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The synthetic cannabinoids ADB-FUBINACA and AMB-FUBINACA accelerate SH-SY5Y proliferation via stimulation of CB1 and CB2 cannabinoid receptors

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Abstract

Background: Synthetic cannabinoids (SC), one of the most popular groups of new psychoactive substances, display a broad pharmacological action close to that of Δ^9-tetrahydrocannabinol (THC). However, while THC is a partial agonist of the cannabinoid receptors type 1 and 2 (CB1 and CB2, respectively), SC present a full and more potent agonistic activity on these receptors [1]. Since new evidence demonstrates that cannabis can accelerate ageing/cell senescence [2,3], we therefore hypothesized that SC might also display this ability. **Objective:** To measure putative SC-induced acceleration of neuronal senescence and, in case of positive effects, to ascertain the extent to which SC-mediated proliferation depends on the effects of the CB1 and CB2. **Methods:** This work began by evaluating neuronal proliferation of SH-SY5Y human neuroblastoma cells after exposure to two trendy SC, ADB-FUBINACA and AMB-FUBINACA. Proliferation was evaluated using the sulforhodamine B (SRB) assay, following exposure to drugs at the biologically-relevant concentrations of 1µM, 1nM and 1pM, for 24h, 48h, 72h, and 96h. Then cells were incubated with 0.5 µM SR141716A and SR144528 (selective inverse agonists for CB1 and CB2, respectively), for 20 min prior to exposure to the SC. **Results:** At 96h, both ADB-FUBINACA and AMB-FUBINACA significantly increased SH-SY5Y proliferation ($p<0.05$) at all tested concentrations (1µM, 1nM and 1pM, respectively: 119%, 125%, and 129% for ADB-FUBINACA; 129%, 140%, and 140% for AMB-FUBINACA), compared to the control. Co-exposure of these SC and the receptor inverse agonists reverted the proliferation increase to values not significantly different from that of the antagonist controls, indicating that CB1 and CB2 are likely involved in this SC-mediated proliferative effect. **Conclusions:** SH-SY5Y proliferation was accelerated after SC exposure. As this increased proliferation results in increased cell divisions, our data suggest that the SC tested may accelerate senescence-related processes. As such, assessing key senescence markers will ensue.

Keywords: cell senescence; ADB-FUBINACA; AMB-FUBINACA

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