

Neurotoxic and neuroprotective effects of THC

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BACKGROUND

Beside its psychotropic action, the cannabis-derived delta-9-tetrahydrocannabinol (THC) may have analgesic and anti-inflammatory effects, and has been proposed for the treatment of multiple sclerosis, for both the control of spasticity and the modulation of brain inflammation. However, the widespread and prolonged use of THC could have toxic effects, that may be mediated by the prolonged activation of CB1 and CB2 receptors, present on different types of neural cells.

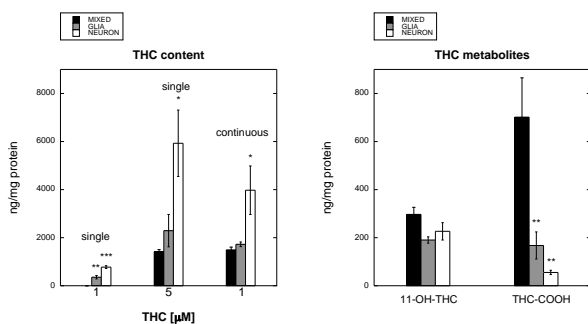
Aggregating brain cell cultures were used as model to study the neurotoxic, the anti-inflammatory and the neuroprotective potential of THC.

The toxic effects of THC were investigated after a single treatment or a continuous treatment of 10 days. Aggregating cultures received a single applications of IFN- γ (50U/ml) and LPS (5 mg/ml) in order to induce an acute inflammation. Whereas a "subchronical" inflammation associated with demyelination was induced by repeated applications of IFN- γ + LPS. To analyze its anti-inflammatory and neuroprotective potential, THC was applied simultaneously with each IFN- γ + LPS treatment.

RESULTS

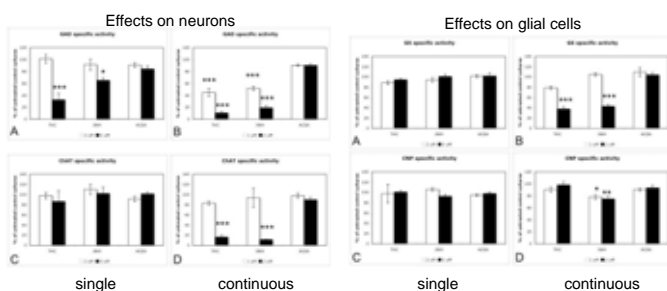
A. Toxic effects of THC

1. THC accumulates and is metabolized in brain cells



Mean \pm sem, n=4, *P<0.05, ** P<0.001, *** P<0.001 significant deviations from mixed cell cultures.

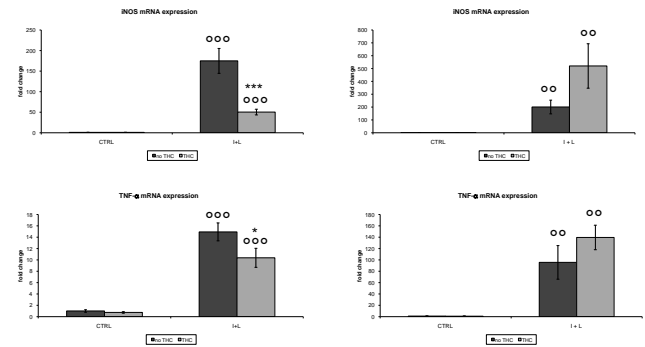
2. Cell type-specific effects of THC and of CB2 and CB1 receptor agonists.



Mean \pm sem, n=4, *P<0.05, ** P<0.001, *** P<0.001 compared to control untreated cultures.

B. Anti-inflammatory and neuroprotective effects of THC

1. Effects of THC on inflammatory markers

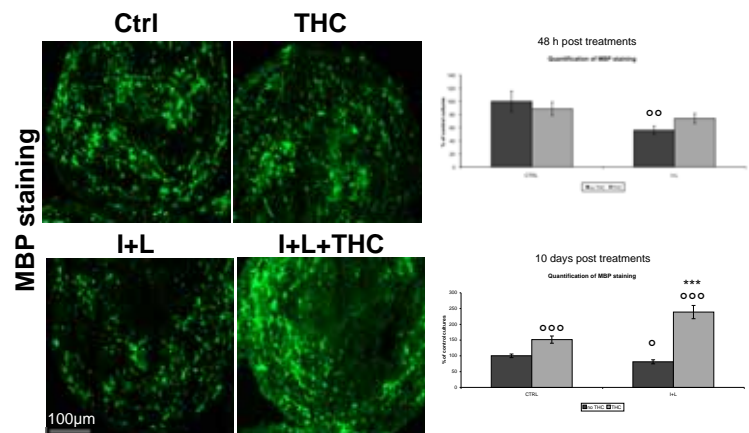


Single I+L treatment

Repeated (3x) I+L treatments

THC 1 μ M, mean \pm sem, n= 6-8, °P<0.01, °°P<0.001 compared to control; **P<0.01,***P<0.001 compared to I+L.

2. THC protects from the IFN- γ + LPS-induced demyelination



Representative images of myelin basic protein (MBP) staining 10 days post treatments.

Mean \pm sem, n= 14-38, °P<0.05, °°P<0.01,°°°P<0.001 compared to control; ***P<0.001 compared to I+L.

SUMMARY

- THC was able to accumulate in brain cells.
- Neuron-glia interactions modulated the uptake and the metabolism of THC.
- Neurons were the most sensitive to THC toxicity.
- The CB2 agonist (JWH 015) exhibited a similar pattern of toxicity than THC, whereas the CB1 agonist (ACEA) showed no toxicity at the tested concentrations.
- THC decreased the IFN- γ + LPS-induced upregulation of the inflammatory markers i-NOS and TNF- α only after an acute but not after a subchronical inflammatory response.
- THC protected partly from IFN- γ + LPS-induced demyelination, and promoted remyelination.