OPIOID-INDUCED HYPERALGESIA

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OBJECTIVES

1. Introduction
2. Opioid Receptor Physiology
3. Tolerance
4. Evidence for Opioid Induced Hyperalgesia
5. The role of NMDA receptors in OIH
6. Novel Mechanisms for OIH
   - TRPV1
   - Spinal NK-1 Receptors
   - L-Calcium Channels
   - Glutamate Transporters
   - Adaptive Homeostasis

INTRODUCTION

Opioids continue to be among the mainstays of pharmacological treatment of moderate to severe pain.

Many patients, especially advanced cancer patients, require high-dose opioid therapy. Clinical efficacy and tolerability is hindered by two phenomena:

- Tolerance
- Opioid-Induced Hyperalgesia
OPIOID RECEPTOR PHYSIOLOGY

Four (so far) classes of opioid receptors

1. Mu
   - Endogenous Ligand – Beta-Endorphin
   - Location – Highly concentrated in outer lamina of dorsal horn of the spinal cord

2. Delta
   - Endogenous Ligand – Enkephalin
   - Location – Diffusely distributed throughout the dorsal horn

3. Kappa
   - Endogenous Ligand – Dynorphin
   - Location – Outer lamina of the dorsal horn of the lumbar sacral cord and are closely associated with input from visceral structures

4. ORL1 (Orphan receptor) (LB)
   - Endogenous Ligand – “Nociceptin”
   - Activation blocks opioid induced antinociception
   - Activated by buprenorphine
   - Location – Cortex, amygdala, hippocampus, septal nuclei, habenula (near pineal body), hypothalamus, spinal cord

Lutfy et al, Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors, J Neurosci. 2003 Nov 12;23(32):10331-7

OPIOID RECEPTOR PHYSIOLOGY

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<th>Mu1</th>
<th>Delta</th>
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<td>Analgesia</td>
<td>Psychomimetic Effects</td>
<td>Spinal Analgesia</td>
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Brain: Limbic System (thalamus, amygdala, hippocampus)
Brainstem: Rostral Ventromedial Medulla (RVM) Periaqueductal Gray (PAG)

Mu and some Delta receptors within the RVM and PAG inhibit pain transmission by second order neurons.
OPIOID RECEPTOR PHYSIOLOGY

Differing potency and efficacy at various receptors.

Action is the sum of all the relevant receptors, activated or inhibited.

Seven subtypes of mu receptors, each with varying affinity for mu agonists. (1)

500 genes influence pain, with 100 variations in the human mu opioid receptor gene alone. (2)

OPIOID RECEPTOR PHYSIOLOGY

Ross, et al. in 2005
Influence of variations in genes that encode for mu receptors and morphine response in cancer patients.

FINDINGS:
No significant differences in mu receptors genes between those responsive and those intolerant to morphine.

* Significant differences in two regulatory proteins
  stat 6 – mu opioid gene transcriptional factor
  arrestin – intracellular regulatory protein

Genetic variation influences responses to morphine.

OPIOID SIGNAL TRANSDUCTION

Seven trans-membrane segments.

G-proteins are intracellular signaling proteins.

Four families (G_i, G_is, G_q, G_12).
**OPIOID SIGNAL TRANSDUCTION**

Inhibits release of substance P release from the presynaptic neuron.

Postsynaptic membrane, opioid receptors mediate hyperpolarization by opening K+ channels.

Phosphokinase C and GPCR kinases phosphorylate opioid receptors, increasing affinity for intracellular arrestin molecules.
Repeated exposure to an opioid that results in decreased therapeutic effect or higher doses to maintain the same effect.

- Innate tolerance
  Genetically determined sensitivity or insensitivity.
- Acquired Tolerance
  Pharmacodynamic
  Pharmacokinetic
  Learned

Pharmacodynamic Tolerance
Adaptation to the changes that occur within a system affected by an opioid, including changes in receptor density or desensitization, such that a response to a given concentration of the drug is reduced.

