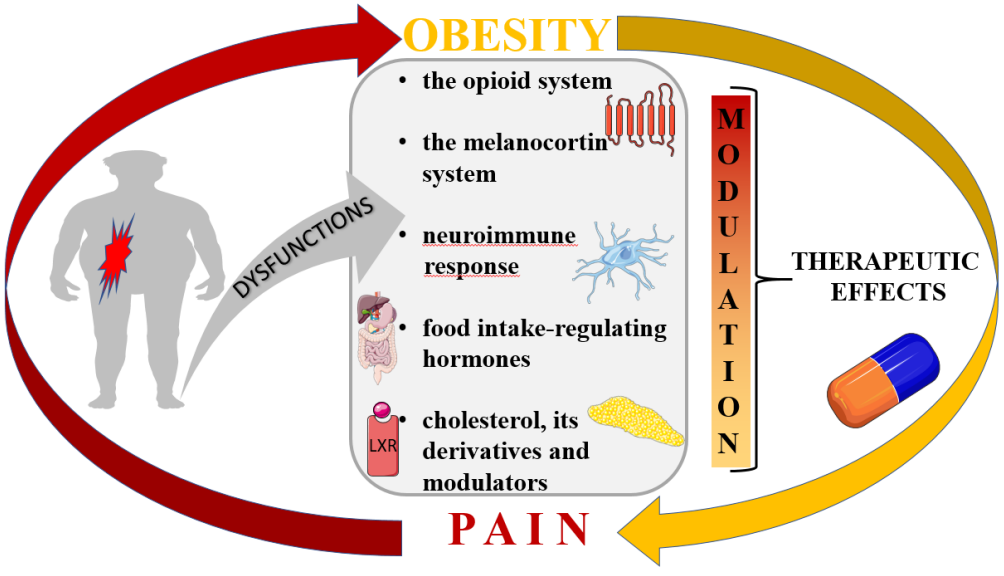
The prevalence of processed foods in the diet, chronic stress and sedentary lifestyle, typical in 21st century Western societies, are not conducive to maintaining a healthy body weight. Meanwhile, obesity is a predictor of many adverse health consequences, including chronic pain. Statistically, people reporting chronic pain to their physician have on average higher total fat mass and waist circumference, as well as higher mean cholesterol and triglyceride levels, which links the metabolic syndrome with an increased risk of developing chronic pain. Furthermore, as clinical studies have shown, obese patients experience chronic pain, including neuropathic pain (i.e. resulting from nerve damage) as more severe than those of normal weight. On the other hand, chronic pain per se may indirectly influence weight gain, through factors such as exercise hang-up, deterioration of sleep quality, side effects of medication, or psychological aspects (so-called "stress eating").

The associations between chronic pain and obesity are therefore complex and multidirectional. The clinical manifestations of these links are reflected in reciprocal dependencies at the tissue and cellular levels. For example, both these pathological conditions are associated with the escalation of the immune response: increased activation of immune system cells, also in the nervous system (**microglia**), and the consequent secretion of inflammatory factors by them, which in turn affects the functions of nociceptive systems, lowering the pain sensitivity threshold. In addition, the results of the latest research reveal a surprising relationship between the processes of cholesterol metabolism and symptoms of hypersensitivity to tactile stimuli, typical of neuropathic pain, through the functions of the liver X receptor (**LXR**). Activation of this receptor regulates physiological lipid metabolism, but also, when activated with an exogenous agonist, reduces the hypersensitivity developed in neuropathy. Further links between nociceptive systems and the regulation of food intake are related to the opioid system and its prohormones. The analgesically acting pro-enkephalin products (**PENK**) influence the food intake through motivational (enkephalin influence) and rewarding (beta-endorphin) action. The so-called hunger and satiety hormones, ghrelin and leptin, not only regulate food intake but also influence nociceptive transmission via receptors expressed on proopiomelanocortin (**POMC**) neurons, which release both pronociceptive (melanotropic hormones - alpha-MSH, adrenocorticotropic hormone - ACTH) and analgesic (opioid peptide beta-endorphin) factors. In turn, both alpha-MSH and ACTH promote pain via the melanocortin type 4 receptor (**MC4R**), which plays an important role in energy homeostatic processes as well. While MC4 dysfunction causes obesity, MC4 blockade attenuates painful hypersensitivity, which probably results i.a. from the fact that the level of pronociceptive MC4R ligands is elevated under nerve injury conditions, which in turn results from compensatory mechanisms arising after nerve trauma.



As the links between adiposis and painful hypersensitivity are so broad, but still not investigated in detail, through accomplishing this project, using in vivo models of obesity, behavioural tests measuring reaction threshold, biochemical analysis methods and in vitro techniques, we hope to discover and describe the common and divergent features of obesity-induced hypersensitivity and neuropathic pain, and to elucidate the cellular causes of the obesity-accompanying exacerbation of neuropathy symptoms, often observed in clinical settings. This will in turn allow for the rational selection of therapeutic targets that would ensure the maximal analgesic efficacy in painful hypersensitivity and in neuropathy states developed under the conditions of adiposis, thanks to taking the characteristics of a specific etiology into account, as well as identifying a marker of an increased risk of neuropathic pain in obese patients.