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Neuroprotection in an experimental model of multiple sclerosis via opening of big conductance, calcium-activated potassium channels

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Background: Openers of big conductance, calcium-activated potassium (BKCa) channels, the major non-CB_1, non-CB_2 cannabinoid receptor vascular target of endocannabinoids (Bondarenko *et al*. 2017, Baker *et al*. 2017), inhibit pathologically-driven neural hyperactivity to control symptoms related to multiple sclerosis (Baker *et al*. 2017). It was hypothesized that they would be neuroprotective during neuroinflammatory, autoimmune disease.

Method. Animal studies were performed consistent with the Animals Act 1986 and EU Directive 2010/EU/63. Human studies conformed with the Declaration of Helsinki and following ethical review (EudraCT 2013-002765-18). Neurodegenerative disease was induced in experimental autoimmune encephalomyelitis in Biozzi ABH mice and was assessed by subjective (neurological scores) and objective (rotarod) clinical outcomes and spinal nerve (neurofilament-specific ELISA) content (Al-Izki et al. 2012). This was treated using BKCa openers.

Results. Consistent with limited expression by leucocytes, treatment of animals and humans with BKCa openers did not induce changes in leucocyte levels in rodents and humans. Likewise, whilst BKCa opening did not inhibit the development of relapsing autoimmunity, they did protect (clinically and neurochemically) against the neurodegeneration caused by autoimmunity in an animal model that has translational value for detecting neuroprotection in multiple sclerosis.

Conclusion. In addition to symptom control, BKCa channel openers have the potential to save nerves from damage. Given their lack of sedative side-effects, which can occur with CB_1 receptor agonists and inhibitions of neural-excitation, in animals and humans, BKCa openers could provide useful stand-alone treatments or add-ons to current disease modifying treatments that block progressive and relapsing multiple sclerosis.

References.

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