Pain

Edna Mao
Group Meeting Literature Talk
October 18th, 2022
What is pain?

Nociceptive pain
Response to noxious stimuli
- Thermal
- Mechanical
- Chemical
First TRP channel identified in 1997

David Julius
University of California, San Francisco
Nobel Prize in Physiology or Medicine, 2021

TRPV1
(Transient receptor potential vanilliond 1)

Heat and chemical sensing

How do we feel pain?

Types of pain sensed:
- Mechanical
- Thermal
- Chemical
- Inflammatory
- Neuropathic

Detected temperature sensation:
- Warm
- Hot
- Cold

**What is pain?**

**Nociceptive pain**
Response to noxious stimuli
- Thermal
- Mechanical
- Chemical

**Inflammatory pain**
Caused by damage to body tissue
How do we feel pain?

- Cell death
- "Inflammatory soup"
- Cytokines: NGF, TNF-α, IL-1β
- Inflammatory peptides + neurotransmitters: Substance P, CGRP, Bradykinin, Glutamate
- Histamine
- Prostaglandins
- Serotonin
- ATP
- K⁺, H⁺
How do we feel pain?

Cytokines  Peptides  Small molecules

Nociceptor
How do we feel pain?

- Cytokines
- Peptides
- Small molecules

Metabotropic receptors (G-coupled protein receptors)

Ionotropic receptors

Membrane depolarization

Downstream signaling

K^+ Na^- Ca^{2+}
Classes of nociceptors

- Acute, sharp pain: Aβ myelinated fibers
  - Myelinated
  - Large diameter
  - Proprioception, light touch

- Dull, throbbing pain: Aδ fibres
  - Lightly myelinated
  - Medium diameter
  - Nociception (mechanical, thermal, chemical)

- Touch and proprioception: Nonpeptidergic C fibers
  - Unmyelinated
  - Small diameter
  - Innocuous temperature, itch
  - Nociception (mechanical, thermal, chemical)
How do we feel pain?

Nociceptive pain:
Stimuli causes pain signal

Neuropathic pain
Damage to nerve results in pain signals being sent without stimuli

Commonly caused by:
- Injury
- Multiple sclerosis
- Diabetes
- Cancer
The pain problem

$635$ billion of treatment cost and lost productivity annually

Yong, R.J.; Mullins, P.M. Bhattacharyya, N. The prevalence of chronic pain among adults in the United States. *Pain*, 2021
Current state of pain medication

Non-steroidal anti-inflammatory drugs (NSAIDs)

- Aspirin
- Ibuprofen
- Naproxen
- Acetaminophen

Opioids

- Morphine
- Codeine
- Oxycodone
- Hydrocodone
- Fentanyl

Anticonvulsants

- Gabapentin

Antidepressants

- Duloxetine
Current state of pain medication

Non-steroidal anti-inflammatory drugs (NSAIDs)
- Aspirin: 1897
- Ibuprofen: 1961
- Naproxen: 1976
- Acetaminophen: 1878

Anticonvulsants
- Gabapentin: 1993

Antidepressants
- Duloxetine: 1993

Opioids
- Morphine
- "1804"
- Codeine: "1813"
- Oxycodone: 1916
- Hydrocodone: 1920
- Fentanyl: 1959
Current state of pain medication

“After 100 years of pain research—old scaffolds, minor improvements?”


Bioorganic & Medicinal Chemistry Letters

Volume 26, Issue 4, 15 February 2016, Pages 1103-1119

Digest paper

New approaches to treating pain

Andrea Wolkerstorfer a, b, Norbert Handler a, Helmut Buschmann b

“In recent years, efforts to identify novel analgesic agents has been disappointing.”
Current state of pain medication

“After 100 years of pain research—old scaffolds, minor improvements?”

“In recent years, efforts to identify novel analgesic agents has been disappointing.”

Targets for pain relief

Cytokines

Peptides

Small molecules

Membrane depolarization

Ionotropic receptors

Metabotropic receptors (G-coupled protein receptors)

Downstream signaling

G protein

K⁺ Na⁺ Ca⁺
Targets for pain relief

- Cytokines
- Peptides
- Small molecules

Metabotropic receptors (G-coupled protein receptors)

G protein

Membrane depolarization

- K⁺
- Na⁺
- Ca⁺

Downstream signaling

Ionotropic receptors
Targets for pain relief

Cytokines

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Metabotropic receptors
(G-coupled protein receptors)

