Anandamide Modulation of Endotoxin-Induced Inflammation

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The endocannabinoid system is comprised of the CB1 and CB2 receptors, the naturally occurring endogenous ligands, anandamide (AEA) and 2-arachidonoyl glycerol (2-AG); and the enzymes involved in their synthesis and degradation. The enzyme fatty acid amide hydrolase (FAAH) preferentially metabolises AEA, and the related N-acyltyethanolamines, N-palmitoylethanolamide (PEA) and N-oleoylethanolamide (OEA). While PEA and OEA do not have activity at CB1 receptors, they are capable of enhancing AEA signaling by competing with AEA at the catalytic site on the FAAH enzyme. All elements of the endocannabinoid system are widely and densely expressed in the mammalian immune system and brain and as such represent an important therapeutic target for a number of peripheral and central inflammatory disorders [1-3].

In vitro and in vivo data, has demonstrated that cannabinoid agonists modulate immune function and inflammatory responses in several preclinical animal models including those association with pain, colitis, sepsis and neurodegenerative disorders [4-7]. For example, data from our lab has demonstrated that the potent cannabinoid agonist HU210 attenuates increases in pro-inflammatory cytokine levels, in particular interleukin(IL)-1β, both peripherally and in discrete brain regions, observed following administration of the endotoxin and toll-like receptor 4 agonist lipopolysaccaride (LPS) [5]. The anti-inflammatory effects of HU210 were shown to be partially mediated by CB2, but not CB1 receptors. Overt psychotropics effects are associated with the administration of potent synthetic CB1 agonists and as such enhancing endocannabinoid tone has been proposed as an alternative means of activating cannabinoid receptors without such concomitant effects. In vitro studies suggest that endocannabinoids elicit anti-inflammatory effects comparable to those of exogenous cannabinoids. Increasing AEA tone, either directly or via inhibition of its degradation or uptake, has been demonstrated to reduce levels of pro-inflammatory cytokines and inflammatory mediators such as tumour necrosis factor (TNFα), IL-1β and nitric oxide in response to immune stimulation in several in vitro systems [8-14]. In many cases, the attenuation of pro-inflammatory cytokine responses is paralleled with an increase in the production of anti-inflammatory cytokines, such as IL-10 [12,15]. Recent data indicates that neuroprotective effects of AEA may be mediated by IL-10 induced increases in the expression of CD200 [16], a membrane glycoprotein expressed on neurons that suppresses immune mediated by IL-10 induced increases in the expression of CD200 [16], a membrane glycoprotein expressed on neurons that suppresses immune

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effects attributed to AEA activity at CB1 and/or CB2 receptors [32,33]. While the immunomodulatory effects of FAAH inhibition have been attributed primarily to AEA activation of CB1 receptors, it is worth noting that associated changes in N-acylethanolamines may account, at least in part, for some of the non-CB1/CB2 receptor mediated effects observed.

In conclusion, increasing evidence support an important role for AEA in modulation of (neuro) inflammatory responses to endotoxin exposure. Given the lack of psychotrophic effects and abuse liability associated with FAAH inhibition, modulation of AEA tone via this means represents an important therapeutic target for inflammatory disorders.

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References