PAIN MODULATION BY NEGATIVE AFFECTIVE STATE: ROLE OF THE ENDOCANNABINOID SYSTEM

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Talk Overview

• Relationship between negative affect/stress and pain
• Fear-induced analgesia
  &
• Anxiety/depression-related hyperalgesia
  – Role of endocannabinoid system (CB$_1$, TRPV1, PPARs, GPR55)
    • Key brain regions
    • Neurochemical and molecular mechanisms
Impact of Stress on Pain

- Pain
- Stress

Intense acute stress/fear
Moderate chronic stress/anxiety

Analgesia
Hyperalgesia

Genetic background

Chance et al. (1978)
Rosecrans et al. (1986)
Flor and Grusser (1999)
Butler and Finn (2009)
Vidal and Jacob. (1986)
Rhudy and Meagher. (2000)
Suarez Roca et al. (2008)
Jennings et al. (2014)
Olango and Finn (2014)
Fear-Conditioned Analgesia (FCA)

• Analgesia expressed during or following exposure to conditioned stress

• Potent form of endogenous analgesia
  – Can be profound, reducing pain in rodents by > 90% at its peak
    (Chance et al., 1978;Fanselow, 1984; Harris & Westbrook, 1995; Finn et al., 2004)

• Expressed in rodents and humans (e.g. Janssen and Arntz, 1996; Flor and Grusser 1999)
Fear-conditioned analgesia represents a useful model for:

• Understanding the physiology and neural substrates of endogenous analgesia

• Elucidating mechanisms underpinning altered pain processing during stress/fear

• Understanding how anticipation and/or memory of pain modulates subsequent responses to noxious stimuli

• Identification of new therapeutic targets for pain- and fear-related disorders
Fear-conditioned analgesia is mediated by activation of the descending inhibitory pain pathway.
The Endocannabinoid System

CB receptors
- CB₁
- CB₂

Endocannabinoids
- Anandamide (AEA)
- 2-AG

Enzymes
- FAAH (AEA, OEA, PEA)
- MAGL (2-AG)

Related targets
- PPARs
- TRPV1
- GPR55

V. Di Marzo
www.endocannabinoid.net
Components of the endocannabinoid system are expressed throughout the descending inhibitory pain pathway.
Pharmacological blockade of \( \text{CB}_1 \) receptor prevents fear-conditioned analgesia

\[
\begin{array}{c}
\text{Composite pain score} \\
\hline
\text{No FC} & \text{FC} \\
\hline
0.8 & 0.4 \\
\hline
\end{array}
\]

\[\ast P<0.05 \text{ vs No FC-Veh}\]

Finn et al. (2004) Eur J Neurosci
Pharmacological blockade of CB₁ receptor prevents fear-conditioned analgesia

*P<0.05 vs No FC-Veh
+P<0.05 vs FC-Veh

Finn et al. (2004) Eur J Neurosci
Pharmacological blockade of CB₁ receptor prevents fear-conditioned analgesia and attenuates the suppression of dorsal horn Zif268 associated with fear-conditioned analgesia.

Finn et al. (2004) Eur J Neurosci
Olango et al. (2014) Eur J Pain

*P<0.05 vs No FC-Veh
+P<0.05 vs FC-Veh
Does blockade of endocannabinoid degradation enhance fear-conditioned analgesia?
FAAH inhibitor enhances fear-conditioned analgesia

* P<0.05 vs No FC-Veh
+ P<0.05 vs FC-Veh

URB597 at 0.3 mg/kg i.p.

Butler et al. (2008) Pain
Which brain region(s) are involved in endocannabinoid-mediated fear-conditioned analgesia?
Evidence for a role of GABAergic and glutamatergic signalling in the basolateral amygdala in endocannabinoid-mediated fear-conditioned analgesia in rats

Kieran Rea, Wedeselam M. Olanga, Brendan Harhen, Daniel M. Kerr, Rachel Galligan, Sean Fitzgerald, Maev Moore, Michelle Roche, David P. Finn

A role for the ventral hippocampal endocannabinoid system in fear-conditioned analgesia and fear responding in the presence of nociceptive tone in rats

Gemma K. Ford, Siobhan Kieran, Kenneth Dolan, Brendan Harhen, David P. Finn

Fear-induced suppression of nociceptive behaviour and activation of Akt signalling in the rat periaqueductal grey: role of fatty acid amidase hydrolase

Ryan K Butler, Gemma K Ford, Michelle Hogan, Michelle Roche, Karen M Doyle, John P Kelly, David A Kendall, Victoria Chapman, and David P Finn
The endocannabinoid system in the dIPAG mediates fear-conditioned analgesia

Olango et al. (2012) Br J Pharmacol

The endocannabinoid system in the basolateral amygdala mediates fear-conditioned analgesia

Rea et al. (2013) Pain
An endocannabinoid mechanism for stress-induced analgesia

Andrea G. Hohmann, Richard L. Suplita, Nathan M. Bolton, Mark H. Neely, Darren Fegley, Regina Mangieri, Jocelyn F. Krey, J. Michael Walker, Philip V. Holmes, Jonathon D. Crystal, Andrea Duranti, Andrea Tontini, Marco Mor, Giorgio Tarzia & Daniele Piomelli

