Analgesics: An Overview & Introduction to Non-Opioid Analgesics

A Companion to the Required Textbook Chapter:
"Non-opioid Analgesics"
CONTEMPORARY DENTAL PHARMACOLOGY
Evidence-Based Considerations
(A.H. Jeske, Ed., 2019)

PHC 721

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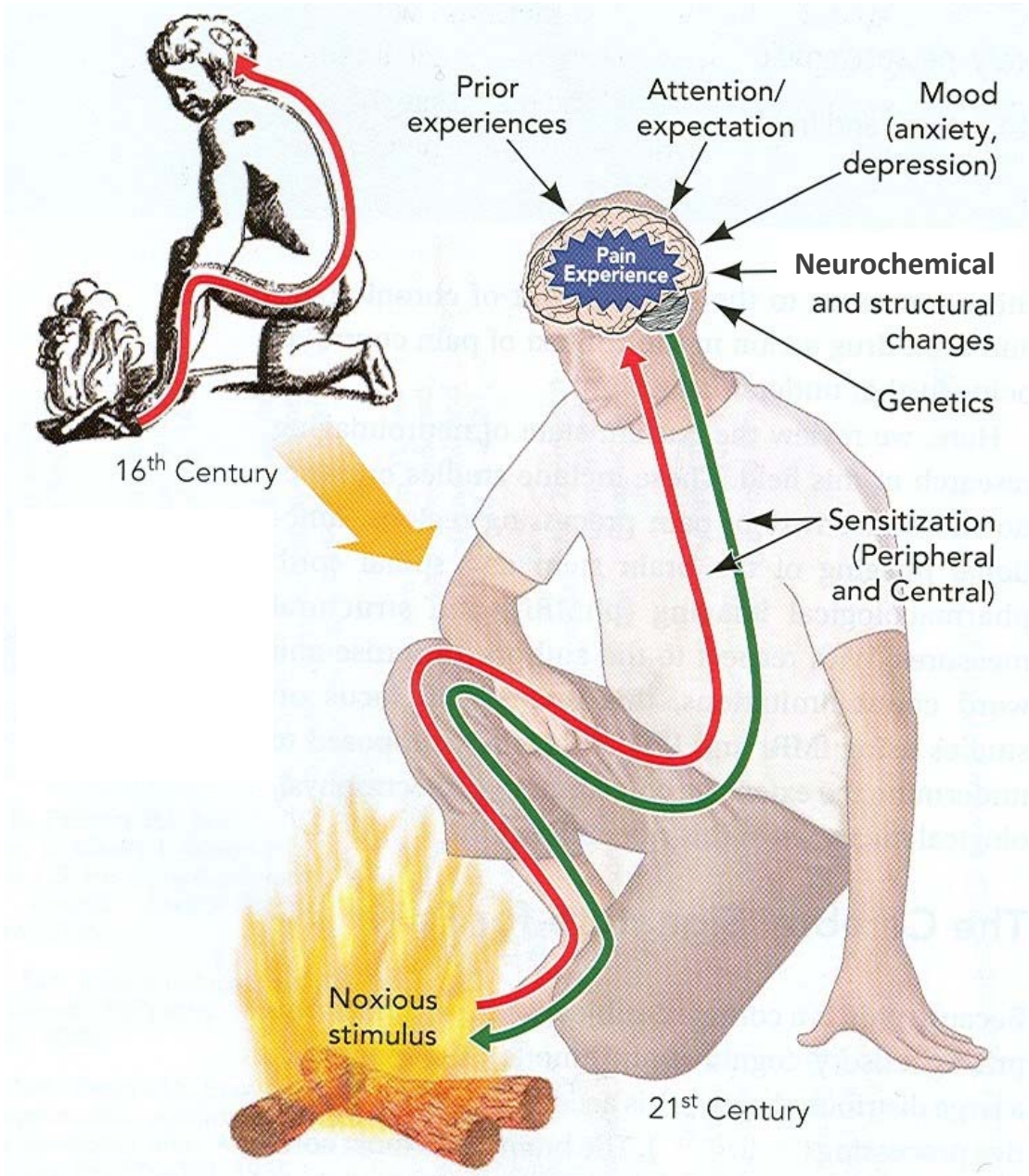
ANESTHESIA

