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Zeissler, M

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**Δ9-TETRAHYDROCANNABINOL IS PROTECTIVE
THROUGH PPAR_γ DEPENDENT MITOCHONDRIAL
BIOGENESIS IN A CELL CULTURE MODEL
OF PARKINSON'S DISEASE**

Marie-Louise Zeissler, Jordan Eastwood, C Oliver Hanemann, John Zajicek,
Camille Carroll. *Plymouth University Peninsula Schools of Medicine and Dentistry*

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Introduction Cannabinoids such as Δ^9 -tetrahydrocannabinol (Δ^9 -THC) are neuroprotective in animal and cell culture models of Parkinson's disease (PD). In a PD cell culture model we recently demonstrated that Δ^9 -THC is neuroprotective through activation of the nuclear receptor peroxisomal proliferator-activated receptor γ (PPAR γ). Furthermore, activation by specific agonists rosiglitazone and pioglitazone, has also been found neuroprotective. PPAR γ is a nuclear receptor whose activation can lead to the expression of proteins involved in the de novo synthesis of mitochondria. One such protein is the PPAR γ co-activator 1 α (PGC1 α) as it co-activates NRF-1 mediated gene expression which is essential for the production of nuclear encoded, mitochondrial proteins. Here we investigate the effect of Δ^9 -THC and pioglitazone on mitochondrial biogenesis.

Methods SH-SY5Y neuroblastoma cells were differentiated with retinoic acid and exposed to the PD relevant mitochondrial complex 1 inhibitor, MPP+. Δ^9 -THC and pioglitazone were co-administered with the minimum concentration of the specific PPAR γ antagonist T0070907 able to block the protective effect of each compound respectively for 48 hours. The production of reactive oxygen species was then measured, proteins were extracted for Western blotting and total DNA was extracted to determine mitochondrial DNA (mtDNA) content by QPCR.

Results Δ^9 -THC resulted in significant inhibition of MPP+ induced oxidative stress which was completely reversed by T0070907 whereas pioglitazone induced reduction in oxidative stress did not seem to be PPAR γ dependent. Accordingly, both pioglitazone and Δ^9 -THC were able to restore MPP+ induced down-regulation of PGC1 α , to the level of untreated control. This effect was inhibited by T0070907 in the case of Δ^9 -THC but not pioglitazone. Whilst NRF1 expression remained unaffected by all treatments, the mitochondrial transcription factor (tfam) which is necessary for mtDNA replication was reduced with MPP+ and up-regulated by Δ^9 -THC only. Similarly, mtDNA content and the mitochondrial marker COX4 were only increased by Δ^9 -THC.

Conclusions Even though Δ^9 -THC and pioglitazone are both protective against MPP+ only Δ^9 -THC induces PPAR γ dependent mitochondrial biogenesis, a mechanism that may be beneficial for the treatment of PD.



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