Pain management in the era of the opioid crisis: a road map provided by the regulation of endogenous opioid antinociception

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Consequences of undertreating chronic pain

- Poor sleep, depression, and anxiety
- Alters brain structure and function
- Decreases gray matter in pain-transmitting areas
- Alters the functional connectivity of cortical regions
- Impairs emotional decision-making
- Decreases prefrontal and thalamic gray matter density
- Decreases motivation via increased long-term depression in the nucleus acumbens

How to reconcile the medical / ethical imperative to manage chronic pain with the opioid crisis?

Endogenous opioids produce analgesia

Opioid receptor block eliminates placebo-induced reduction of postoperative dental pain) (Levine, el al., Lancet 2: 654-7, 1978)

Opioid receptor block enhances cal pain (Levine, et al., Nature 272: 826-7, 1978)

Expectation of pain relief activa nu–opioid receptors in the human brain (Zubieta, et al., J. Neurosci. 25: 7754-62, 2005)

Placebo analgesia correlates wit hanced endogenous opioid activity (Wager, et al., PNAS 104: 11056-61, 2007)

Spatially directed expectation of pain relief produces opioid-mediated pain reduction only on body part targeted by the expectation (Benedetti, et al., JNeurosci 19: 3639-48, 1999)

Proof of concept that harnessing endogenous opioids can be an effective strategy for managing pain

Clinical usefulness- - Pharmacological strategies?

Strategy for defining drug targets for harnessing endogenous opioid activity

Identify physiological states in which opioid responsiveness is turned on/off

Stages of estrus cycle

⇩

Determine mechanisms responsible

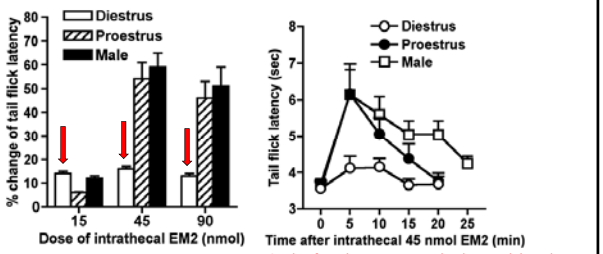
⇩

Validate that determinants of responsiveness to exogenous opioids likely to pertain to *endogenous* opioids

Males or females? Females

Endogenous opioid? Endomorphin 2

Estrous cycle stages are natural physiological states associated with variable spinal EM2 analgesia



Lack of analgesia not simply due to delayed onset.

Understanding on/off mechanisms for i.t. EM2 analgesia could point the way for manipulating endogenous EM2 activity

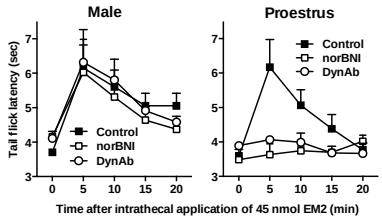
Liu, et al., J. Pain 14: 1522-1530, 2013

Common Chronic Pain Disorders are More Prevalent and severe in Women than men

	Population Prevalence	F:M Ratio
Migraine	15-20%	2-3:1
Tension-Type Headache	4-5%	2:1
Temporomandibular Disorders	4-12%	1.5:1
Irritable Bowel Syndrome	15-20%	2:1
Rheumatoid Arthritis	1%	2.5:1
Osteoarthritis (age > 45)	> 80% (age 65)	1.5:1 – 4:1
Interstitial Cystitis	0.5%	9:1
Fibromyalgia	2-3%	6:1

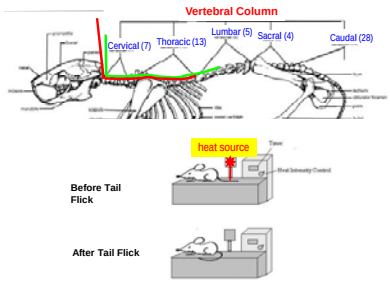
Could result from dysfunctional endogenous opioid system(s); analgesic effects of turning on endogenous opioids might be more apparent.

Spinal EM2 analgesia in females (not males) requires dynorphin/KOR in addition to MOR activation



Spinal EM2 mechanisms more multifaceted in females than males, providing an additional handle on manipulating endogenous EM2 analgesia

Assumption: Characteristics of *endogenous* opioid utilization can be inferred from responsiveness to their exogenous application



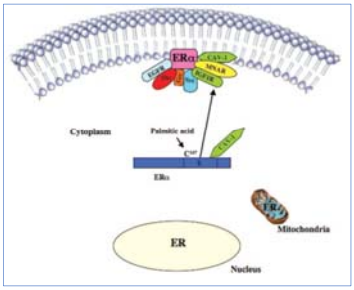
Preview

Absence of spinal EM2 analgesia during diestrus results from active suppression.