Loss of sensation (Latin *Aesthesis* – “Sensation”)

ANALGESIA

Insensibility to pain without loss of consciousness (Greek *Algos* – “Pain”)

Pain perception: ancient and current concepts



Neuroscience Background

Nerve Fiber Types, Nociceptors

Neuronal Fiber Classification:

- Aα/Aγ - Heavy Myelination/Large Diameter/Fast/High Frequency - Somatic Motor Neurons
- Aβ - Heavy Myelination/Large Diameter/Fast/High Frequency - Tactile and Proprioceptors
- **Aδ - Light Myelination/Smaller Diameter/Slower /Lower Frequency - Pain**, Thermal, Pressure
- B - Light Myelination - Autonomic Preganglionic (Sympathetic & Parasympathetic)
- **C - Unmyelinated/Smallest Diameter/Slow - Pain**, Thermal, **Postganglionic Sympathetic**

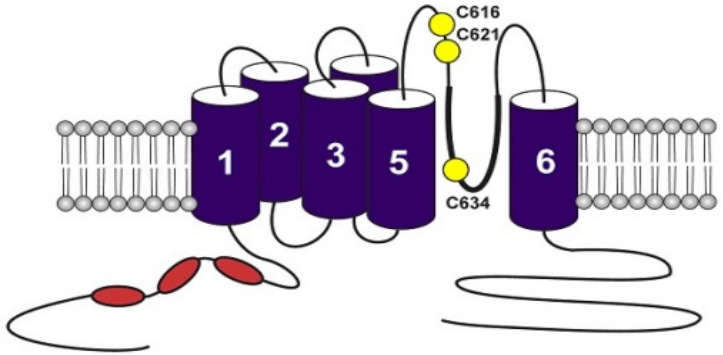
Nociceptors (Latin: *Nocere*, 'to hurt'): Endings that initiate the sensation of pain
Nociception: the perception of pain

Three Classes of Somatic Nociceptors:

- **Aδ Mechanosensitive & Aδ MechanoThermal Nociceptors** - First Pain (sharper, shorter lasting)
- **C Polymodal Nociceptors** - Second Pain (duller/burning, longer lasting)

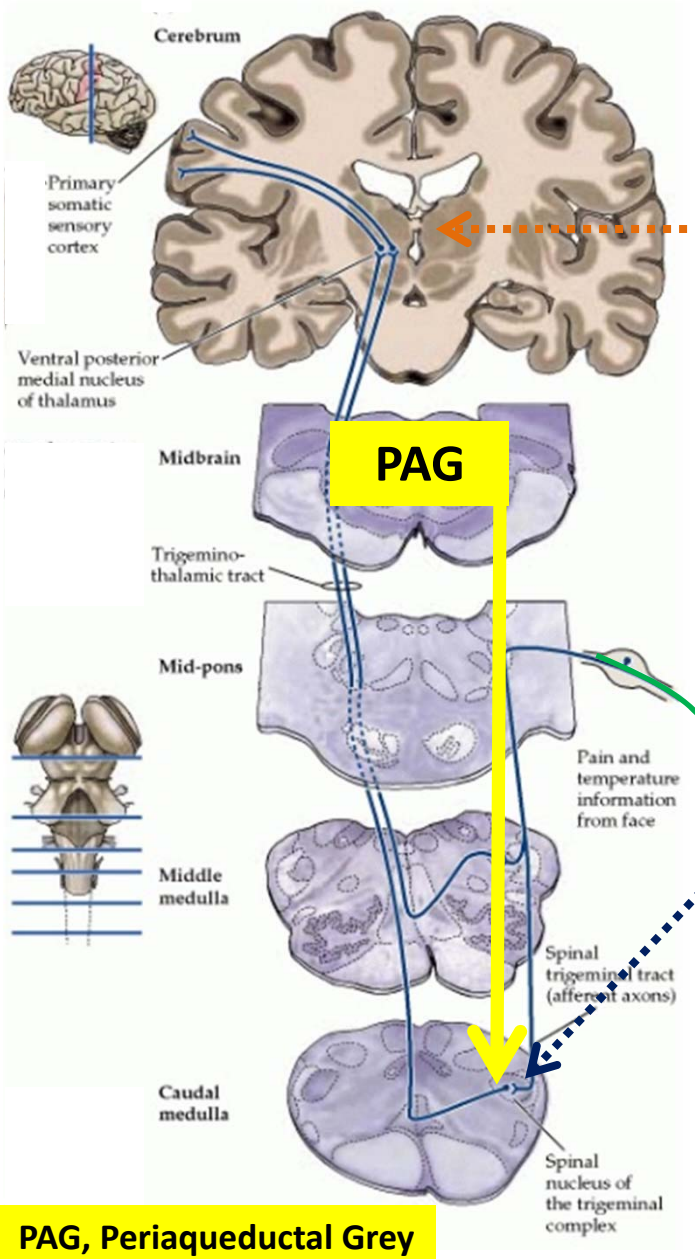
TRPV1:

