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Cannabinoid-induced cell death in endometrial cancer cells: involvement of TRPV1 receptors in apoptosis.

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Abstract

Among a variety of phytocannabinoids, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most promising therapeutic compounds. Besides the well-known palliative effects in cancer patients, cannabinoids have been shown to inhibit in vitro growth of tumor cells. Likewise, the major endocannabinoids (eCBs), anandamide (AEA) and 2-arachidonoylglycerol (2-AG), induce tumor cell death. The purpose of the present study was to characterize cannabinoid elements and evaluate the effect of cannabinoids in endometrial cancer cell viability. The presence of cannabinoid receptors, transient receptor potential vanilloid 1 (TRPV1), and endocannabinoid-metabolizing enzymes were determined by qRT-PCR and Western blot. We also examined the effects and the underlying mechanisms induced by eCBs and phytocannabinoids in endometrial cancer cell viability. Besides TRPV1, both EC cell lines express all the constituents of the endocannabinoid system. We observed that at concentrations higher than 5 μM, eCBs and CBD induced a significant reduction in cell viability in both Ishikawa and Hec50co cells, whereas THC did not cause any effect. In Ishikawa cells, contrary to Hec50co, treatment with AEA and CBD resulted in an increase in the levels of activated caspase -3/-7, in cleaved PARP, and in reactive oxygen species generation, confirming that the reduction in cell viability observed in the MTT assay was caused by the activation of the apoptotic pathway. Finally, these effects were dependent on TRPV1 activation and intracellular calcium levels. These data indicate that cannabinoids modulate endometrial cancer cell death. Selective targeting of TPRV1 by AEA, CBD, or other stable analogues may be an attractive research area for the treatment of estrogen-dependent endometrial carcinoma. Our data further support the evaluation of CBD and CBD-rich extracts for the potential treatment of endometrial cancer, particularly, that has become non-responsive to common therapies.

KEYWORDS: Apoptosis; Endocannabinoids; Endometrial cancer; Phytocannabinoids

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