

UC Irvine

UC Irvine Previously Published Works

Title

Neuropathic Pain Unmasks Delta Opioid Receptor-Mediated Analgesia

Permalink

<https://escholarship.org/uc/item/8xj2t3z2>

Authors

Ong, Edmund W

Holdridge, Sarah V

Sutherland, Karen Anne

et al.

Publication Date

2016

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

# Neuropathic Pain Unmasks Delta Opioid Receptor-Mediated Analgesia

Edmund W. Ong<sup>1,2</sup>, Sarah V. Holdridge<sup>1</sup>, Karen Anne Sutherland<sup>1</sup>,  
Stacey A. Armstrong<sup>1</sup>, Anna M.W. Taylor<sup>3</sup>, Lihua Xue<sup>1</sup> and  
Catherine M. Cahill<sup>1,2</sup>

 Author Affiliations

## Abstract

Clinically-used opioid drugs overwhelmingly act at the mu-type opioid receptor (MOPr). MOPr agonists are good analgesics and are the gold-standard for treating moderate and severe pain. However, MOPr agonists are considerably less effective in treating neuropathic pain. Delta-type opioid receptor (DOPr) agonists also have analgesic effects, but none are yet used clinically. Here, we use *in vivo* models of neuropathic pain to examine the analgesic effects of DOPr agonists.

We first show that spinally-administered DOPr agonists (DPDPE, SNC80, Deltorphin II, and DSLET) are antiallodynic in neuropathic pain, as has previously been reported.

Second, we demonstrate that DOPr-mediated thermal antinociception is, in fact, augmented in neuropathic pain. That is, DOPr agonists produce greater thermal antinociception to the same noxious stimulus in neuropathic animals than in control animals. This is in contrast to the MOPr agonist morphine, which produces less thermal antinociception in neuropathic pain (mirroring the reduction in clinical efficacy). Interestingly, despite all tested DOPr agonists being antiallodynic in neuropathic pain, only two (Deltorphin II and DSLET) show augmented thermal antinociception. These data expand on previous reports demonstrating that DOPr activation modulates thermal nociception. Further, the divergent effects at MOPr and DOPr in neuropathic pain demonstrate that DOPr agonists produce thermal antinociception via DOPr, not MOPr.

Third, we assess the effect of DOPr agonism on integrated neuropathic pain affect using the conditioned place preference (CPP) paradigm. Spinally-administered Deltorphin II produces CPP in neuropathic animals, but not controls.

Fourth, we show that blockade of DOPr by the antagonist Naltrindole produces a conditioned place aversion (CPA) in neuropathic animals, but not controls. This confirms and extends literature reports that genetic knockout of DOPr is pronociceptive and suggests the presence of DOPr-mediated endogenous analgesia in neuropathic pain.

Fifth, we use neonatally-administered capsaicin to ablate capsaicin-sensitive primary afferents. Destruction of these neurons prevents the augmentation of DOPr-mediated thermal antinociception in neuropathic pain, implicating these peripheral afferents as potential sites of action. Contrastingly, the ablation of capsaicin-sensitive primary afferents does not affect DOPr-mediated antiallodynic effects in neuropathic pain.

The results provide further evidence that neuropathic pain leads to the unmasking of DOPr-mediated analgesia and augmentation of its endogenous activity. Meanwhile, the selective sensitivity to neonatal capsaicin suggests a role for neuronal type-specific, ligand-biased agonism in DOPr analgesia.

## Support or Funding Information

This work was supported by grants from the Canadian Institutes of Health Research (MOP121915, MOP394808), the Canada Research Chairs Program, Pfizer Canada, the J.P. Bickell Foundation, the Harry Botterell Foundation, and the Ontario Innovation Trust/Canadian Foundation for Innovation to CMC. EWO was a recipient of a postgraduate scholarship from NSERC. SVH was a recipient of a postgraduate fellowship from Queen's University.

## Footnotes

This abstract is from the Experimental Biology 2016 Meeting. There is no full text article associated with this abstract published in The FASEB Journal.

antagonism as novel analgesics  
Thomas Joaquín Fernández et al.,  
FASEB J, 2017

Efficacy at the Mu Opioid Receptor:  
Insights from Orthosteric and Allosteric  
Ligands

Kathryn E Livingston<sup>1</sup> et al., FASEB J,  
2016

Allosteric Modulation of the Mu-Opioid  
Receptor: Probe Dependence and Role  
of Na<sup>+</sup> Ions

Kathryn Livingston<sup>1</sup> and John  
Traynor<sup>1</sup>, FASEB J, 2015

A biased mu-opioid receptor positive  
allosteric modulator that does not alter  
receptor regulation

Kathryn E Livingston and John R  
Traynor, FASEB J, 2016

Nhan Le et al., RxEconsult

Researchers discover tolerance  
mechanism in chronic morphine  
treatment [↗](#)

AZoNetwork, 2010

International study shows potential new  
therapy to treat patients with  
neuropathic pain [↗](#)

AZoNetwork, 2015

SLU researcher discovers way to block  
pain pathway [↗](#)

AZoNetwork, 2014

Powered by **Trend MD**