Membrane depolarization

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Ionotropic receptors

K⁺ Na⁺ Ca⁺
Targets for pain relief

Prostaglandin E$_2$

Cyclooxygenase (COX) enzymes

Arachidonic acid

Ibuprofen
**NSAIDs**

**COX-2**
Expression induced in sites of inflammation

**COX-1**
- Expressed evenly throughout body tissue
- "Housekeeping" roles include maintaining stomach mucosa

Non-selective COX inhibitor
**NSAIDs**

- **COX-2 inhibited**
  - Pain reduced

- **COX-1 inhibited**
  - Gastrointestinal side effects
    - Ulcers, acid reflux
  - Renal dysfunction

Non-selective COX inhibitor
Selective COX-2 inhibitors

Celecoxib
Approved 1998

Rofecoxib
Approved 1999

Valdecoxib
Approved 2001

Etoricoxib
Approved 2002*

COX-2/COX-1 selectivity

<table>
<thead>
<tr>
<th>Drug</th>
<th>COX-2/COX-1 selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>30</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>272</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>61</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>344</td>
</tr>
</tbody>
</table>

Values for non-selective NSAIDS:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>0.7</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.5</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Selective COX-2 inhibitors

COX-1

Me

Me

O

OH

Ile-523

COX-2

Me

Me

O

OH

Val-523

Hydrophobic binding pocket

Llorens, O; Perez, J. J.; Palomer, A; Mauleon, D. Structural basis of the dynamic mechanism of ligand binding to cyclooxygenase. 1999, Bioorg. Med. Chem. Lett. 9, 2779–2784.
Selective COX-2 inhibitors

Llorens, O; Perez, J. J.; Palomer, A; Mauleon, D. Structural basis of the dynamic mechanism of ligand binding to cyclooxygenase. 1999, Bioorg. Med. Chem. Lett. 9, 2779–2784.
Selective COX-2 inhibitors

Pi-stacking

Hydrophobic binding pocket

Reduced degrees of freedom

Hydrogen bonding

Selective COX-2 inhibitors

"Selective COX 2 inhibitors are associated with a moderately increased risk of vascular events, largely attributable to a twofold increased risk of myocardial infarction."

NSAIDs

**COX-2**
Biosynthesis of prostacyclin
- Vasodilation
- Decreases platelet aggregation

**COX-1**
Biosynthesis of thromboxane
- Vasoconstriction
- Promotes platelet aggregation
**NSAIDs**

**COX-2 inhibited**
- Prostaglandin synthesis inhibited
  - Vasoconstriction
  - Increased platelet aggregation

**COX-1 inhibited**
- Thromboxane synthesis inhibited
  - Vasodilation
  - Decreased platelet aggregation

Non-selective COX inhibitor

Chemical structure: Me\(\text{C}_2\text{H}_5\)\(\text{C}_6\text{H}_4\text{C}(-\text{OH})\)
**NSAIDs**

**COX-2 inhibited**
Prostaglandin synthesis inhibited
- Vasoconstriction
- Increased platelet aggregation

**Increased risk of hypertension, thrombosis, and cardiovascular events**

**COX-1**
Biosynthesis of thromboxane
- Vasoconstriction
- Promotes platelet aggregation
Selective COX-2 inhibitors

Celecoxib

Rofecoxib

Valdecoxib

Etoricoxib

Black box warning
Merck voluntarily withdraws from market in 2004, faces multiple lawsuits
Pfizer withdraws from market in 2005 and is fined $2.3 billion

Cardiovascular Risk

- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS and CLINICAL TRIALS).
Selective COX-2 inhibitors

Celecoxib

102\textsuperscript{nd} most prescribed medication in 2019

Rofecoxib

FDA encourages return to market

Valdecoxib

Prodrug version available in EU

Etoricoxib

Never approved in US, approved in >80 countries worldwide

Cardiovascular Risk

- **CELEBREX** may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).
Targets for pain relief

Cytokines

Peptides

Small molecules

Metabotropic receptors (G-coupled protein receptors)

Membrane depolarization

Downstream signaling

K⁺ Na⁺ Ca⁺

Ionotropic receptors

G protein
Migraines
Discovery of CGRP

Calcitonin-gene-related-peptide (CGRP)

Discovery of CGRP

- CGRP levels are increased in saliva and plasma during migraine
- Chronic migraine patients show increased levels of CGRP in blood even when pain-free
- CGPR levels return to normality after triptans administration and headache resolution
- IV infusion of CGRP can induce migraine-like attacks in patients

Pioneering work in the 1990’s demonstrated CGRP’s role in migraine pathophysiology

Receptor physiology

CGRP

Trigeminal nerve: Primary site of migraine pain

Migraine pain amplification circuitry

First small molecule antagonist of CGRP receptors

**MK-3207**
Discontinued during Phase I trials in 2011

**Telcagepant (MK-0974)**
Prematurely terminated during Phase II clinical trials in 2014

Heightened aminotransferase levels found in patients:
Red flag for potential liver toxicity