Transient Receptor Potential (TRP) family
Voltage-sensitive, permeable to Na^+ & Ca^{2+},
ligand-gated: capsaicin (hot peppers),
acid, anandamide (cannabinoid); 45°C



TRPV1

Trigeminal Pain Pathway



PAG, Periaqueductal Grey

Cingulate & Insular Cortex:
Affective-Motivational (Aversive) Aspect of Pain

Somatosensory Cortex
Sensory Discriminative Aspect of Pain

Thalamus
Midline Nuclei

Thalamus
VPM Nucleus

Contralateral Trigeminothalamic Tract

Crossing to the contralateral side

Trigeminal Complex in the Brainstem
Spinal Nucleus
Subnucleus Interpolaris & Subnucleus Caudalis
(cell bodies of 2nd order neurons)

Spinal Trigeminal Tract

Trigeminal Ganglion
(cell bodies of 1st order neurons)

Trigeminal Nerve

Free Nerve Endings

Noxious Stimulus

PAG

TRPV1

Opioids

Acetaminophen ???

NSAIDs

Sensitization

Activation of Nociceptive Pathways (ALS)…

…by
Nociceptive Inputs

…by
Non-Nociceptive Inputs
(low-threshold mechanoreceptors)

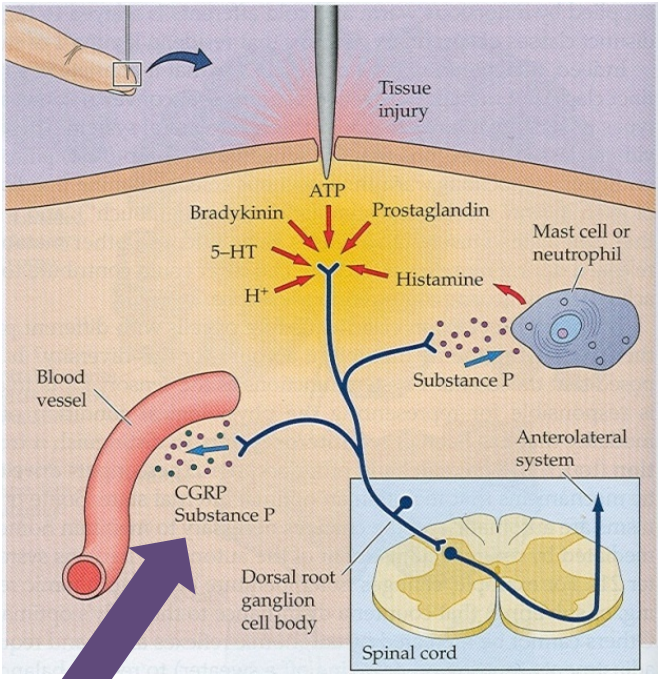
Allodynia

Increase in Excitability of
2nd order Neurons
in Dorsal Horn of Spinal Cord

Central Sensitization

High level of activity
in 1st order neuron
cell body in Dorsal Root Ganglion

Hyperalgesia



Release of
Sensory Neuropeptides
Calcitonin Gene-Related Peptide (CGRP)
Substance P

Axon Reflex

Activation of
Axon Collateral

Vasodilation
↑Blood Vessel Permeability
Histamine Release (Mast Cells)

