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Proapoptotic effect of endocannabinoids in prostate cancer cells

O Orellana-Serradell 1, C E Poblete 1, C Sanchez 1, E A Castellón 1, I Gallegos 2, C Huidobro 3, M N Llanos 4, H R Contreras 1

Affiliations

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Abstract

In the early stages, prostate cancer is androgen-dependent; therefore, medical castration has shown significant results during the initial stages of this pathology. Despite this early effect, advanced prostate cancer is resilient to such treatment. Recent evidence shows that derivatives of Cannabis sativa and its analogs may exert a protective effect against different types of oncologic pathologies. The purpose of the present study was to detect the presence of cannabinoid receptors (CB1 and CB2) on cancer cells with a prostatic origin and to evaluate the effect of the in vitro use of synthetic analogs. In order to do this, we used a commercial cell line and primary cultures derived from prostate cancer and benign prostatic hyperplasia. The presence of the CB1 and CB2 receptors was determined by immunohistochemistry where we showed a higher expression of these receptors in later stages of the disease (samples with a high Gleason score). Later, treatments were conducted using anandamide, 2-arachidonoyl glycerol and a synthetic analog of anandamide, methanandamide. Using the MTT assay, we proved that the treatments produced a cell growth inhibitory effect on all the different prostate cancer cultures. This effect was demonstrated to be dose-dependent. The use of a specific CB1 receptor blocker (SR141716) confirmed that this effect was produced primarily from the activation of the CB1 receptor. In order to understand the MTT assay results, we determined cell cycle distribution by flow cytometry, which showed no variation at the different cell cycle stages in all the cultures after treatment. Treatment with endocannabinoids resulted in an increase in the percentage of apoptotic cells as determined by Annexin V assays and caused an increase in the levels of activated caspase-3 and a reduction in the levels of Bcl-2 confirming that the reduction in cell viability noted in the MTT assay was caused by the activation of the apoptotic pathway. Finally, we observed that endocannabinoid treatment activated the Erk pathway and at the same time, produced a decrease in the activation levels of the Akt pathway. Based on these results, we suggest that endocannabinoids may be a beneficial option for the treatment of prostate cancer that has become nonresponsive to common therapies.

Figures

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