Spinal estrogenic signaling combines with $mGluR_1$ signaling to suppress spinal EM2 antinociception.

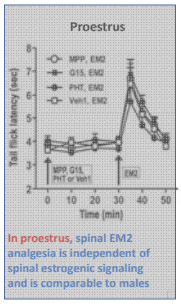
Reversal of this suppression is anti-allodynic in an animal model of chronic pain

Nuclear estrogen receptors translocate to and signal within the plasma membrane

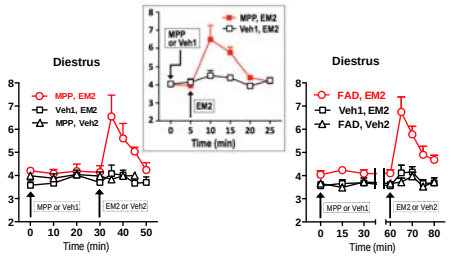


Rapid onset of effect of ERα block indicates mediation by *membrane ERα*

Spinally produced estrogens and their signaling during *diestrus* blocks spinal EM2 analgesia



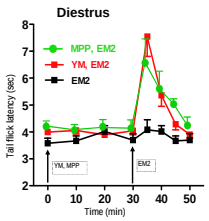
In proestrus, spinal EM2 analgesia is independent of spinal estrogenic signaling and is comparable to males

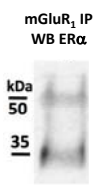


In diestrus, spinally produced estrogens via mERα suppress spinal EM2 analgesia

Liu, et al., Pain 158: 1903-1914, 2017

$mGluR_1$ activity is required to suppress spinal EM2 analgesia during diestrus





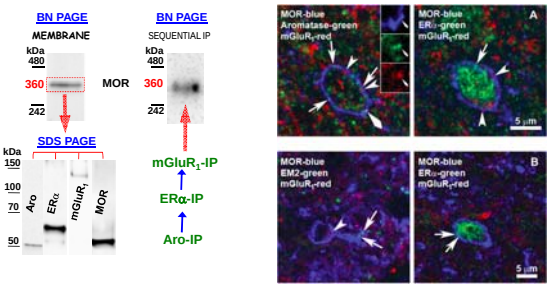
Suppression of spinal EM2 analgesia during diestrus requires $mGluR_1$ as well as mERα activation.

Coincidence of time course for mERα and $mGluR_1$ suppression of spinal EM2 antinociception suggests suppression mechanism involves their direct interaction

Liu, et al., Pain 158: 1903-1914, 2017

Dynamic interactions among Aro, mERα, mGluR$_1$, and MOR underlie diestrus-associated suppression of spinal EM2 analgesia

A complex containing MOR, mGluR$_1$ aromatase, and ERα is expressed in neurons apposed by EM2 varicosities



Neuronal co-expression consistent with *in vivo* existence of oligomer and its ability to modulate EM2 analgesic responsiveness- - regulation of responses to i.t. EM2 in diestrus likely mirrors that of endogenous EM2

Liu, et al., Pain 158: 1903-1914, 2017

Targets for facilitating endogenous spinal EM2 analgesia during diestrus

Spinal mERα

Spinal mGluR$_1$

Spinal aromatase

BLOCK

Increase spinal EM2 analgesic responsiveness and, by inference, endogenous opioid analgesia

In diestrus, spinal EM2 antinociception is suppressed by spinal estrogen/mERα/$mGluR_1$ signaling

QUESTION

Is the loss of suppression during proestrus sufficient for spinal EM2 analgesia to be manifest?

OR

are new signaling strategies also required, which would further identify pharmacological targets for manipulating endogenous spinal opioid analgesia?

Essentials for spinal EM2 antinociception during proestrus

Switch endogenous mGluR substrate from mERα to glutamate

↓

Importance of endogenous biased agonism at mGluRs

↓

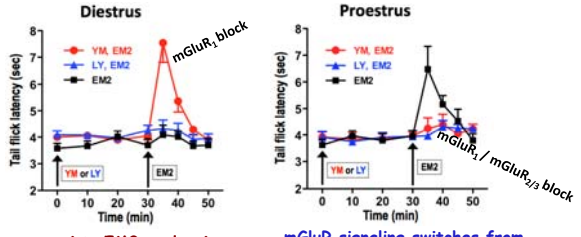
Glutamate signaling via $mGluR_1$ as well as $mGluR_{2/3}$

↓

↑ Spinal dynorphin/KOR signaling

Implications: manipulating glutamate availability and Dyn/KOR signaling could enhance endogenous EM2 opioid analgesic signaling