Role of the basolateral nucleus of the amygdala in endocannabinoid-mediated stress-induced analgesia

Katherine Connell, Nathan Bolton, Daniel Olsen, Daniele Piomelli, Andrea G. Hohmann

Activation of Type 5 Metabotropic Glutamate Receptors and Diacylglycerol Lipase-α Initiates 2-Arachidonoylglycerol Formation and Endocannabinoid-Mediated Analgesia

Laura C. Gregg, Kwang-Mook Jung, Jessica M. Spradley, Elysia Nyias, Richard L. Suplita II, Andreas Zimmer, Masahiko Watanabe, Ben Mackie, Irvin Katona, Daniele Piomelli, Andrea G. Hohmann & colleagues
Role of the mPFC in Pain and Fear

- **Affective/cognitive components of pain and fear** (Tolle *et al*., 2001; Singer *et al*., 2004; Xie *et al*., 2009; Etkin *et al*., 2011; O’Hara *et al*., 2005; Wiech *et al*., 2008)

- **Top-down modulation of the descending inhibitory pain pathway** (Millan 2002; Butler and Finn 2009)

- **Expression of conditioned fear to a noxious stimulus** (Corcoran & Quirk, 2007; Sierra-Mercado *et al*., 2011)

- **Opposing Influences of PrL and IL on conditioned fear** (Sierra-Mercado *et al*., 2011; Vidal-Gonzalez *et al*., 2006) and **formalin-induced conditioned place avoidance** (jiang *et al*., 2014)

- **Role for the endocannabinoid system in the mPFC in stress, emotionality** (McLaughlin *et al*., 2014), **fear** (Draycott *et al*., 2014; Lin *et al*., 2009) and **pain** (Ji and Neugebauer 2014)

- **CB₁ receptor antagonism in the PrL attenuates fear-induced analgesia elicited by GABA_A receptor blockade in the ventromedial hypothalamus** (de Freitas *et al*., 2013)
Fear-conditioned analgesia expressed

McGowan, Rea et al. unpublished

*P<0.05 vs NFC-VEH
Fear-conditioned analgesia attenuated by microinjection of CB$_1$ receptor antagonist into the PrL or IL cortex

McGowan, Rea et al. unpublished

$^+$P<0.05 vs FC-VEH
Differential effects of FAAH inhibition in PrL vs IL cortex

McGowan, Rea et al. unpublished

+P<0.05 vs FC-VEH

McGowan, Rea et al. unpublished
Summary I: supraspinal regulation of fear-conditioned analgesia

- Mediated by the endocannabinoid system in:
  - Dorsolateral PAG
  - BLA
  - Ventral hippocampus

And

- mPFC
  - Similar role for CB₁ in PrL vs IL
    - AEA/2-AG
  - Differential effects of FAAH inhibition in PrL vs IL
    - PrL: AEA?
    - IL: PEA, OEA? PPARs?
  - ACC (see poster no. 92, Louise Corcoran)
Pain-related alterations in the PPARα signalling system in the rat ACC

Okine et al., (2014) Br J Pharmacol
Pharmacological blockade of PPARα in the ACC delays the onset of second phase formalin-evoked nociceptive behaviour

Okine et al., (2013) Br J Pharmacol
Pharmacological blockade of PPAR\(\gamma\) in the ACC reduces formalin-evoked nociceptive behaviour

\[\text{Composite pain score} \]

\[\text{Time bins (5 min)}\]

\[\text{Veh}\]

\[\text{GW9662 (PPAR}\gamma\text{ antagonist)}\]

\(*p < 0.05\)

Okine et al. Unpublished
Pharmacological blockade of TRPV1 in the ACC reduces formalin-evoked nociceptive behaviour

**p<0.01, *p<0.05

Okine et al. Unpublished
Pharmacological blockade of GPR55 in the ACC reduces formalin-evoked nociceptive behaviour

Okine et al. Unpublished

**p<0.01, *p<0.05
GPR55 receptor blockade reduces levels of Phospho-ERK in the ACC

**p<0.01 CID vs. Vehicle

**p<0.01 CID vs. Vehicle

Okine et al. Unpublished
Summary II

• Pharmacological blockade of PPAR\(\alpha\), PPAR\(\gamma\), TRPV1 and GPR55 in the ACC reduces formalin-evoked nociceptive behaviour
  – Facilitatory/permissive role for these receptors in the ACC in pain
Impact of Stress on Pain

Pain

Stress

Intense acute stress/fear

Moderate chronic stress/anxiety

Analgesia

Hyperalgesia

Genetic background
% of primary care patients with pain disorder and co-existent mood disorder

Von Korff and Simon (1996) Br J Psychiatry
Exacerbation of pain by anxiety is associated with increased activity in the entorhinal cortex.

