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The CB2 cannabinoid receptor signals apoptosis via ceramide-dependent activation of the mitochondrial intrinsic pathway.

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Abstract

Delta9-tetrahydrocannabinol and other cannabinoids exert pro-apoptotic actions in tumor cells via the CB2 cannabinoid receptor. However, the molecular mechanism involved in this effect has remained elusive. Here we used the human leukemia cell line Jurkat-that expresses CB2 as the unique CB receptor-to investigate this mechanism. Our results show that incubation with the selective CB2 antagonist SR144528 abrogated the pro-apoptotic effect of Delta9-tetrahydrocannabinol. Cannabinoid treatment led to a CB2 receptor-dependent stimulation of ceramide biosynthesis and inhibition of this pathway prevented Delta9-tetrahydrocannabinol-induced mitochondrial hypopolarization and cytochrome c release, indicating that ceramide acts at a pre-mitochondrial level. Inhibition of ceramide synthesis de novo also prevented caspase activation and apoptosis. Caspase 8 activation-an event typically related with the extrinsic apoptotic pathway-was also evident in this model. However, activation of this protease was post-mitochondrial since (i) a pan-caspase inhibitor as well as a selective caspase 8 inhibitor were unable to prevent Delta9-tetrahydrocannabinol-induced loss of mitochondrial-membrane transmembrane potential, and (ii) cannabinoid-induced caspase 8 activation was not observed in Bcl-xL over-expressing cells. In summary, results presented here show that CB2 receptor activation signals apoptosis via a ceramide-dependent stimulation of the mitochondrial intrinsic pathway.

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