Opioid-Induced Hyperalgesia (OIH)

Jean You, MD

Vista Pain Center, Kennewick, WA

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Historical Considerations

Rosshach's Observation (1880):

- "When dependence on opioids finally becomes an illness in itself, opposite effects such as restlessness, sleep disturbance, hyperesthesia, neuralgia, and irritability become manifested.“

Albutt's Observation (1870):

- Albutt observed that potent analgesia from morphine could actually result in increasing pain.

Accumulating Evidence:

- There is accumulating evidence suggesting that opioid analgesics lead not only to analgesia but also to hyperalgesia. Human studies on former opioid addicts maintained on Methadone have documented this effect.

Focus on Opioid Metabolites:

- Studies have focused on the toxic effects of opioid metabolites, with neurological side effects including irritability and allogynia.

Definition of OIH

- A state of nociceptive sensitization following acute or chronic exposure to opioids.
- Paradoxical enhancement of the pain which might or might not be original underlying pain.
- The prevalence of OIH are not available.
- Mechanisms of OIH are not yet understood.

Characteristics

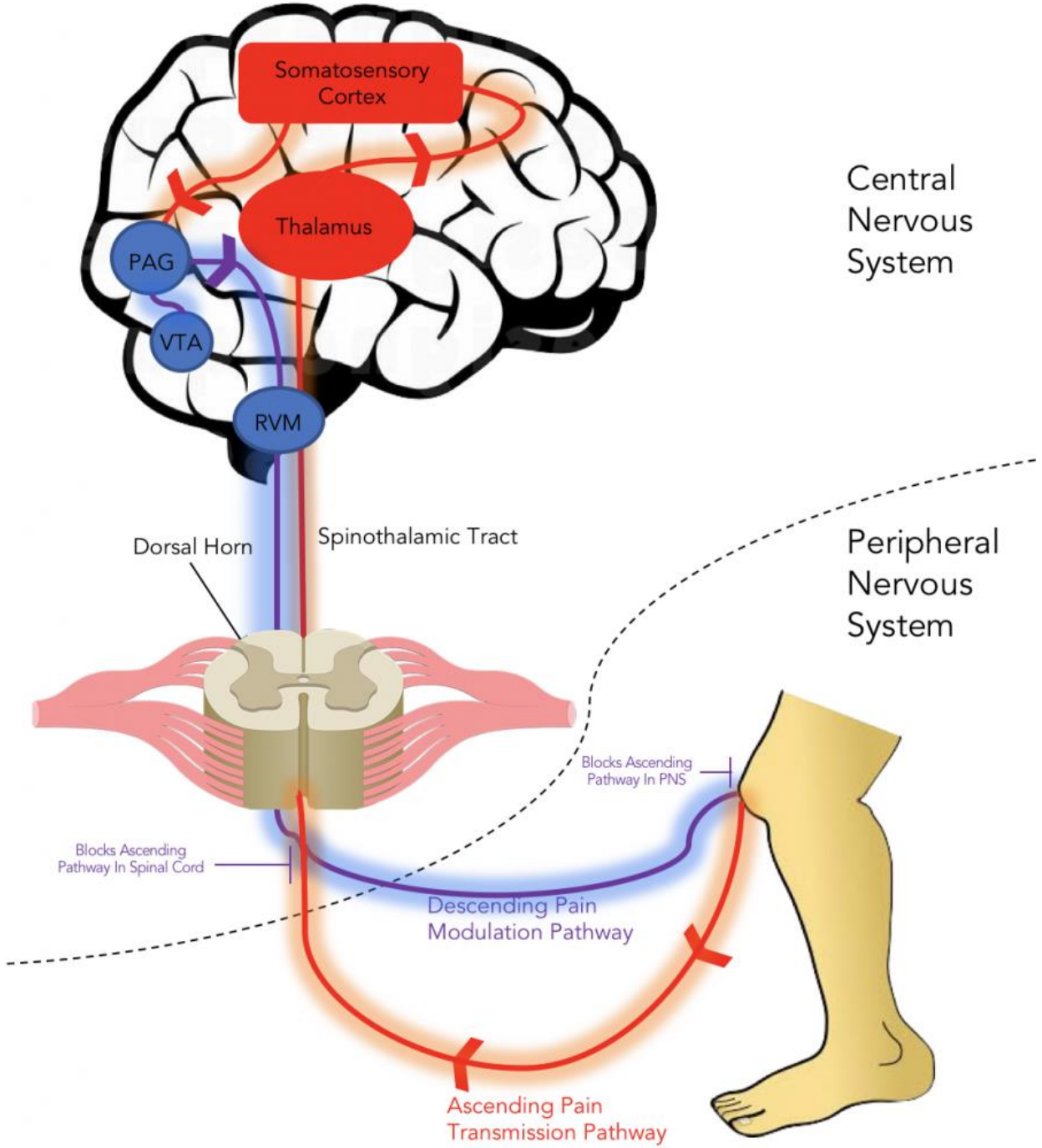
- Pain intensity is higher than original pain.
- Diffused pain is poorly defined in terms of quality and location.
- Pain threshold and tolerability are reduced.