**CGRP receptor antagonists**

**The “gepants”**

- **Ubrogepant**
  Approved 2019

- **Rimegepant**
  Approved 2020

**Monoclonal antibodies**

- Erenumab (Approved 2018)
- Fremanezumab* (Approved 2018)
- Galcanezumab* (Approved 2018)

*Preventative

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Targets for pain relief

Cytokines

Inflammatory peptides

Small molecules

Metabotropic receptors
(G-coupled protein receptors)

Membrane depolarization

Downstream signaling

Ionotropic receptors

K⁺ Na⁺ Ca⁺
Cannabinoid receptors

Nav1.8 ion channels

Nerve growth factor/TrkA signaling pathway

NMDA receptors

Neurotransmitters

Targets for pain relief

Opioids

Morphine

“the world’s oldest drug”

Isolated in 1804 as active ingredient in opium

Papaver somniferum
Main classes of opioid receptors

μ opioid receptor (MOR)

δ opioid receptor (DOR)

κ opioid receptor (KOR)

Nociceptin opioid peptide receptor (NOR)

The μ opioid receptors

Involved in the regulation of:
- Mood and nociception
- Reward and aversion processing

Opioids: Mechanism of action

MOR

“G-coupled-protein receptor”

H₂N

Opioids: Mechanism of action

Opioids: Mechanism of action

H₂N

Ligand binding

Heterotrimeric G protein recruited

α β γ

GTP

GDP

Opioids: Mechanism of action

H₂N

Ligand binding

H₂O

G protein
dissociates

α

β

γ

Opioids: Mechanism of action

Opioids: Mechanism of Action

Opioids: Mechanism of action

Opioids: Mechanism of action

Opioids: Mechanism of action

Overall:
Membrane hyperpolarization
Inhibition of neuronal activity

Opioids: Mechanism of action

Peripheral nervous system
- Inhibit release of substance P

Central nervous system
- Inhibited release of GABA
- Increase in release of dopamine

Opioids: Mechanism of adverse effects

High expression of MOR in stomach and gastrointestinal track

<table>
<thead>
<tr>
<th>Opioid actions</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>gastric motility ↓</td>
<td>delayed gastric emptying</td>
</tr>
<tr>
<td>pyloric tone ↑</td>
<td>nausea, vomiting</td>
</tr>
<tr>
<td>lower esophageal sphincter ↓</td>
<td>gastroesophageal reflux ↑</td>
</tr>
<tr>
<td>gastric juice secretion ↓</td>
<td>delayed digestion</td>
</tr>
<tr>
<td>pancreatic and biliary secretion ↓</td>
<td>delayed digestion</td>
</tr>
<tr>
<td>fluid secretion ↓</td>
<td>delayed transit</td>
</tr>
<tr>
<td>propulsion ↓</td>
<td>delayed transit, absorption</td>
</tr>
<tr>
<td>propulsion ↓</td>
<td>bloating, distension, constipation</td>
</tr>
<tr>
<td>circular smooth muscle contractions ↑</td>
<td>spasm, abdominal cramps</td>
</tr>
<tr>
<td>fluid absorption ↑</td>
<td>hard, dry stool</td>
</tr>
<tr>
<td>anal sphincter tone ↑</td>
<td>incomplete evacuation</td>
</tr>
</tbody>
</table>

Areas of brainstem which regulate breathing also display high expression of MOR and DOR

Respiratory depression

Opioids: Mechanism of adverse side effects

MOR euphoria and reward

KOR dysphoria and aversion

“Hedonic balance”
Opioids: Mechanism of adverse side effects

- MOR euphoria and reward
- Chronic activation leads to tolerance
- Euphoric effects diminished

- KOR dysphoria and aversion
- Heightened dysphoric effects
- Withdrawal symptoms
Three Waves of Opioid Overdose Deaths

Wave 1: Rise in Prescription Opioid Overdose Deaths
Wave 2: Rise in Heroin Overdose Deaths Started in 2010
Wave 3: Rise in Synthetic Opioid Overdose Deaths Started in 2013

Designing safer opioids

How can we design safer opioid receptor ligands?
Designing safer opioids

- First approved “biased opioid receptor agonist”
- Approved in 2020 for IV use in hospitals to treat moderate to severe acute pain

Oliceridine
Opioids: Mechanism of action

Opioids: Mechanism of action

Opioids: Mechanism of action

Opioids: Mechanism of action

Opioids: Mechanism of action

- G-protein decoupling
- Receptor internalization

Opioids: Mechanism of action

β-arrestin-dependent pathways

Sensitization and tolerance

G-protein decoupling

Receptor internalization

β-arrestin signaling pathway

β-arrestin knockout mice

% MPE = maximum possible effect

Prolonged anesthesia in β-arrestin knockout mice

Decreased adverse effects of morphine in β-arrestin knockout mice


Decreased levels of constipation

Decreased respiratory depression
Opioids: Mechanism of action

G protein-dependent signaling pathway

β-arrestin

Sensitization, tolerance, adverse side effects

β-arrestin

Analgesic effects

Opioids: Mechanism of action

Biased opioid ligand

H$_2$N

β-arrestin

G protein-dependent signaling pathway

Analgesic effects

Adverse effects diminished?

