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BLOCKADE OF THE 2-AG HYDROLASE ABHD6 AS A NOVEL THERAPEUTIC STRATEGY IN DEMYELINATION

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Activation of cannabinoid CB1/CB2 receptors is considered a useful therapeutic strategy for the treatment of demyelinating inflammatory disorders such as multiple sclerosis. Nevertheless, the clinical utility of exogenous cannabinoids is limited by the appearance of unwanted responses related to memory and learning impairment. Recent evidence indicates that blocking the enzymatic metabolism of the main endocannabinoid 2-arachidonoylglycerol (2-AG) may engage therapeutic benefits against neuroinflammation whilst limiting adverse effects. We have shown that pharmacological inhibition of the major 2-AG degrading enzyme monoacylglycerol lipase (MAGL) elicits myelin protective and anti-inflammatory effects in vivo and protects oligodendrocytes in vitro from excitoxicity (Bernal-Chico et al., 2015). Nevertheless, chronic administration of MAGL inhibitors induces desensitization of brain CB1 receptors, an undesirable effect that may attenuate the clinical efficacy of these compounds. Here we have evaluated the potential of targeting α/β hydrolase domain containing 6 (ABHD6), responsible of approximately 4% of 2-AG hydrolysis as novel strategy to treat demyelination. Our data show that chronic ABHD6 inhibition ameliorates disease progression, prevents myelin damage and attenuates inflammation in the autoimmune encephalomyelitis and cuprizone models of demyelination without eliciting widespread desensitization of brain CB1 receptors. Experiments in cultured oligodendrocytes and neurons suggest that protection from excitotoxicity is not a relevant mechanism underlying the beneficial efficacy of ABHD6 inhibitors in vivo. Collectively, these results provide evidence supporting the potential use of ABHD6 inhibitors for therapeutic intervention in white matter injury. Funded by the Basque Government, MINECO, ARSEP Foundation, WOP Foundation and CIBERNED