Evidence shows that many of the mechanisms related to this type of tolerance involve the NMDA receptor.
Pharmacokinetic Tolerance
Changes in the distribution or metabolism of the opioid after repeated drug administration resulting in reduced concentration of the opioid in the blood or at the sites of drug action.

The most common mechanism of this phenomenon is an increase in the rate of metabolism of the opioid.

Learned Tolerance
Reduction in the effects of an opioid as result of mechanisms that are learned.
One type of learned tolerance is conditioned or associative tolerance. Learned mechanism that develops when environmental cues are consistently paired with the administration of a drug.

Tolerance may or may not justify an opioid dose escalation.

May be the first sign of opioid-induced hyperalgesia, suggesting a reduction of the opioid dose.

The issue is how to distinguish the two elements:
- Opioid Tolerance
- Opioid-Induced Hyperalgesia
Three proposed mechanisms are associated with desensitization of G-protein coupled receptors (GPCR):
- Receptor phosphorylation
- Receptor internalization/sequestration
- Receptor decoupling

Internalization of the receptor was originally thought to contribute to tolerance by decreasing the numbers of receptors.

However, increased internalization (endocytosis) of receptors shown to dramatically decrease opioid tolerance. (7)

Morphine fails to promote endocytosis of receptors. (3-6)

Current concept: desensitization and receptor internalization reduce tolerance development. (2)
Desensitization occurs when the intracellular regulatory proteins or enzymes are activated.

Activation "decouples" the opioid receptor from the G-protein.

This switch changes the receptor to a non-analgesic G-protein, decreasing analgesia activity. (8)
Multiple studies which have concluded that opioid administration can unexpectedly cause:

- Hyperalgesia (enhanced pain response to noxious stimuli)
- Allodynia (pain elicited by innocuous stimuli)

Witnessed in both acute and chronic opioids use and observed in both animal models and humans. The contribution of opioid tolerance versus opioid induced hyperalgesia is not known.

Acute administration of Opioids results in dose dependent increases in receptor latency:

1. Thermal
2. Chemical
3. Mechanical

With repeated exposure the effect of given dose of opioid will decrease in magnitude or duration of action. Tolerance is shown by a rightward displacement of the dose response curve.

Animal studies demonstrate opioid induced hyperalgesia, with systemic or intrathecal opioids.

Rivat et al in 2005, rats given chronic intrathecal bolus injections of morphine showed nonspecific pain related behaviors:

- Fighting
- Scratching
- Aggression
Repeated opioid dosing can lead to a progressive, lasting increase in pain sensitivity. Increased cold hyperalgesia seen in methadone maintenance patients.

Seen in rat studies after subcutaneous fentanyl boluses using the Randall-Sellitto test.

Decreased nociceptive thresholds lasting as long as five days after fentanyl boluses. (Rivat et al. 2009)

Decreased nociceptive thresholds with bolus dose may be withdrawal. Progressive reduction of nociceptive thresholds seen also with continuous intrathecal infusions. Thermal hyperalgesia and tactile allodynia was observed in animals even with continuous opioid infusion. Active cellular mechanism. NMDA receptor and OIH.
Recent Studies and Proposed Novel Mechanisms

Transient receptor potential vanilloid-1 (TRPV-1), ligand-gated, non-selective cation channels. (7,8)

Molecular transducer of noxious thermal and chemical stimuli.

Important role in the development of inflammation-induced hyperalgesia. (7-10)

Inflammation increases the expression of TRPV-1.

TRPV1 wild type and TRPV1 knock out mice to explore TRPV1's role in hyperalgesia formation.

Conclusions:
1. Morphine subQ elicited both thermal and tactile hypersensitivity in TRPV1 WT mice, but not in the KO mice.
2. Oral TRPV1 antagonist reversed both thermal and tactile hypersensitivity induced in WT mice.
3. TRPV1 is essential in morphine-induced hyperalgesia.