Qualitative changes in contribution of mGluRs to spinal EM2 analgesia during diestrus and proestrus



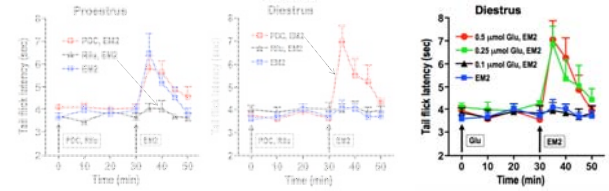
$mGluR_1$ suppress i.t. EM2 analgesia; no effect of $mGluR_{2/3}$ block

mGluR signaling switches from suppressive to facilitative

$mGluR_1$ and $mGluR_{2/3}$ both essential for spinal EM2 analgesia

Liu, et al., J. Neurosci, 37: 11181-11191, 2017

Glutamate is essential for spinal EM2 analgesia during proestrus; biased agonism at $mGluR_1$



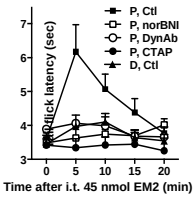
Proestrus: block of glutamate release eliminates spinal EM2 analgesia
Diestrus: block of glutamate reuptake facilitates spinal EM2 analgesia
Diestrus: intrathecal glutamate facilitates spinal EM2 analgesia

Liu, et al., J. Neurosci, 37: 11181-11191, 2017

Why is glutamate essential?

Spinal EM2 analgesia is dependent on Dynorphin/KOR

Fig. :



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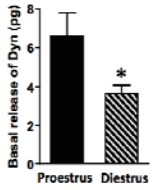
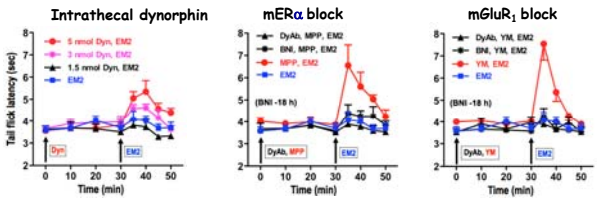


Spinal Dyn release decreases in diestrus

Liu, et al., J. Neurosci, 37: 11181-11191, 2017

Hypothesis: Lack of spinal EM2 analgesia during diestrus results from deficiency in spinal Dyn-KOR signaling .

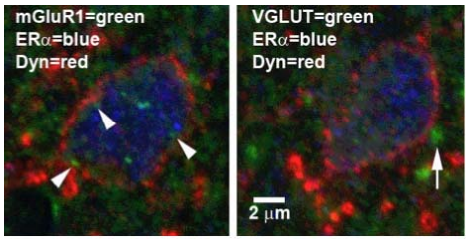
Spinal mERα/$mGluR_1$ signaling inhibits Dyn/KOR signaling, which is essential for spinal EM2 analgesia



Unmasking spinal EM2 analgesia in diestrus by mERα or $mGluR_1$ block results from restoration of threshold levels of spinal dynorphin/KOR signaling characteristic of proestrus.

Liu, et al., J. Neurosci, 37: 11181-11191, 2017

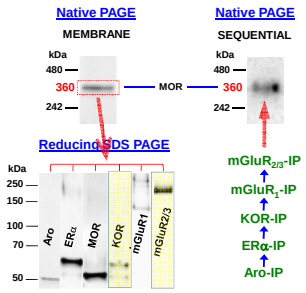
Cellular basis for cycling between mERα/mGluR$_1$-inhibited and glutamate/mGluR$_1$-activated dynorphin release



Glutamatergic terminal apposes spinal neuron expressing mGluR$_1$, ERα, and Dyn apposed by (Liu, et al., J. Neurosci, 37: 11181-11191, 2017)

mERa and glutamate positioned to regulate spinal Dyn release, thereby modulating MOR activation by exogenous/endogenous EM2

Oligomer containing Aro, mERa, mGluR$_1$, mGluR$_{2/3}$, MOR and KOR



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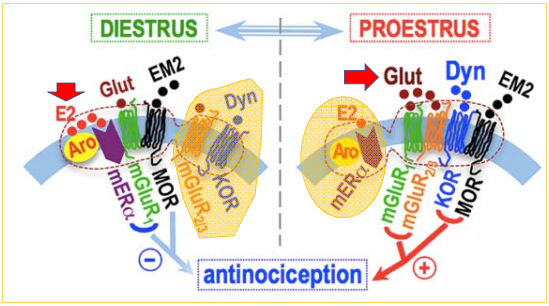
Molecular components of suppression vs. facilitation of spinal EM2 antinociception



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Targets for facilitating spinal EM2 analgesia during diestrus

