



Provided by the author(s) and NUI Galway in accordance with publisher policies. Please cite the published version when available.

Title	Anandamide modulation of endotoxin-induced inflammation
Author(s)	Kerr, Daniel M.; Henry, Rebecca; Roche, Michelle
Publication Date	2013-12-20
Publication Information	Kerr DM, Henry R, Roche M (2013) 'Anandamide Modulation of Endotoxin-Induced Inflammation' <i>Anatomy and Physiology</i> , 4:e130. doi: 10.4172/2161-0940.1000e130
Publisher	OMICS International
Link to publisher's version	http://www.omicsonline.org/open-access/anandamide-modulation-of-endotoxininduced-inflammation-2161-0940.1000e130.php?aid=23483
Item record	http://hdl.handle.net/10379/5749
DOI	http://dx.doi.org/10.4172/2161-0940.1000e130

Downloaded 2022-08-14T22:15:20Z

Some rights reserved. For more information, please see the item record link above.



Anandamide Modulation of Endotoxin-Induced Inflammation

Daniel M Kerr, Rebecca Henry and Michelle Roche*

Physiology, NCBES Galway Neuroscience Centre and Centre for Pain Research, National University of Ireland Galway, Ireland

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 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)-1 β , both peripherally and in discrete brain regions, observed following administration of the endotoxin and toll-like receptor 4 agonist lipopolysaccharide (LPS) [5]. The anti-inflammatory effects of HU210 were shown to be partially mediated by CB₁, but not CB₂ receptors. Overt psychotropic 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 (TNF) α , IL-1 β 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 TNF α levels in plasma [23]. Similarly, systemic administration of the endocannabinoid re-uptake inhibitor AM404, augmented LPS-induced increases in TNF α levels while concurrently attenuating plasma IL-1 β and IL-6 levels [23]. On investigation of the receptor mechanisms underlying this effect, we revealed that the AM404-induced attenuation of IL-1 β was prevented by antagonism of the CB₁ receptor. In comparison, antagonism of CB₁, CB₂, PPAR γ and TRPV1 receptors attenuated the AM404-induced potentiation of TNF α following LPS administration [23] indicating possible involvement of one or all of the aforementioned receptors in this response. In accordance with this data, De Laurentis and co-workers demonstrated that AEA activation of hypothalamic CB₁ receptors facilitates LPS-induced increases in plasma TNF α 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-1 β 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 CB₁ receptor antagonism attenuates, LPS-induced hypothermia [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]. Our data demonstrated that enhanced AEA tone following URB597 failed to alter LPS-induced increases in plasma corticosterone levels [28]. Hypothalamic TNF α 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-1 β and TNF α levels,

*Corresponding author: Michelle Roche, Physiology, National University of Ireland Galway, University Road, Galway, Ireland, Tel: +353 91 495427; E-mail: michelle.roche@nuigalway.ie

Received December 17, 2013; Accepted December 18, 2013; Published December 20, 2013

Citation: Kerr DM, Henry R, Roche M (2013) Anandamide Modulation of Endotoxin-Induced Inflammation. Anat Physiol 4: e130. doi:10.4172/2161-0940.1000e130

Copyright: © 2013 Kerr DM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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-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.

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.