Neuroinflammation

Peripheral Sensitization

Release of
Inflammatory Mediators:
Bradykinin, Histamine, Serotonin,
Prostaglandins*, etc.*

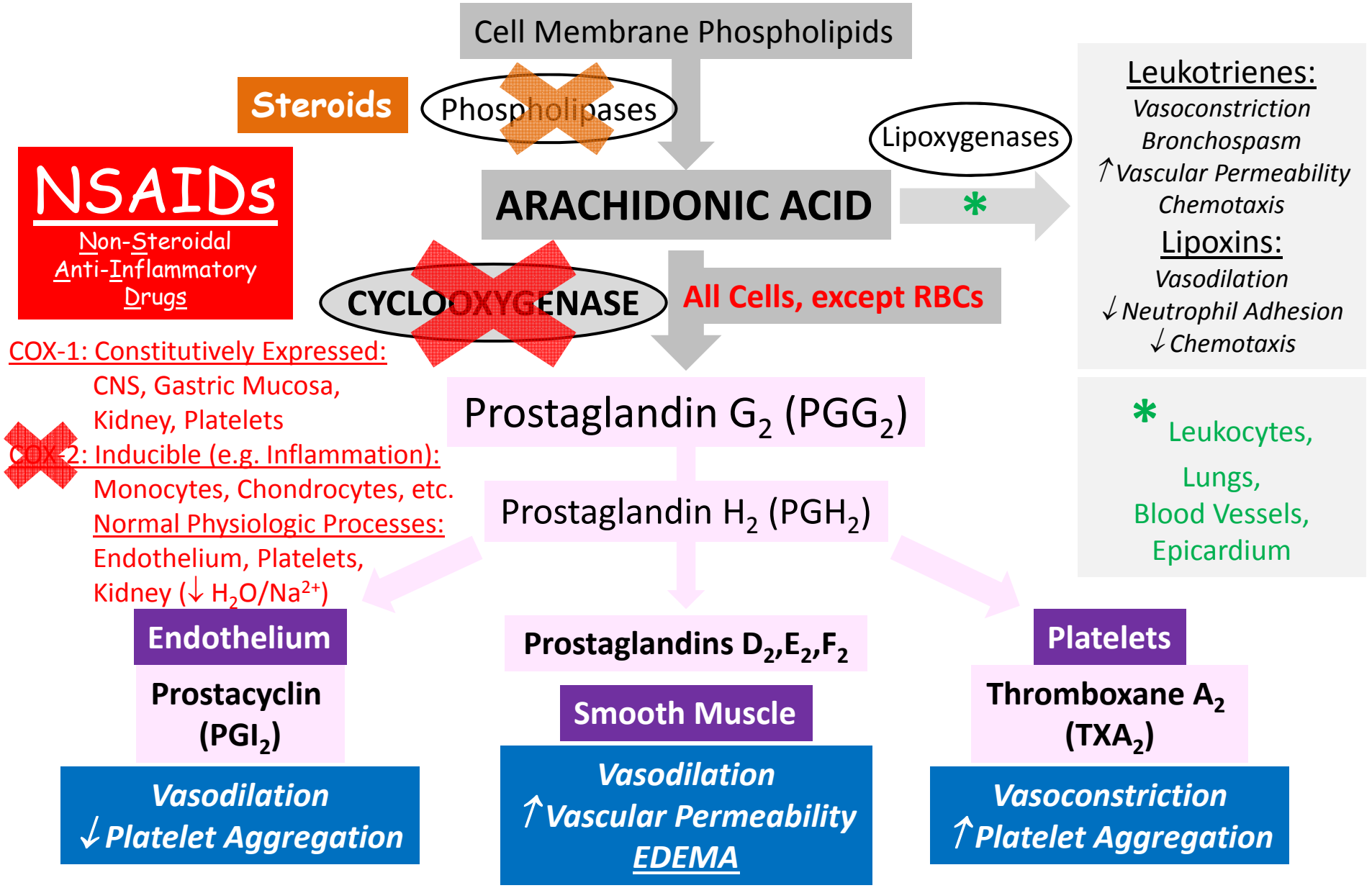
Stimulation
of Nociceptor Ending

Noxious Stimulus

Tissue Damage
(e.g. cuts, scrapes, bruises)