Back to oliceridine…


<table>
<thead>
<tr>
<th></th>
<th>G-protein</th>
<th>β-arrestin</th>
</tr>
</thead>
<tbody>
<tr>
<td>pEC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>7.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Efficacy (rel. to morphine)</td>
<td>108%</td>
<td>236%</td>
</tr>
</tbody>
</table>

- Increase potency
- Reduce β-arrestin efficacy
- Mitigate cardiovascular risk
Oliceridine in vivo studies

Relative to morphine:
- More potent
- Comparable levels of G-coupling efficiency
- Highly reduced β-arrestin recruitment

Mice studies show reduced adverse effects

Development and approval of oliceridine

**Oct. 2018**
Oliceridine rejected by FDA in a 7-8 vote for inadequate safety profile

**Feb. 2020**
After obtaining further data, Trevena resubmits application for approval

**Aug. 2020**
Oliceridine approved by FDA in an 8-7 vote
## Development and approval of olliceridine

<table>
<thead>
<tr>
<th>ADVERSE EVENTS (AEs) IN ≥5% OF PATIENTS</th>
<th>PLACEBO (n=162)</th>
<th>OLINVYK ≤27% mg (n=316)</th>
<th>IV MORPHINE (n=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any TEAE</td>
<td>73</td>
<td>86</td>
<td>96</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>35</td>
<td>52</td>
<td>70</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td>10</td>
<td>26</td>
<td>52</td>
</tr>
<tr>
<td>Headache (%)</td>
<td>30</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>Dizziness (%)</td>
<td>11</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Constipation (%)</td>
<td>9</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hypoxia (%)</td>
<td>3</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Pruritus (%)</td>
<td>6</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Sedation (%)</td>
<td>5</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Somnolence (%)</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Back pain (%)</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hot flush (%)</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Pruritus generalized (%)</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>
Doubts of β-arrestin mechanism

How much can the adverse effects of opioids be attributed to β-arrestin-dependent signaling pathways?
- Re-examining the original mice knockout studies
- New studies on the relationship between G-proteins, β-arrestin, and adverse effects

Do biased opioid receptor ligands selectively activate G-protein-dependent signaling pathways?
- Re-examining the assays used to study biased opioid receptor ligands
- Re-examining the proposed mechanism of action of biased opioid receptor ligands
Approaches for designing safer opioids

**Allosteric opioid receptor modulators:**
Positive allosteric modulators enhance binding affinity

Approaches for designing safer opioids

Multifunctional opioid ligands:
- Target multiple opioid receptors
- Target opioid and nonopioid receptors

Darcq, E., Kieffer, B.L. Opioid receptors: drivers to addiction?. *Nat Rev Neurosci.* 2018, 19, 499–514.
Approaches for designing safer opioids

**Multifunctional opioid ligands:**
- Target multiple opioid receptors
- Target opioid and nonopioid receptors

**NFEPP:** pH-sensitive fentanyl derivative

Approaches for designing safer opioids

**Multifunctional opioid ligands:**
- Target multiple opioid receptors
- Target opioid and nonopioid receptors

**MDAN-21:** bivalent MOR-DOR agonist

Oxymorphone (MOR)

Naltrindone (DOR)

Darcq, E., Kieffer, B.L. Opioid receptors: drivers to addiction?. *Nat Rev Neurosci.* 2018, 19, 499–514.
Conclusion

Challenges:
- Difficulties in translating preclinical models to humans
- Insufficient understanding of mechanisms behind pain

Table 2. NIH Expenditures per Affected Person in the United States for 6 Major Chronic Conditions

<table>
<thead>
<tr>
<th>Chronic Condition</th>
<th>Dollars Per Affected Person*</th>
</tr>
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<tbody>
<tr>
<td>Heart disease</td>
<td>48</td>
</tr>
<tr>
<td>Diabetes</td>
<td>41</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2,562</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>97</td>
</tr>
<tr>
<td>Cancer</td>
<td>431</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>4</td>
</tr>
</tbody>
</table>