Opioid Receptor Physiology

- **3 Types:** mu, delta, and kappa receptors
- Highly concentrated in the dorsal horn of the **spinal cord** (a guinea pig), **brain**, and PVM&PAG of **brain stem**
- Most of the opioids are predominantly mu agonists, with 7 subtypes.
- Gene variations of opioid receptors can account for individual differences in pain sensitivity, analgesic response, and the risk of psychological dependency

Mechanism of Analgesia

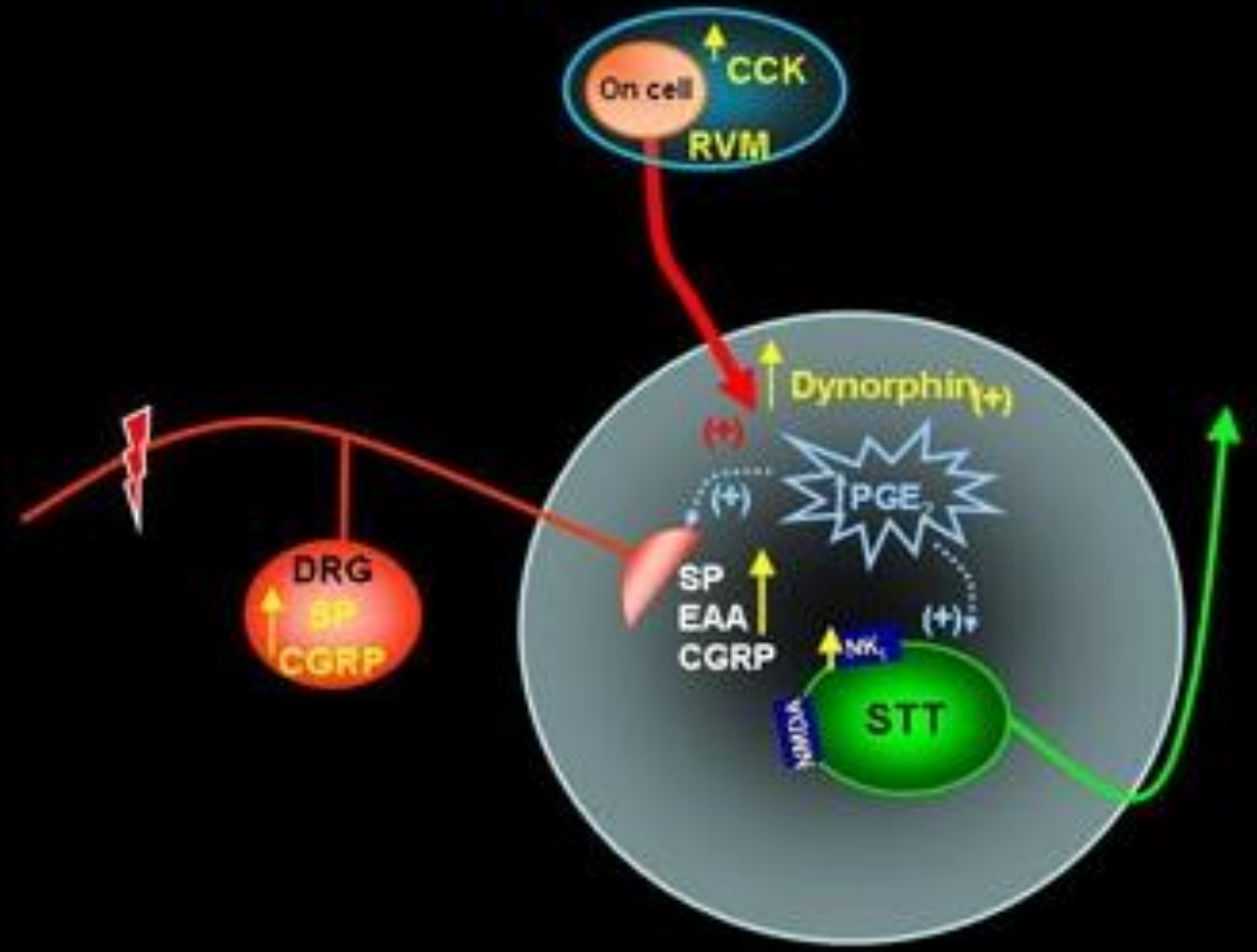
- Activating **pre-synaptic** opioid receptors (G-protein) leads to reduced intracellular cAMP concentration, decreased calcium ion influx, and thus **inhibits the release of excitatory neurotransmitters (glutamate, substance P)**.
- Binding to **post-synaptic** opioid receptors evokes **hyperpolarization** of the neuronal membrane, decreasing the probability of generating an action potential.


