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Impact of cannabidiol and delta-9-tetrahydrocannabinol in the angiogenic role of extravillous trophoblasts

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Abstract

Background: Cannabis is the most consumed illicit drug in Europe. Alongside, the medicinal use of cannabinoids is rising. Indeed, a formulation that combines the major phytocannabinoids, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) in a 1:1 proportion (Sativex[®]), is already available for the management of multiple sclerosis. Nevertheless, a lot remains unknown in relation to cannabinoid's impact in reproductive health, namely during pregnancy. Our research group already reported the negative effects of isolated CBD and THC in placental trophoblast cells, such as the induction of apoptosis and autophagy [1,2]. **Objective:** Considering that extravillous trophoblasts (EVT) participate in the remodeling of maternal vessels and produce factors that play a role in angiogenesis during placentation, our goal was to evaluate the effects of CBD and THC, isolated or in combination (1:1), in EVT's angiogenic role, using the HTR-8/SVneo cell line (ATCC, USA). **Methods:** HTR-8/SVneo cells were treated with CBD, THC and CBD plus THC (1:1), at a concentration of 2 μ M. Their effects on the gene expression of the angiogenesis-related factors *VEGFA*, *PGF*, *FLT1* and *sFLT1* were assessed through RT-PCR. Tube formation assay was used to functionally evaluate HTR-8/SVneo endothelial cell-like behavior. Activation of STAT3 signaling pathway, involved in angiogenesis, was assessed by Western blot. **Results:** The mRNA levels of *PGF* were upregulated in CBD and CBD plus THC-treated cells, while *VEGFA* and *FLT1* were not affected. On the other hand, all the treatments increased the expression of the potent anti-angiogenic factor *sFLT1* and decreased tube formation. Moreover, STAT3 was activated in all treated cells. **Conclusions:** Our results demonstrate that CBD and THC, either alone or in combination, may affect placental angiogenesis, through dysregulation of relevant players and interference on the endothelial-behavior of EVT cells. Therefore, the exposure to these cannabinoids can have a harmful impact in critical phases of placental development.

Keywords: cannabinoids; extravillous trophoblasts; placenta; angiogenesis

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