ABSTRACT

Background: Cannabis and cannabinoids are frequently used for recreational and therapeutic purposes, but people tend to overlook the associated risks that comes with them. Cannabinoid-associated use disorders and dependence are alarmingly increasing, and an effective treatment is currently lacking. Recently, the growth hormone secretagogue receptor (GHSR1A) antagonism was proposed as a promising mechanism for drug addiction therapy. However, the role of GHS-R1A and its endogenous ligand ghrelin in cannabinoid abuse remains unclear.
Aim: The principal aim of this research thesis was to further investigate whether the GHS-R1A antagonist JMV2959 could reduce the WIN55,212-2 intravenous self-administration (IVSA) and the tendency to relapse, but also reduce the tetrahydrocannabinol (THC)-induced conditioned place preference (CPP).
Methods: In a rat model, the intravenous self-administration directly measured the rat's response to the reinforcement effects of WIN55,212-2 as spontaneous drug-seeking and consumption with pretreatments of GHS-R1A antagonist/JMV2959 or saline. Further, the behavioural changes in rats were observed on the conditioned place preference apparatus which monitored the influence of JMV2959 on the THC effects.
Findings: Following the ongoing WIN55,212-2 self-administration, JMV2959 3 mg/kg was administered intraperitoneally 20 min before for three daily consequent 120-min IVSA sessions, which significantly reduced the number of the active lever-pressing, the number of infusions, and in extent, the cannabinoid intake. Pretreatment with JMV2959 also suggested the reduction of the WIN55,212-2-seeking/relapse-like behaviour tested in rats on the 12 day of the forced abstinence period. Conversely, the pretreatment with ghrelin, significantly increased the cannabinoid IVSA as well as enhanced the relapse-like behaviour. Co-administration of ghrelin with JMV2959 abolished/reduced the significant efficacy of the GHS-R1A antagonist in the cannabinoid IVSA. Furthermore, the pretreatment with JMV2959 significantly and dose-dependently reduced the manifestation of THC-induced CPP. The THC-CPP development was also reduced after the simultaneous administration of JMV2959 with THC during conditioning.
Conclusions: The overall findings on this research documented the significant contribution of ghrelin / GHS-R1A in the cannabinoid's pro-addictive effects and supported further research into ghrelin antagonism as a potential new therapeutic direction in these addictions.

Key words
tetrahydrocannabinol (THC); synthetic cannabinoid; WIN55,212-2; ghrelin; GHS-R1A; JMV2959; intravenous self-administration (IVSA); conditioned place preference (CPP)