Ploghaus et al. (2001) J Neurosci
Sites and mechanisms mediating stress-induced hyperalgesia

Jennings et al. (2014) Prog Neurobiol
Animal models of SIH: Role of endoC system

**Neurogastroenterology**

Reciprocal changes in vanilloid (TRPV1) and endocannabinoid (CB1) receptors contribute to visceral hyperalgesia in the water avoidance stressed rat

S Hong,1 J Fan,1 E S Kemmerer,2 S Evans,2 Y Li,1 J W Wiley1

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www.neuropsychopharmacology.org

Therapeutic Potential of Inhibitors of Endocannabinoid Degradation for the Treatment of Stress-Related Hyperalgesia in an Animal Model of Chronic Pain

Ermelinda Lomazzo1, Laura Bindila1, Floor Remmers1, Raissa Lerner1, Claudia Schwitter1, Ulrich Hoheisel2 and Beat Lutz3

**J Neurogastroenterol Motil.** Vol. 16 No. 3 July, 2010
DOI: 10.5056/jnm.2010.16.3.281
Journal of Neurogastroenterology and Motility

The Role of Peripheral Cannabinoid Receptors Type 1 in Rats With Visceral Hypersensitivity Induced by Chronic Restraint Stress

Lei Shen, MD, Xiao-jun Yang, MD, Wei Qian, MD and Xiao-hua Hou, MD*
Is there a role for the endocannabinoid system in pain hyper-responsivity in negative affective states?  
(Angiety/depression-related hyperalgesia)
The Wistar-Kyoto rat as a model of anxiety/depression-related hyperalgesia

Burke et al. (2010) Neuroscience
Impaired endocannabinoid signalling in the rostral ventromedial medulla underpins genotype-dependent hyper-responsivity to noxious stimuli

Kieran Rea a,c,1, Weredeselam M. Olango a,c,1, Bright N. Okine a,c, Manish K. Madasu a,c, Iseult C. McGuire a,c, Kathleen Coyle a,c, Brendan Harhen c, Michelle Roche b,c, David P. Finn a,c,*

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b Physiology, School of Medicine, National University of Ireland, Galway, Ireland
c NCBES Galway Neuroscience Centre and Centre for Pain Research, National University of Ireland, Galway, Ireland
Higher 2-AG levels and lower CB₁ receptor mRNA expression in the LPAG of WKY rats compared with SD rats

Jennings, Olango, Okine et al., Unpublished
Intra-LPAG administration of the CB$_1$ receptor agonist ACEA reduces formalin-evoked nociceptive behaviour in SD rats but not in WKY rats

Jennings et al., Unpublished
Intra-LPAG administration of the CB₁ receptor agonist ACEA reduces formalin-evoked nociceptive behaviour in SD rats but not in WKY rats

Jennings et al., Unpublished
Intra-LPAG administration of the CB₁ receptor agonist ACEA reduces formalin-evoked nociceptive behaviour in SD rats but not in WKY rats.

Jennings et al., Unpublished

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**5 min Time bins**

**Composite Pain Score**

**SD**

- Vehicle
- ACEA
- ACEA+AM251

**WKY**

**Composite Pain Score**

**Jennings et al., Unpublished**
Intra-IPAG administration of ACEA increases c-Fos expression in the RVM and decreases c-Fos expression in the spinal cord of SD, but not WKY, rats.

* $p<0.05$ vs SD Vehicle

Jennings et al., Unpublished
Summary III

- WKY rats:
  - High anxiety/depression-related behaviour
  - Hyperalgesia
    - Reduced CB$_1$R and increased 2-AG levels in the LPAG
    - Differential responsivity to intra-LPAG admin of CB$_1$R agonist
      - Nociceptive behaviour
      - C-Fos expression in RVM and DH

- Role for TRPV1 (see poster no. 13, Manish Madasu)
- Dysfunction of the endocannabinoid system in PAG/RVM circuitry may contribute to exacerbated nociceptive responding in a genotype associated with negative affect
Role of supraspinal endocannabinoid system in postoperative pain following inguinal hernia repair surgery?

Development and Characterization of a Novel, Anatomically Relevant Rat Model of Acute Postoperative Pain

Dara Bree, †, ‡, § Orla Moriarty, †, ‡, § Cliona M. O’Mahony, †, ‡, § Bradley Morris, †, ‡, § Karen Bannerton, †, ‡ Daniel C. Broom, § John P. Kelly, †, ‡ Michelle Roche, †, ‡ and David P. Finn †, ‡

Bree et al. 2015 J Pain
Bree, Moriarty et al. Unpublished
Conclusions

Endocannabinoids may play a pivotal role in regulating the balance between fear, anxiety/depression and pain

- The precise nature of this regulation may depend on:
  - Levels and types of endocannabinoids/related lipids
  - Receptors activated (e.g. CB₁, PPARs, TRPV1, GPR55…)
  - Brain region and neural circuitry (e.g. GABA vs glutamate)

- Other models? (Post-op pain following inguinal hernia repair, Neuropathic pain in WKY, IFN-α - induced hyperalgesia – Marie Fitzgibbon, Poster no. 94)

- These data may be relevant to the development of endoC-based therapeutics where anxiety/depression and pain are co-morbid
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