ABSTRACT

Background: Ghrelin, an orexigenic appetite stimulating peptide, in addition to promoting energy balance, contributes to the rewarding effects associated with overeating. It also seems to play an important role in the rewarding/reinforcing effects of alcohol and addictive stimulants. The involvement of the ghrelin mechanisms in cannabinoid and opioid misuse and addiction have been under-researched.
Aims: The principal aim of this research thesis was to investigate whether the pretreatment with the growth hormone secretagogue receptor 1A (GHS-R1A) antagonist (JMV2959) could reduce the cannabinoid receptor type 1 (CB1R) agonist WIN55,212-2–induced dopamine efflux in the nucleus accumbens shell (NACSh), which is considered a crucial trigger impulse of the addiction process. Also, test whether JMV2959 can influence the WIN55,212-2 and fentanyl-induced effects on the endocannabinoids N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) and the gama-aminobutyric acid (GABA) content in the NACSh, and in extend, to specify the involvement of GHS-R1A located in the ventral tegmental area (VTA) and the NACSh in the observed accumbens changes. Furthermore, to test whether the JMV2959 pretreatment could reduce the cannabinoid [tetrahydrocannabinol (THC) and WIN55,212-2] induced behavioural stimulation.
Methods: In vivo microdialysis was used to determine the changes of dopamine and its metabolites in the NACSh in rats following the synthetic aminoalklylindol cannabinoid WIN55,212-2 administration into the posterior VTA with and without the ghrelin antagonist pretreatment (JMV2959, 3 mg/kg i.p. 20 min before WIN55,212-2 administration) and also to determine the WIN55,212-2 and fentanyl effects on anandamide, 2-AG and GABA accumbens content. The behavioural changes in rats were observed on the fully automated behaviour recognition system (LABORAS) apparatus which monitored the effects of JMV2959 on the THC and WIN55,212-2.
Findings: The WIN55,212-2 administration induced significant accumbens dopamine release, which was significantly reduced by the 3 mg/kg i.p. JMV2959 pretreatment. Simultaneously, the cannabinoid-increased accumbens dopamine metabolic turnover was significantly augmented by the JMV2959 pretreatment. The intracerebral WIN55,212-2 administration also increased the endocannabinoid anandamide and the 2-AG extracellular levels in the NACSh, which was moderately but significantly attenuated by the JMV2959 pretreatment. Moreover, the cannabinoid-induced decrease in accumbens GABA levels was reversed by the JMV2959 pretreatment. The pretreatment with JMV2959 (administered systemically, into the NACSh or VTA) reversed the dose dependent fentanyl-induced anandamide increase in the NACSh, resulting in a significant anandamide decrease and intensified the fentanyl-induced decrease in accumbens 2-AG levels. The behavioural study in the LABORAS apparatus showed that JMV2959 pretreatment significantly and dose-dependently reduced the systemic THC/WIN55,212-2-induced behavioural stimulation in rats.
Conclusions: The overall findings on this research documented the significant contribution of ghrelin / GHS-R1A in the cannabinoid's and opioid's pro-addictive effects and supported further research into ghrelin antagonism as a potential new therapeutic direction in these addictions.

Key words
cannabis – THC - WIN55,212-2 - opioids – fentanyl - ghrelin – GHS-R1A - JMV2959 – NACSh - VTA