Targets of Non-Opioid Analgesics

Prostaglandins – Mediators of Inflammation



Inflammatory Response: A Friend & A Foe

Tissue Injury (trauma, surgery) ⇒ **A Friend** ⇒ Normal Repair
- *Neutropenia (e.g. cancer chemotherapy) ⇒ Fulminant Infection*

Autoimmune Diseases ⇒ **A Foe** ⇒ Destruction of Normal Tissues
- *Gout, Rheumatoid Arthritis ⇒ Progressive Destruction of Joints*

Infection ⇒ **A Friend** ⇒ Production of Cytokines, Antibodies, etc.
- *Acute Dental Infections, Flu Vaccine, COVID-19 Vaccine, etc.*

Tumor -Edema (Histamine ⇒↑ Vascular Permeability ⇒ ↑ Interstitial Fluid)
Rubor – Redness (Histamine ⇒ Vasodilation ⇒ ↑ Blood Flow)
Calor – Heat (Histamine ⇒ Vasodilation ⇒ ↑ Blood Flow & Heat Dissipation)
Fever - (Pyrogens, e.g., microbial, IL-1 ⇒ Hypothalamus ⇒ ↑ Thermal Set Point ⇒ ↑ Migration & Activity of Immune Cells in mild-moderate fevers)

Dolor - Pain (↑ Vascular Permeability ⇒ Neuroinflammation ⇒ Sensitization)
Functio Laesa – Functional Loss (Pain & Mechanical Limitations)

Limited mouth opening

Diminished Quality of Life for 4-6 days

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Salicylates:
Aspirin (Acetylsalicylic Acid)*
Diflunisal

Propionic Acid Derivatives:
Ibuprofen (Advil®, Motrin®)*
Naproxen (Aleve®)*
Ketoprofen
Fenoprofen
Flurbiprofen

