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Neuroprotection in an experimental model of multiple sclerosis via fatty acid amide hydrolase or monoacylglycerol lipase inhibition

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Background: Direct stimulation of cannabinoid CB_1 receptors has neuroprotective potential in a variety of conditions (Pryce et al. 2003) and this has been shown using *Cannabis sativa* plant-based cannabinoids in animals models and in human multiple sclerosis (Pryce et al. 2015). It was hypothesized that indirect stimulation of the CB_1 receptor through augmentation of the endocannabinoid levels would be neuroprotective during neuroinflammatory, autoimmune disease. This aspect has been shown with inactivation of fatty acid amide hydrolase (FAAH) to augment anandamide (Webb et al. 2005). It hypothesized that augmentation of two-arachidonoyl glycerol with monoacylglycerol lipase (MAGL) inhibitors would be neuroprotective in neuroinflammatory disease.

Method. Animal studies, incorporating ethical review were performed consistent with the Animals Act 1986 and EU Directive 2010/EU/63. Neurodegenerative disease was induced in relapsing experimental autoimmune encephalomyelitis in Biozzi ABH mice and was assessed by subjective (neurological scores) and objective (rotarod) clinical outcomes and assessment of spinal nerve content (Al-Izki et al. 2012). This was treated using FAAH and MAGL inhibitors.

Result. Non-sedative doses of endocannabinoid inhibitors were not-immunosuppressive allowing the development of paralytic experimental autoimmune encephalomyelitis following induction with spinal cord autoantigens. However, evidence of neuroprotection, shown by enhanced recovery from influence of the neurodegenerative, inflammatory penumbra occurring during relapsing disease, occurred following delivery of a number of FAAH inhibitors and also with the MAGL-inhibitor JZL-184.

Conclusion. Blockade of endocannabinoid breakdown offers neuroprotective potential in neuroinflammatory disease. Although tetrahydrocannabinol was neuroprotective in people with multiple sclerosis with more rapidly progressing disease in MS, the perceived failure of the trial of tetrahydrocannabinol (Zajicek *et al*. 2013, Pryce *et al*. 2015), means that it is unlikely that this approach will be developed. Likewise recent issues with the clinical inhibition of FAAH, using BIA 10-2474 (Mallet *et al*. 2016), make FAAH blockade a concern. However, MAGL inhibitors are in clinical development and the data suggests that they may have utility in control neurodegeneration in multiple sclerosis.

References

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