2013-11

9TETRAHYDROCANNABINOL IS PROTECTIVE THROUGH PPAR DEPENDENT MITOCHONDRIAL BIOGENESIS IN A CELL CULTURE MODEL OF PARKINSON'S DISEASE

Zeissler, M

10.1136/jnnp-2013-306573.150
Journal of Neurology, Neurosurgery & Psychiatry
BMJ

150 **Δ9–TETRAHYDROCANNABINOL IS PROTECTIVE THROUGH PPARγ 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*

10.1136/jnnp-2013-306573.150

Introduction Cannabinoids such as Δ9–tetrahydrocannabinol (Δ9–THC) are neuroprotective in animal and cell culture models of Parkinson's disease (PD). In a PD cell culture model we recently demonstrated that Δ9–THC is neuroprotective through activation of the nuclear receptor peroxisomal proliferator–activated receptor γ (PPARγ). Furthermore, activation by specific agonists rosiglitazone and pioglitazone, has also been found neuroprotective. PPARγ 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 PPARγ co–activator 1 α (PGC1α) 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 Δ9–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+. Δ9–THC and pioglitazone were co–administered with the minimum concentration of the specific PPARγ 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 Δ9–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 PPARγ dependent. Accordingly, both pioglitazone and Δ9–THC were able to restore MPP+ induced down–regulation of PGC1α, to the level of untreated control. This effect was inhibited by T0070907 in the case of Δ9–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 Δ9–THC only. Similarly, mtDNA content and the mitochondrial marker COX4 were only increased by Δ9–THC.

Conclusions Even though Δ9–THC and pioglitazone are both protective against MPP+ only Δ9–THC induces PPARγ dependent mitochondrial biogenesis, a mechanism that may be beneficial for the treatment of PD.

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 and Camille Carroll

J Neurol Neurosurg Psychiatry 2013 84: e2
doi: 10.1136/jnnp-2013-306573.150