EFFECTS OF SYNTHETIC CANNABINOIDS ON MEMORY, LEARNING, EXPLORATION BEHAVIOR, AND THEIR ALTERATIONS IN ENDOCANNABINOID LEVELS

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論文題名 ： EFFECTS OF SYNTHETIC CANNABINOIDS ON MEMORY, LEARNING, EXPLORATION BEHAVIOR, AND THEIR ALTERATIONS IN ENDOCANNABINOID LEVELS（合成カンナビノイドの記憶、学習、探索行動及び内因性カンナビノイドレベルへの影響）

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論　文　内　容　の　要　旨

This research investigates two representative families of synthetic cannabinoids (SCs), 1) those comprising an indole/indazole core structure, MDMB-CHMINACA, 5F-ADB-PINACA , APICA; and, 2) those with a γ-carboline core structure, including CUMYL-PeGACLONE and 5F-CUMYL-PeGACLONE. The primary focus is on the evolution of behavioral responses following SC exposure. The study examines locomotive faculties in terms of exploration and velocity faculties disruption, the manifestation of anxiety-like symptoms, and the impairment of memory and learning abilities, particularly the capacity to recognize novel objects. These assessments were conducted at short-term (1 h), long-term (3 h), and extended-term (5 h) intervals post drug treatment. Additionally, the accumulation of endocannabinoids (ECs), anandamide (AEA), and 2-arachidonoyl glycerol (2-AG) in the hippocampus was measured. Alterations in the ECs' metabolic enzymes - phospholipase D (PD) and diacylglycerol lipase (DAG) (biosynthesis enzymes for AEA and 2-AG, respectively), and fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (degrading enzymes for AEA and 2-AG, respectively)- were quantified following specific drug treatment time frames protocols. This study aims to clarify the relationship between biochemical changes in EC metabolic enzymes and the resulted behavioral responses. Significant impairment in exploration and motion faculties induced by SCs (1 mg/kg), resulted in hindered motion displacement and decreased velocity among subjects. This detrimental effect was consistent across all SCs examined. Importantly, co-treatment of SCs with AM-251, a CB1 receptor antagonist, both at a 1 mg/kg dose did not mitigate the adverse effects, indicating that SCs may override the antagonist effects of AM-251 at higher doses. Conversely, lower doses (0.05 mg/kg) of SCs showed partial recovery of effects, suggesting a dose-dependent relationship between SCs and AM-251. The manifestation of anxiety-like symptoms as a consequence of SCs exposure exhibited a significant increase in aversion to open spaces at low doses of SC exposure, along with strong manifestations of thigmotaxis particularly evident at early time points post drug -administration. Although mobility was not completely abolished at low doses, exploration decreased, and subjects exhibited a tendency to remain in corners, simulating enclosed spaces, with static motion next to walls, suggesting the elicitation of anxiety symptoms. Conversely, at high doses, catalepsy effects were prominently observed, overshadowing anxiety-like manifestations. Our findings indicate that SCs may induce anxiety-like symptoms, particularly at low doses, with these effects progressively developing thorough time and at higher doses. With regards to the impact in cognitive functions, significant impairment in memory and learning during the initial 3 h following administration of MDMB-CHMINACA was seen.

Similarly, 5F-ADB-PINACA exhibited memory impairment at 3 hours post-drug administration, suggesting that SCs containing indole/indazole cores are predisposed to disrupt memory and learning in the early stages of drug exposure. Although the 1 mg/kg dose induced catalepsy effects, hindering proper assessment of novel objects in recognition trials, the inability to effectively discriminate objects at 5 h post-drug treatment further confirmed the cognitive impairment effects of these SCs. Notably, γ-carboline core-based SCs at 0.05 mg/kg, PeGACLONE and 5F-CUMYL-PeGACLONE, exhibited opposing effects during the novel object recognition trials. With the former showing a decreased tendency towards object recognition and the latter displaying an increased familiarization tendency towards a novel object. However, both lacked a significant discrimination or preference towards a novel object, indicating a loss of spatial perception.

Indole/indazole core SCs decreased mRNA levels of FAAH, and MAGL, influencing AEA and 2-AG levels in the hippocampus, which may contribute to behavioral responses. SCs with γ-carboline core structures initially increase MAGL mRNA levels, followed by an increase in PD and DAG mRNA levels at a 1 h and 3 h, respectively. Subsequently, a decrease in both DAG and MAGL levels was observed at 5 h. These findings may indicate that SCs have different effects on EC metabolic enzymes depending on their structure. With regard to the alteration of 2-AG levels in hippocampus, hippocampal levels were elevated, and serum concentrations were reduced, suggesting an inverse mechanism of endocannabinoid accumulation and distribution in response to SC exposure. Further studies may be required to fully elucidate this phenomenon. Nevertheless, this study highlights the potential of reduced serum 2-AG levels as a common biomarker of SC consumption. This research demonstrated that SCs have significant detrimental effects, even when co-treated with the CB1 receptor antagonist AM-251, suggesting involvement of alternative signaling pathways. The research highlighted the potent and dose-dependent nature of SCs, showing behavioral disruptions and alterations in mRNA levels of endocannabinoid biosynthesis and metabolic enzymes. These effects varied across different SC compounds and were evident at both high (1 mg/kg) and low doses (0.05 mg/kg). Our findings emphasize the unpredictable and complex nature of SCs' adverse effects on behavior and cognition, underscoring the need for further investigation into their mechanisms.