References

1. Centonze D, Finazzi-Agrò A, Bernardi G, Maccarrone M (2007) The endocannabinoid system in targeting inflammatory neurodegenerative diseases. *Trends Pharmacol Sci* 28: 180-187.
2. Orgado JM, Fernández-Ruiz J, Romero J (2009) The endocannabinoid system in neuropathological states. *Int Rev Psychiatry* 21: 172-180.
3. Roche M, Finn DP (2010) Brain CB₂ receptors: Implication for Neuropsychiatric disorders. *Pharmaceuticals*. 3: 2517-2553.
4. Tschöp J, Kasten KR, Nogueiras R, Goetzman HS, Cave CM, et al. (2009) The cannabinoid receptor 2 is critical for the host response to sepsis. *J Immunol* 183: 499-505.
5. Roche M, Diamond M, Kelly JP, Finn DP (2006) In vivo modulation of LPS-induced alterations in brain and peripheral cytokines and HPA axis activity by cannabinoids. *J Neuroimmunol* 181: 57-67.
6. Rea K, Roche M, Finn DP (2007) Supraspinal modulation of pain by cannabinoids: the role of GABA and glutamate. *Br J Pharmacol* 152: 633-648.
7. Pertwee RG (2012) Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. *Philos Trans R Soc Lond B Biol Sci*. 367: 3353-3363.
8. Chang YH, Lee ST, Lin WW (2001) Effects of cannabinoids on LPS-stimulated inflammatory mediator release from macrophages: involvement of eicosanoids. *J Cell Biochem* 81: 715-723.
9. Facchinetti F, Del Giudice E, Furegato S, Passarotto M, Leon A (2003) Cannabinoids ablate release of TNF α in rat microglial cells stimulated with lipopolysaccharide. *Glia* 41: 161-168.
10. Ortega-Gutiérrez S, Molina-Holgado E, Guaza C (2005) Effect of anandamide uptake inhibition in the production of nitric oxide and in the release of cytokines in astrocyte cultures. *Glia* 52: 163-168.
11. Tham CS, Whitaker J, Luo L, Webb M (2007) Inhibition of microglial fatty acid amide hydrolase modulates LPS stimulated release of inflammatory mediators. *FEBS Lett* 581: 2899-2904.
12. Correa F, Hernangómez M, Mestre L, Loria F, Spagnolo A, et al. (2010) Anandamide enhances IL-10 production in activated microglia by targeting CB₂ receptors: roles of ERK1/2, JNK, and NF- κ B. *Glia* 58: 135-147.
13. Correa F, Docagne F, Mestre L, Clemente D, Hernangómez M, et al. (2009) A role for CB₂ receptors in anandamide signalling pathways involved in the regulation of IL-12 and IL-23 in microglial cells. *Biochem Pharmacol* 77: 86-100.
14. Benito C, Tolón RM, Castillo AI, Ruiz-Valdepeñas L, Martínez-Orgado JA, et al. (2012) β -Amyloid exacerbates inflammation in astrocytes lacking fatty acid amide hydrolase through a mechanism involving PPAR- δ , PPAR- γ and TRPV1, but not CB₁ or CB₂ receptors. *Br J Pharmacol* 166: 1474-1489.
15. Correa F, Hernangomez-Herrero M, Mestre L, Loria F, Docagne F, et al. (2011) The endocannabinoid anandamide downregulates IL-23 and IL-12 subunits in a viral model of multiple sclerosis: evidence for a cross-talk between IL-12p70/IL-23 axis and IL-10 in microglial cells. *Brain Behav Immun* 25: 736-749.
16. Hernangómez M, Mestre L, Correa FG, Loria F, Mecha M, et al. (2012) CD200-CD200R1 interaction contributes to neuroprotective effects of anandamide on experimentally induced inflammation. *Glia* 60: 1437-1450.
17. Molina-Holgado F, Molina-Holgado E, Guaza C (1998) The endogenous cannabinoid anandamide potentiates interleukin-6 production by astrocytes infected with Theiler's murine encephalomyelitis virus by a receptor-mediated pathway. *FEBS Lett*. 433: 139-142.
18. Kerr DM, Downey L, Conboy M, Finn DP, Roche M (2013) Alterations in the endocannabinoid system in the rat valproic acid model of autism. *Behav Brain Res* 249: 124-132.
19. Salaga M1, Sobczak M1, Fichna J2 (2013) Inhibition of fatty acid amide hydrolase (FAAH) as a novel therapeutic strategy in the treatment of pain and inflammatory diseases in the gastrointestinal tract. *Eur J Pharm Sci* 52C: 173-179.
20. Roques BP, Fournié-Zaluski MC, Wurm M (2012) Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain. *Nat Rev Drug Discov* 11: 292-310.
21. Maccarrone M, Gubellini P, Bari M, Picconi B, Battista N, et al. (2003) Levodopa treatment reverses endocannabinoid system abnormalities in experimental parkinsonism. *J Neurochem* 85: 1018-1025.
22. Jean-Gilles L, Feng S, Tench CR, Chapman V, Kendall DA, et al. (2009) Plasma endocannabinoid levels in multiple sclerosis. *J Neurol Sci* 287: 212-215.
23. Roche M, Kelly JP, O'Driscoll M, Finn DP (2008) Augmentation of endogenous cannabinoid tone modulates lipopolysaccharide-induced alterations in circulating cytokine levels in rats. *Immunology* 125: 263-271.
24. De Laurentis A, Fernandez-Solari J, Mohn C, Burdet B, Zorrilla Zubilete MA, et al. (2010) The hypothalamic endocannabinoid system participates in the secretion of oxytocin and tumor necrosis factor- α induced by lipopolysaccharide. *J Neuroimmunol* 221: 32-41.
25. Murphy N, Cowley TR, Blau CW, Dempsey CN, Noonan J, et al. (2012) The fatty acid amide hydrolase inhibitor URB597 exerts anti-inflammatory effects in hippocampus of aged rats and restores an age-related deficit in long-term potentiation. *J Neuroinflammation* 9: 79.
26. Eljaschewitsch E, Witting A, Mawrin C, Lee T, Schmidt PM, et al. (2006) The endocannabinoid anandamide protects neurons during CNS inflammation by induction of MKP-1 in microglial cells. *Neuron* 49: 67-79.
27. Mestre L, Correa F, Arévalo-Martín A, Molina-Holgado E, Valenti M, et al. (2005) Pharmacological modulation of the endocannabinoid system in a viral model of multiple sclerosis. *J Neurochem* 92: 1327-1339.
28. Kerr DM, Burke NN, Ford GK, Connor TJ, Harhen B, et al. (2012) Pharmacological inhibition of endocannabinoid degradation modulates the expression of inflammatory mediators in the hypothalamus following an immunological stressor. *Neuroscience* 204: 53-63.
29. Hollis JH, Jonaidi H, Lemus M, Oldfield BJ (2011). The endocannabinoid arachidonylethanolamide attenuates aspects of lipopolysaccharide-induced changes in energy intake, energy expenditure and hypothalamic Fos expression. *J Neuroimmunol* 233: 127-134.
30. Steiner AA, Molchanova AY, Dogan MD, Patel S, Pétervári E, et al. (2011) The hypothermic response to bacterial lipopolysaccharide critically depends on brain CB₁, but not CB₂ or TRPV1, receptors. *J Physiol* 589: 2415-2431.
31. Hill MN, Tasker JG (2012) Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic-pituitary-adrenal axis. *Neuroscience* 204: 5-16.
32. Booker L, Kinsey SG, Abdullah RA, Blankman JL, Long JZ, et al. (2012) The fatty acid amide hydrolase (FAAH) inhibitor PF-3845 acts in the nervous system to reverse LPS-induced tactile allodynia in mice. *Br J Pharmacol* 165: 2485-2496.
33. Naidu PS, Kinsey SG, Guo TL, Cravatt BF, Lichtman AH (2010) Regulation of inflammatory pain by inhibition of fatty acid amide hydrolase. *J Pharmacol Exp Ther* 334: 182-190.

Citation: Kerr DM, Henry R, Roche M (2013) Anandamide Modulation of Endotoxin-Induced Inflammation. *Anat Physiol* 4: e130. doi:10.4172/2161-0940.1000e130