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# Anandamide Modulation of Endotoxin-Induced Inflammation

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The endocannabinoid system is comprised of the $CB_1$ and $CB_2$ receptors, the naturally occurring endogenous ligands, anandamide (AEA) and 2-arachidonyl glycerol (2-AG); and the enzymes involved in their synthesis and degradation. The enzyme fatty acid amide hydrolyase (FAAH) preferentially metabolises AEA, and the related *N*-acylethanolamines, *N*-palmitoylethanolamide (PEA) and *N*-oleoylethanolamide (OEA). While PEA and OEA do not have activity at $CB_{1/2}$ 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 $CB_1$, but not $CB_2$ receptors. Overt psychotropic effects are associated with the administration of potent synthetic $CB_1$ 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 (TNF)α, 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 activity by interacting with its receptor on microglia. However, it should be noted that enhancing AEA tone has also been demonstrated to enhance IL-6 levels in astrocyte culture preparations [10,17]. In addition, genetic deletion of FAAH in astrocytes exacerbated their inflammatory phenotype against β-amyloid [14]. Thus, AEA may attenuate or enhance inflammatory reactions depending on the conditions under investigation. *In vitro* data has provided us with an understanding of the molecular and cellular mechanism underlying the effects of AEA, effects which have now been substantiated in several *in vivo* models. Data from our group and others have demonstrated enhanced AEA levels in several animal models including those relating to autism [18], inflammatory and neuropathic pain [19,20], Parkinson's disease [21] and Multiple sclerosis [22], disorders with a well characterized inflammatory component. Data from our group has provided some of the first evidence of an immunomodulatory role for enhanced anandamide tone *in vivo* following systemic bacterial endotoxin administration. We demonstrated that inhibition of AEA degradation following administration of the FAAH inhibitor URB597, potentiated LPS-induced increases in TNFα levels in plasma [23]. Similarly, systemic administration of the endocannabinoid re-uptake inhibitor AM404, augmented LPS-induced increases in TNFα levels while concurrently attenuating plasma IL-1β and IL-6 levels [23]. On investigation of the receptor mechanisms underlying this effect, we revealed that the AM404-induced attenuation of IL-1β was prevented by antagonism of the $CB_1$ receptor. In comparison, antagonism of $CB_1$, $CB_2$, PPARγ and TRPV1 receptors attenuated the AM404-induced potentiation of TNFα following LPS administration [23] indicating possible involvement of one or all of the aforementioned receptors in this response. In accordance with this data, De Laurentiis and co-workers demonstrated that AEA activation of hypothalamic $CB_1$ receptors facilitates LPS-induced increases in plasma TNFα levels [24]. Examination of the effects of AEA on central inflammatory responses has revealed that enhancing AEA tone attenuates microglial activation and pro-inflammatory cytokine expression in several neuroinflammatory animals models [15,25-27]. Recent data from our lab has demonstrated that systemic administration of URB597 enhances central AEA levels and attenuates LPS-induced increase in IL-1β expression while concurrently augmenting suppressor of cytokine signalling (SOCS)-3 (and tended to do so also for IL-6) expression in the hypothalamus [28]. AEA modulation of endotoxin-induced cytokine changes in the hypothalamus may ameliorate the associated sickness response, including changes in body temperature, hypophagia, hypothalamic-pituitary-adrenal (HPA) axis activation and hyperalgesia. Recent evidence has demonstrated that AEA attenuates LPS-induced fever and hypophagia [29], most likely via modulation of hypothalamic cytokine expression. Furthermore, central AEA has been shown to increase, while $CB_1$ receptor antagonism attenuates, LPS-induced hypothermia [30], further demonstrating a role for AEA-$CB_1$ in modulation of thermal responses to systemic inflammation. Increasing evidence demonstrates that endocannabinoids act to inhibit stress-induced HPA axis activation [31]. Our data demonstrated that enhanced AEA tone following URB597 failed to alter LPS-induced increases in plasma corticosterone levels [28]. Hypothalamic TNFα may underlie the LPS-induced increase in plasma corticosterone, an effect not altered by URB597. In addition, pharmacological and genetic FAAH inhibition has been shown to reduce LPS-induced nociceptive behaviour tactile allodynia, oedema and associated increases in IL-1β and TNFα levels,

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effects attributed to AEA activity at $CB_1$ and/or $CB_2$ receptors [32,33]. While the immunomodulatory effects of FAAH inhibition have been attributed primarily to AEA activation of $CB_1$ receptors, it is worth noting that associated changes in *N*-acylethanalomines may account, at least in part, for some of the non-$CB_{1/2}$ 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 psychotropic 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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