

ROLE OF LOX PATHWAY AND ENDOCANNABINOID SYSTEM IN ANTITUMOR ACTIVITY OF CANNABIDIOL, A NON-PSYCHOACTIVE CANNABINOID

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We recently reported that the non-psychoactive cannabinoid compound cannabidiol (CBD) is able to kill glioma cells, either *in vivo* or *in vitro*, independently of cannabinoid receptor stimulation (1,2). However, the biochemical mechanisms underlying the antitumoral effect of CBD has not been clearly clarified. On this background, in the present work we performed biochemical analysis both on glioma tumor tissues excised by nude mice exposed *in vivo* to CBD and on U87 glioma cell culture treated *in vitro* with the cannabinoid, evaluating the involvement of both COX and LOX pathways, or of the endocannabinoid system.

The *in vivo* exposure to CBD significantly decreased in tumor tissues the 5-LOX activity and content by about 40%, paralleled by the decrease (25%) of its product LTB₄. In contrast, the COX activity and level and PGE₂ amount were unaffected by the treatment. Besides, the *in vivo* treatment with CBD, markedly stimulated (175%) in tumor tissues the hydrolytic activity of fatty acid amide hydrolase (FAAH, the main anandamide-degrading enzyme). Concomitantly, a decrease in anandamide (AEA) level (30%) and in CB1 receptor binding (25%) was observed. The involvement of LOX enzyme in the antiproliferative effect of CBD was confirmed by data obtained in *in vitro* experiments. The pretreatment of U87 glioma cells with MK-886, a specific inhibitor of 5-LOX activity at doses per se not affecting cell viability, was able to significantly enhance the antimitotic effect induced by CBD (MTT test). In contrast, when the pretreatment was carried out with indomethacin (COX-1/-2 inhibitor) or celecoxib (COX-2 inhibitor), no change was observed on CBD effect. The *in vitro* study of the endocannabinoid system revealed that CBD was able to induce a concentration-related increase of FAAH activity in U87 cells. Moreover, when FAAH overexpressing U87 cells were used, it was found a significant reduced rate of growth compared to U87 WT (by MTT and Trypan blue exclusion tests).

In conclusion, the present investigation indicates that CBD exerts its antitumoral effects through the modulation of LOX pathway and endocannabinoid system, suggesting a possible interaction of both systems in controlling tumoral growth.

1) Massi P., Vaccani A., Ceruti S., Colombo A., Abbracchio M.P., Parolaro D. (2004) J. Pharmacol. Exp. Ther. 308:838-845.

2) Massi P., Vaccani A., Bianchessi S., Costa B., Macchi P., Parolaro D. (2006) Cell. Mol. Life Sci. 63: 2057-2066.