Somatosensory Cortex
Thalamus
PAG
VTA
RVM
Central Nervous System
Dorsal Horn
Spinothalamic Tract
Peripheral Nervous System
Blocks Ascending Pathway In PNS
Blocks Ascending Pathway In Spinal Cord
Descending Pain Modulation Pathway
Ascending Pain Transmission Pathway

Hypothesized Mechanisms of Hyperalgesia

- OIH likely results from multifactorial changes in the CNS with opioid exposure; it is largely believed to be due to dysfunctional facilitation of the descending pathway.
- Neuroplastic changes in the RVM medulla lead to activation of descending facilitation via "on-cells".
- Descending facilitation leads to the upregulation of spinal dynorphin and enhanced release of primary afferent neurotransmitters, increasing pain.
- Activation of the central glutaminergic system via NMDA causes sensitization of spinal neurons.
- Increased levels of dynorphin lead to the release of excitatory neuropeptides such as CGRP and CCK.

Descending Facilitation Enhances Spinal Sensitization



Diagnosing OIH

- Challenging due to lack of standard diagnosis criteria
- Pain is not necessary located at the source of injury or disease, instead, as generalized, diffused, and ill defined
- No progression or worsening of the underlying condition
- Increase in perceived pain with an increase in opioid use
- No necessary only for chronic opioid use, also arise in a short course of opioids

Clinical Warnings for OIH

- Increased pain in absence of disease progression
- Unexplained pain or diffuse allodynia unassociated with the original pain
- Increased levels of pain with increasing opioid dosage

Differential Diagnosis of OIH

- Opioid tolerance
- Opioid dependency and withdrawal
- Opioid use disorder (OUD)

Tolerance

- A state of adaptation in which exposure to a drug results in a decrease in the drug's effects over time.
- Tolerance not only develops to the analgesic effects of opioids but also to other adverse effects, such as nausea, sedation, and pruritus.
- The decreased efficacy of the drug can be overcome by increasing the dose.

Hyperalgesia vs. Tolerance

Hyperalgesia

- Increase sensitivity to pain
- Worse with increasing in opioid dose

Tolerance

- Decrease sensitivity to opioids
- Relief with increasing in opioid dose

Opioid withdrawal and Opioid use disorder

- Withdrawal is a set of clinical signs and symptoms that develop from opioid cessation, resulting in the absence of Mu receptor stimulation and increased NE levels. Symptoms improve with opioid escalation.
- OUD is the uncontrolled use of opioids despite adverse outcomes. Possible desensitization to opioids may lead to tolerance and withdrawal symptoms.

