Comparison of \( \Delta 9 \)-tetrahydrocannabinolic acid A (THCA-A) and Delta-9-tetrahydrocannabinol (THC) in neuronal cell functions

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\[ \Delta 9 \text{-tetrahydrocannabinolic acid A (THCA-A)} \] is a compound produced in the female cannabis plant that might serve as an endogenous tissue-protective signal. When heated, it can be converted into THC, although it is not always complete. While research on its pharmacological properties is limited, available evidence suggests that THCA-A may have therapeutic analgesic effects unrelated to its conversion to THC. This study compared the effects of THCA-A to THC on cell signaling in N18TG2 mouse neuroblastoma cells expressing the CB1 cannabinoid receptor using cAMP and ERK phosphorylation assays. We found that both THC and THCA-A induced CB1-dependent signaling in a dose-dependent manner. THC inhibited initial-rate FSK-stimulated cAMP accumulation (four minutes) in a dose-dependent fashion (1 \( \mu \)M: 77 ±7.2% of FSK stimulation). Co-incubation with CB1R antagonist SR141716 1 \( \mu \)M reversed the THC-mediated inhibition to (102 ±9.9% of FSK stimulation). THCA-A also inhibited FSK-stimulated cAMP accumulation in a dose-dependent fashion (1 \( \mu \)M: 55 ±8.8% of FSK stimulation). This effect was reversed by co-incubation with SR141716 (1 \( \mu \)M) to (99 ±5.3% of FSK stimulation). In N18TG2 cells treated with the diacylglycerol lipase inhibitor, tetrahydrolipstatin (THL, Orlistat; 1 \( \mu \)M for two hours), ERK phosphorylation was assessed after four minutes of incubation with the drugs using the in-cell western assay. THC stimulated ERK phosphorylation in a dose-dependent manner (1 \( \mu \)M, 140 ±8% over basal). Coincubation with SR141716 inhibited this stimulation (110 ±1.8%). Similarly, THCA-A induced a dose-dependent ERK phosphorylation (1 \( \mu \)M, 134 ±9% over basal) that was inhibited in the presence of 1 \( \mu \)M SR141716A (121 ±7% over basal). In conclusion, in our hands, both THC and THCA-A could stimulate CB1-dependent signaling in the N18TG2 neuroblastoma cell line. Future studies will explore other signaling pathways and binding targets (e.g., PPARs, GPR-55) that may be involved in the analgesic effects of this agent.

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