## Summary

This dissertation deals with the narrow issue of the new perspective research direction, which is research of the possibility of using ghrelin antagonism in the treatment of opioid addiction, which has been rarely studied yet. It summarizes the general principles of neurobiological mechanisms of drug addiction as well as treatment guidelines and procedures based on these findings. The definition of addiction as a disease together with the factors contributing to its formation and course, are presented in this dissertation. The definition includes individual repetitive phases (cycles) of the substance addiction, along with a description of the anticipated involvement of individual brain structures and basic neuromediators involved in these phases, including references to the most important literary findings on the role of ghrelin in the mechanisms of addiction, focused on mechanism of action of ghrelin in the opioid addiction. In the experimental part, the results of the CNS microdialysis experiments in rats, using the GHS-R1A antagonist (JMV2959 pretreatment), were presented in both acute single dose morphine experiment and sub-chronic experiment in which morphine was administered in increasing doses for five consecutive days. The results are presented in relation to changes in the level of dopamine, the major neuromediator involved in addiction processes, where the administration of the GH-R1A antagonist significantly reduced dopamine levels during the acute and sub-chronic experiment. In the dopamine metabolites, 3-methoxythyramine (3-MT) levels, then caused a significant reduction in its concentration increase after the administration of the lower dose of morphine (5 mg / kg, s.c.). Whilst in the 3,4-dihydroxyphenylacetic acid (DOPAC), the higher dose of morphine (10 mg / kg, s.c.), caused the opposite effect and a similar effect was also observed for the homovanilic acid (HVA), in all acute experiments. Similar effect was also observed in dopamine metabolites during the sub-chronic morphine application experiments. Furthermore, the dissertation delineates the influence of the endocannabinoid system and changes in anandamide (AEA) levels, where the antagonist administration reversed the morphine- induced increase and, on the contrary, caused a statistically significant reduction in its concentration levels in the acute and chronic experiment. In the 2-arachidonylglycerol (2- AG), the administration of the antagonist significantly deepened its decrease in the concentration levels in both the acute and sub-chronic experiment. The effect of the abovementioned administration of the ghrelin receptor antagonist on behavioral changes in

the experimental animals (categories - immobility, locomotion, catalepsy and stereotypes), was observed. The JMV2959 premedication significantly reduced morphine-induced behavioral sensitization in both acute and sub-chronic experiment. Furthermore, we confirmed, that pretreatment with JMV2959 significantly reduced the morphine-induced conditioned place preference (CPP) in rats. We observed, that 1, 3 and 6 mg/kg doses of JMV2959 did not significantly influence the rat spontaneous explorative activity in the „open-field“ arena. The presented results support further research of using ghrelin antagonism as a possible treatment of opioid addiction.

**Keywords:**

Opioid addiction, orexigenic hormones, morphine, ghrelin receptor, nucleus accumbens, in vivo microdialysis, conditioned place preference, spontaneous explorative activity, behavioral changes