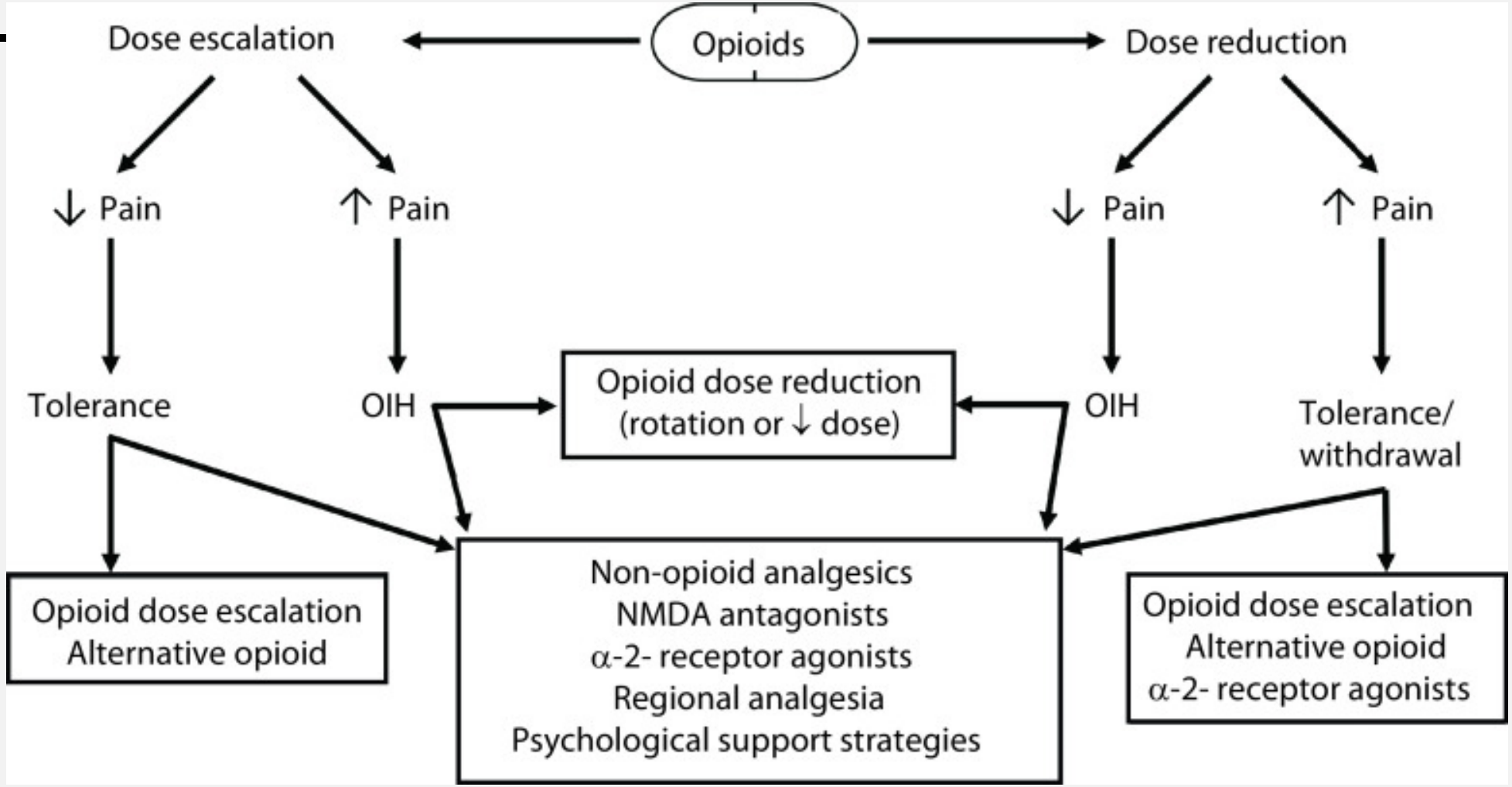
Other Differentiations

- Fibromyalgia
- Clinical exacerbation of pre-existing pain
- Disease progression
- Increase physical activity
- Increase stress
- Interval injury
- Other

Management of OIH

- Also challenging and time consuming
- Weaning down or opioids: collaborative patient-physician relationship, strong support system, psychological therapy, etc.
- Rotate to different class of opioids: multiple case studies have reported improved analgesia with opioid rotation
- Adjuvants: NSAIDs, acetaminophen, anticonvulsants, antidepressants, muscle relaxers, etc.