Changes induced by morphine exposure are similar to those in inflammatory injury suggesting common mechanisms. Both show upregulation in the spinal cord:
- Spinal Dynorphin
- CGRP
- Substance P

TRPV1 KO mice lack ability to develop opioid-induced hyperalgesia. Inflammation-induced hyperalgesia and OIH is due to upregulation of peripheral TRPV1 channels.
Role of spinal NK-1 receptor-expressing neurons supporting fentanyl-induced hypersensitivity.

Conclusions:
Acute Fentanyl enhances mechanical hypersensitivity in surgical pain induced by plantar incision in rats.

Neurokinin-1 (NK-1) and spinal dynorphin are necessary for the development and maintenance of opioid induced hyperalgesia.

NK-1 hypersensitivity produced by acute fentanyl administration. In non-operated rats, fentanyl induced analgesia was followed by prolonged hypersensitivity.

Fentanyl also enhanced pain induced by plantar incision.
Ablation of NK-1 neurons with Saporin reduced sensory hypersensitivity in fentanyl-treated rats that underwent incision compared with those that did not.

Spinal dynorphin increased by 30% and 66% in fentanyl- and fentanyl/incision-treated rats.
Antiserum to dynorphin attenuated hypersensitivity in fentanyl-treated rats.
NK-1 receptors have important roles in the promotion of OIH in ascending and descending pain pathways.
Several types of calcium channels identified:
N type, L type, P/Q type, R type, T type
Blockade of L-type calcium channels (using calcium blocker antarrhythmics and antihypertensives) in abolishing opioid-induced sensory hyperalgesia and tolerance.
Mice received twice-daily intrathecal injections of 10 mcg morphine alone or in combination with 10 mcg amlodipine for 8 days. Repeated injections enhanced tactile and thermal stimuli.

Hypersensitivity prevented with coadministration of amlodipine.
Mice receiving morphine for 8 days had significant rightward shifts on response curves.
Amlodipine with morphine showed no tolerance or hyperalgesia.
Suggests that amlodipine can prevent opioid-induced hyperalgesia.
Role of glutamate transporters (GTs) in the development of morphine tolerance and thermal hyperalgesia.

Chronic morphine induced a dose-dependent down-regulation of GTs in the dorsal horn.

GT down-regulation was mediated through opioid receptors.

Morphine-induced GT down-regulation reduced in vivo glutamate homeostasis, in morphine-treated rats.

Down-regulation of GTs exhibited a correlation with morphine tolerance and thermal hyperalgesia.

Glutamate transporter inhibitor (PDC) potentiated, while riluzole reduced tolerance and thermal hyperalgesia.
GLUTAMATE AND OIH

GT activity by PDC were mediated through NMDA receptor, noncompetitive NMDA antagonist blocked both morphine tolerance and thermal hyperalgesia.

Spinal GTs may contribute to morphine tolerance and OIH by regulating glutamate homeostasis.

OIH IS IT NORMAL?


Some interesting conclusions:
Opioid-induced hyperalgesia is not abnormal.
"It is normal response that serves to remember danger following threats in an ancestral environment"
Pain hypersensitivity induced by opioids is adaptive.
Common mechanisms underlie OIH.
Adaptive and beneficial in the ancestral environment, now it is non adaptive.

OIH IS IT NORMAL?

Opioid-induced hyperalgesia following an initial opioid dose is not passive, but a first step leading to pain sensitization.

Opioids reinforce a nociceptive memory contributing to chronic pain.

Example: Fentanyl enhanced carrageenan-induced hyperalgesia and reinforced pain sensitization shown by response to second injection (16). Rivat et al. 2002
Opioids might contribute to neuronal plasticity in chronic pain.

Opioids are not good therapeutic agents for preemptive analgesia.

Eisenach: opioid-induced hyperalgesia indicates that opioids may contribute to pre-emptive hyperalgesia, not analgesia. (17)

CONCLUSIONS:

- This data may lead us to rethink how we use opioids in the chronic non-malignant pain setting.
- Addition of Ca2+ channel blockers, other novel agents?
- NMDA receptor antagonists and antagonists of anti-opioid receptor systems may decrease central sensitization and chronic pain.

REFERENCES