Spinal mERα
Spinal $mGluR_1$
Spinal aromatase
Glutamate transporter

BLOCK → Augment spinal EM2 analgesia

Increase Dynorphin/KOR activity

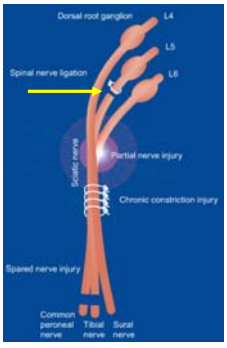
Prerequisites for maintaining spinal EM2 analgesia during proestrus

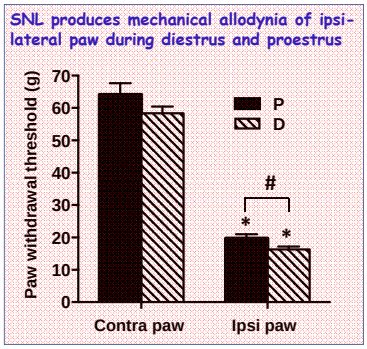
Glutamate/$mGluR_1$/$mGluR_{2/3}$,dynorphin/KOR

Predictions in a model of chronic pain

Blockade of spinal mERα or $mGluR_1$ or glutamate transporter (glutamate reuptake) during diestrus will be anti-allodynic (analgesic), increasing response thresholds to tactile stimulation

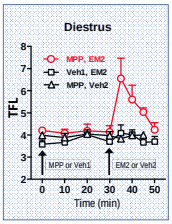
Blockade of $mGluR_1$ during proestrus will exacerbate mechanical allodynia, decreasing response thresholds to tactile stimulation

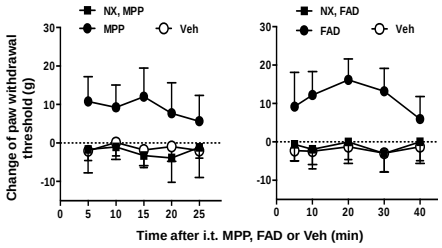




Liu, et al., JPain, 20: 234-243, 2019

Disruption of spinal estrogenic signaling in diestrus produces opioid-mediated anti-allodynia *in the absence of exogenous opioid*





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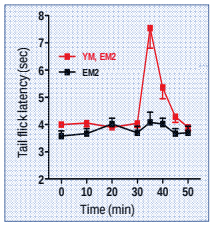
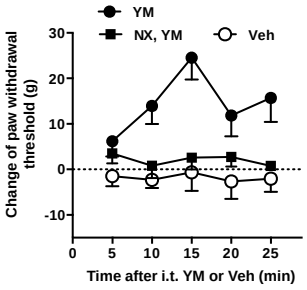
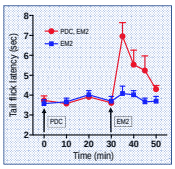
Spinal mGluR$_1$ block in SNL rats produces opioid-mediated anti-allodynia during diestrus in the absence of exogenous opioid





Liu, et al., J Pain, 20: 234-243, 2019

Inhibition of spinal glutamate reuptake during diestrus in SNL rats produces opioid-mediated anti-allodynia in the absence of exogenous opioid



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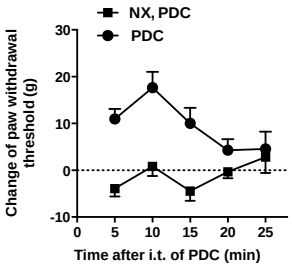

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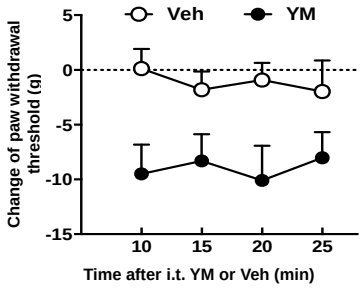
Spinal mGluR$_1$ blockade in spinal SNL rats enhances allodynia during proestrus



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Deleterious effects of undertreating of chronic pain

- Poor sleep, depression, and anxiety
- Alters brain structure and function
- Decreases gray matter in pain-transmitting areas
- Alters the functional connectivity of cortical regions
- Impairs emotional decision-making
- Decreases prefrontal and thalamic gray matter density
- Decreases motivation via increased long-term depression in the nucleus acumbens

Take home message

Chronic pain is a health risk - a progressive disease that has long-lasting negative effects on the brain.

Restricting the use of opioids to manage pain (as is currently widely practiced) should be balanced by an awareness of health consequences of undermanaging pain.

Developing drugs to harness endogenous opioids for pain relief may be an effective approach to accessing the undeniably enormous pain relieving effects of opioids while limiting addiction to opioids and their abuse.

Collaborators

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