Management of OIH /Tolerance /Withdrawal



Modulation of OIH

- **NMDA Receptor Antagonists:** Ketamine and dextromethorphan
- Some evidence shows perioperative administration of low dose Ketamine might reduce postoperative hyperalgesia, but no large randomized controlling trials proving this
- 3 large trials were unable to find any clinical difference between MorphiDex and morphine alone.

Modulation of OIH

- **Methadone** is a mu agonist and a weak NMDA antagonist.
- Multiple reports have shown that opioid rotation to methadone significantly improves tolerance and OIH.
- Disadvantages and Risks: complex conversion with very high MME, increased cardiac risks, worsening sleep apnea, increased mortality, etc.

Modulation of OHI

- **COX2 inhibitor** inhibits prostaglandin synthesis in the spinal cord, modulates NMDA receptor function, and thus inhibits the expression of OIH
- Human studies have shown evidence that the **A2 agonist**, clonidine, and tizanidine attenuate the expression of OIH.

Modulation of OIH

- Combining opioids with a low dose of an opioid antagonist Naloxone can prevent tolerance and hyperalgesia
- Studies have shown significant pain relief with the combination of an opioid and naltrexone, compared to using an opioid alone
- Low dose of Naloxone used alone can reduce opioid tolerance, but not alter hyperalgesia

Buprenorphine

- Partial mu receptor agonist and kappa receptor antagonist
- Spinal Dynorphin, a kappa agonist, increases during opioid administration and plays an important role in OIH
- Unique in treating both chronic pain and OIH
- High safety profile compares to other opioids

Case Study

64-year-old male with medical history for depression, anxiety, and migraine. Patient presents with chronic low back for 20 years after a work related injury. He reports that he was lifting a heavy box, strained his back, and started to have low back pain ever since. He had complete work up and was told to have bulging discs of lumbar spine. He was not recommended for surgical. He has had physical therapy, chiropractic therapy, and massage therapy, which all made his pain worse. He also had multiple epidural injection and nerve ablation without significant improvement. Patient complains of pain cross low back which up to his upper back and down to bilateral hips with episodes of sciatic pain. He also complains pain of neck, shoulder, hips, knees all over his joints. He has been on opioid pain killer for years and on oxycodone 20mg #196 every 28 days for last 2 years. He states that he could not take gabapentin, lyrica, and antidepressants which caused suicidal ideation. The muscle relaxers and OTD did not help at all. He state that nothing has helped and he has to take oxycodone to be able to get up from bed and to function little bit. He said that his current prescribing doctor is retiring and he has been finding another physician to continue his pain management.

Case Study

On exam, he walks with a straight cane without significant gait abnormality; he is very irritable and can’t not sit still; he looks anxious and depressed; there was no significant neuromuscular physical findings.

Recent imaging study showed mild to moderate multilevel degenerative changes of lumbar spine without significant spinal stenosis and nerve root impingement.

Discussion

- Is more investigation needed? Consider factors such as disease progress, injury, stress, physical activity, etc.
- What is the assessment for OIH?
- Management strategies include patient education, opioid tapering, opioid rotation, use of suboxone, adjuvants, methadone, and detox programs.

Conclusion

- **Recognition:** Be aware of OIH when opioid treatment fails.
- **Increase in Atypical Pain:** Note a paradoxical response (increased ill-defined pain) to opioid use.
- **Mechanisms Not Clearly Understood:** May involved in activation of the glutaminergic system and descending facilitation.
- **Management Strategies:** Implement patient education and social support system, avoidance of high doses, opioid tapering, opioid rotation, utilization of adjuvants, consideration of **buprenorphine**, psychological therapy, detoxification, etc.

Thank you!