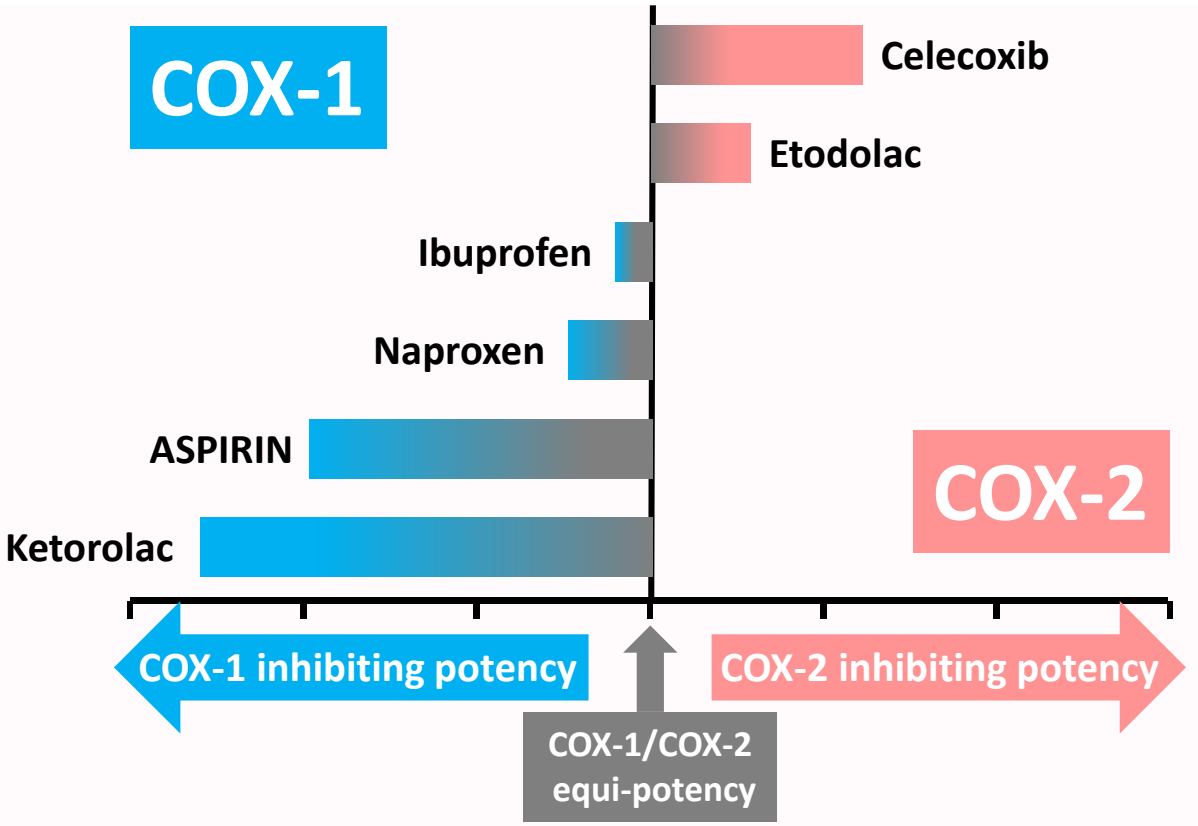
Pyrrole Derivatives:
Ketorolac

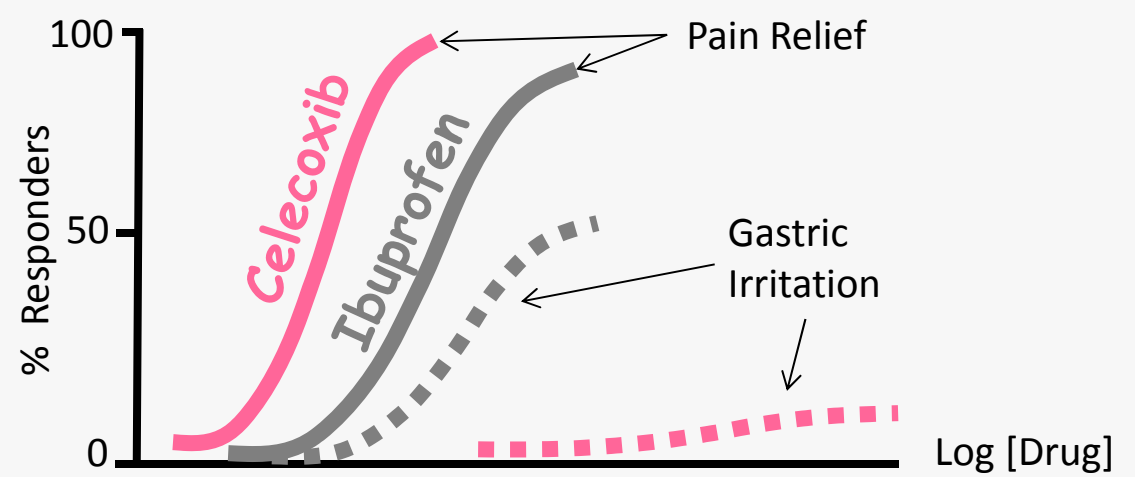
Indole and Indene Derivatives:
Etodolac
Indomethacin

Phenylacetic Acid Derivatives:
Diclofenac

Selective COX-2 Inhibitor:
Celecoxib (Celebrex®)

**** FDA-approved for over-the-counter (OTC) use:***
≤10 days for pain; ≤3 days for fever; Max. single/daily doses < Prescription





NSAIDs: Pharmacodynamics

Mechanism of Action and Therapeutic Effects:

Irreversible (acetylation; Aspirin) or **Reversible Competitive (NSAIDs)** **Inhibition of Cyclooxygenase (COX)**, resulting in **Inhibition of Prostaglandin (PG) synthesis** and the following effects associated with ↓ PGs:

- **Anti-Inflammatory** (↓ PG ⇒ ↓ vasodilation,↓ vascular permeability and ↓ action of other mediators)
- **Anti-Pyretic** (↓ PG ⇒ ↓ the thermal set point of the body in the Hypothalamus)
- **Analgesic** (↓ PG ⇒ ↓ neuroinflammation/sensitization of nociceptive endings and central terminals)
- **Anti-Platelet** (↓ PG ⇒ ↓ TXA_2 ⇒ ↓ Platelet Aggregation)

