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<td><strong>Author(s)</strong></td>
<td>Kerr, Daniel M.; Henry, Rebecca; Roche, Michelle</td>
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<tr>
<td><strong>Publication Date</strong></td>
<td>2013-12-20</td>
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<tr>
<td><strong>Publisher</strong></td>
<td>OMICS International</td>
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<tr>
<td><strong>Link to publisher's version</strong></td>
<td><a href="http://www.omicsonline.org/open-access/anandamide-modulation-of-endotoxin-induced-inflammation-2161-0940.1000e130.php?aid=23483">http://www.omicsonline.org/open-access/anandamide-modulation-of-endotoxin-induced-inflammation-2161-0940.1000e130.php?aid=23483</a></td>
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<td><a href="http://hdl.handle.net/10379/5749">http://hdl.handle.net/10379/5749</a></td>
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<td><strong>DOI</strong></td>
<td><a href="http://dx.doi.org/10.4172/2161-0940.1000e130">http://dx.doi.org/10.4172/2161-0940.1000e130</a></td>
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Anandamide Modulation of Endotoxin-Induced Inflammation

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Anandamide (AEA), the naturally occurring endogenous lipid, is a potent agonist at cannabinoid receptors (CB1 and CB2). AEA is an endocannabinoid that is rapidly degraded by the fatty acid amide hydrolase (FAAH) enzyme. However, recent studies suggest that AEA, by mediating its effects through CB1 receptors, may have significant anti-inflammatory role in the mammalian immune system (as well as in the brain), and may be expressed in both the periphery and the central nervous system. In vitro and in vivo studies have demonstrated that cannabinoids are capable of enhancing AEA signaling by competing with AEA at the catalytic site on the FAAH enzyme. The enzyme fatty acid amide hydrolase (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 CB1 receptors, they are capable of enhancing AEA signaling by competing with AEA at the catalytic site on the FAAH enzyme. Therefore, a number of peripheral and central inflammatory disorders [1-3].

In vitro and in vivo data, has demonstrated that cannabinoids 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 peripheral blood mononuclear cells (PBMC) [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 [26]. AEA modulation of endotoxin-induced cytokine changes in the hypothalamus may ameliorate the associated sickness response, including changes in body temperature, hypothagia, 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 CB1 receptor antagonism attenuates, LPS-induced hypoactivity and thermoregulation [30], further demonstrating a role for AEA-CB1 in modulation of thermal responses to systemic inflammation. Increasing evidence demonstrates that endocannabinoids act to inhibit stress-induced HPA axis activation [31].

Received December 20, 2013; Accepted December 18, 2013; Published December 20, 2013


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http://dx.doi.org/10.4172/2161-0940.1000e130

Kerr et al., Anat Physiol 2013, 4:1

Volume 4 • Issue 1 • 1000e130

Anatomy & Physiology

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-arachidonyl 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-acylethanolamines, 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 cannabinoids 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 peripheral blood mononuclear cells (PBMC) [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 [26]. 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 CB1 receptor antagonism attenuates, LPS-induced hypoactivity and thermoregulation [30], further demonstrating a role for AEA-CB1 in modulation of thermal responses to systemic inflammation. Increasing evidence demonstrates that endocannabinoids act to inhibit stress-induced HPA axis activation [31].

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http://dx.doi.org/10.4172/2161-0940.1000e130
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/C₂ 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.

Acknowledgements

Funding provided by Science Foundation Ireland Research Frontiers Project (Grant no. 11/RFP/NES/3175) and the Discipline of Physiology, National University of Ireland Galway.

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