Dental Indications:

- Acute Pain associated with dental pathology (pulpitis, dentoalveolar abscesses, post-impaction, etc.)
- Mild to Moderate Post-procedural Pain
- TMJ Disorders (Naproxen; Celecoxib in long-term, i.e., weeks, treatment ⇒ minimize GI side effects)

Adverse Effects – Side Effects / *Contraindications*:

- **GI:** Gastrointestinal bleeding, ulceration → perforation, dyspepsia, nausea / *Peptic Ulcer Disease*
- **Kidney:** ↓RBF-GFR (acute failure), H_2O/Na^{2+} retention, analgesic-associated nephropathy (chronic use)/ *Hypertension, Tx: Diuretics, RAA Inhibitors, Beta-blockers (↓ Efficacy), Lithium (↓ Clearance ⇒ Li^+ toxicity)*
- **Dental:** Slower tooth movement / *Orthodontic treatment*
- **Cardiovascular:** Thrombotic events, e.g. myocardial Infarction, stroke **[Celecoxib]** / *Cardiovascular Disease*
- **Blood:** ↓ Platelet aggregation **[Aspirin]** / *Thrombocytopenia, Tx: Anticoagulants (e.g., Warfarin, Heparin)*
- **Respiratory:** Bronchoconstriction **[Aspirin/Salicylates]** / *Asthma*
- **Endocrine:** Hyper- or Hypoglycemia with Insulin and oral hypoglycemic drugs **[Aspirin]** / *Diabetes*
  Salicylate toxicity (damage to gastric mucosa) on steroid withdrawal **[Aspirin]** / *Steroid therapy*
- Reye's Syndrome in Children **[Aspirin/Salicylates]** / *Viral infections in children or teenagers*
- Increase in Plasma Urate **[Low Doses of Aspirin/Salicylates]** / *Gout*

All NSAIDs** share a common mechanism of action ⇒ qualitatively **similar therapeutic and adverse effects.

Acetaminophen: Pharmacodynamics

Mechanism of Action and Therapeutic Effects:

The exact **mechanism** or sites of action are **unknown**.

Proposed mechanisms: i) COX inhibition (COX-3, CNS neuronal COX?);
ii) peripheral analgesic action, but inhibited by peroxides from leukocytes?;
iii) activation of spinal 5-HT pathways; iv) inhibition of nitric oxide synthase…

Compared with Aspirin:

- **Anti-Pyretic** – EQUIVALENT POTENCY and EFFICACY
- **Analgesic** - EQUIVALENT POTENCY and EFFICACY
- **Anti-Inflammatory** - VERY WEAK
- **Anti-Platelet** – NO EFFECT

CHEMICAL NAME:

N-acetyl-*p*-aminophenol

BRAND NAME:

PARACETAMOL = ACETAMINOPHEN

Indications:

- **The antipyretic analgesic of choice when NSAIDs cannot be used due to contraindications**
  - *It* does not reduce inflammation, but can be effective in treating pain resulting from it;
  - *Aspirin and other NSAIDs are far superior for inflammatory conditions, e.g., pericoronitis.*
- **Post-operative dental pain (up to 3 g/day)**
  - *Aspirin and Acetaminophen are similarly effective in relieving pain after 3rd molar extraction*
  - *Most often used in combination with an opioid analgesic*
- First-line therapy for osteoarthritis despite NSAIDs being more efficacious.
- The anti-pyretic of choice in children and teenagers (not associated with Reye's syndrome)

Adverse Effects – **Toxic Effects (doses over 4 g/day)**:

High therapeutic index ⇒ rare side effects (neutropenia, thrombocytopenia). Allergy is rare (skin eruptions).
Overdose: Liver damage (nausea, jaundice- days later), acute RENAL toxicity, analgesic nephropathy (chronic).
Alcohol: CYP2E1 induction by alcohol ⇒ ↑ Phase 1 toxic metabolite; and glutathione depleted in alcoholics.
Protective effect of simultaneous alcohol (CYP2E1 occupied by alcohol ⇒ ↓ toxic metabolite production);
Greatest risk of hepatotoxicity after acute alcohol consumption (CYP2E1 induced and unoccupied by alcohol).