NSAID PHARMACOLOGY

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What is an NSAID?

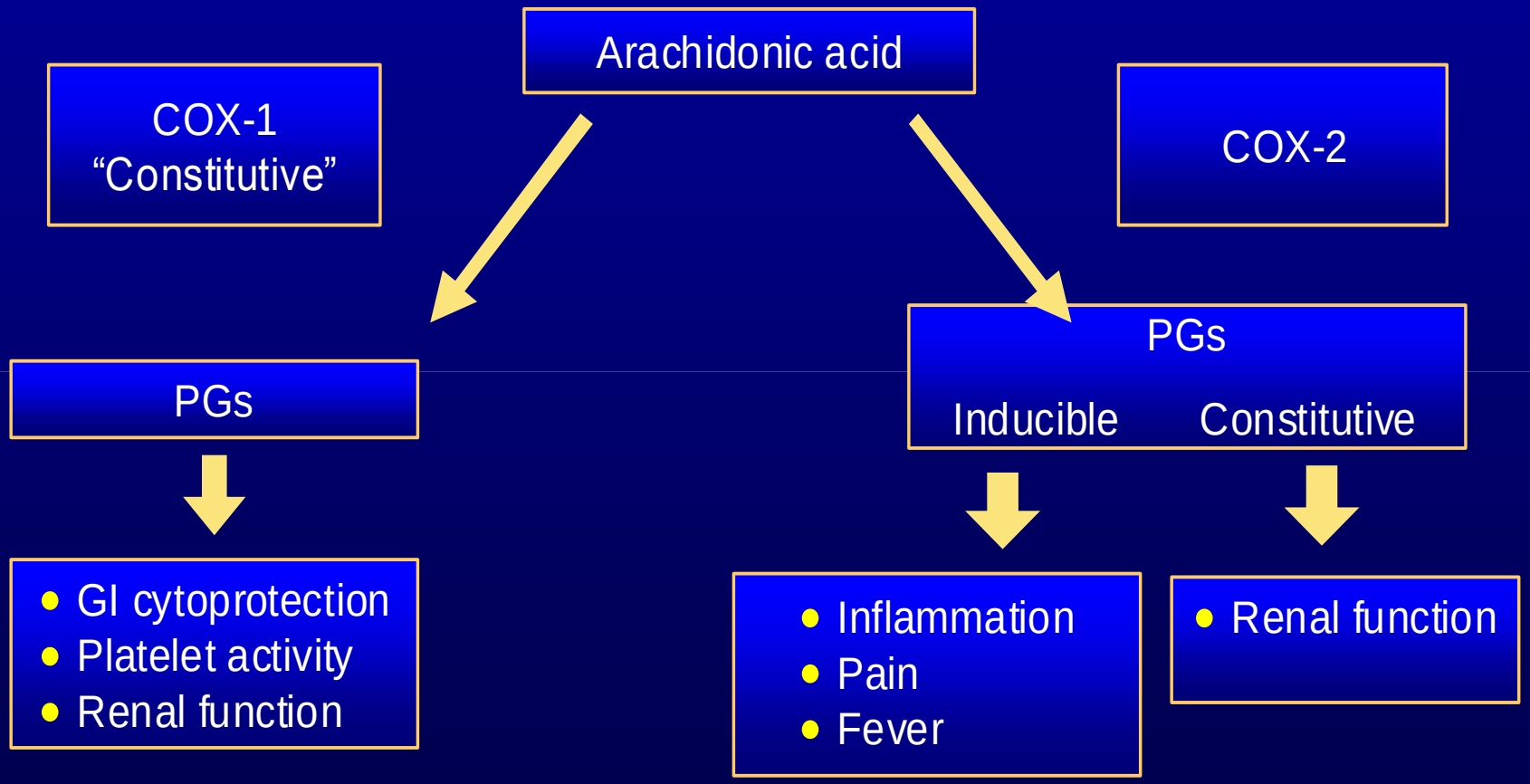
- Non steroidal Anti-inflammatory Drugs
- Weak organic acid
- Binds to serum proteins (albumin)
- Main anti-inflammatory properties due to inhibition of prostaglandin synthesis by blocking the enzyme prostaglandin G/H synthase (PGHS) also called cyclooxygenase (COX).

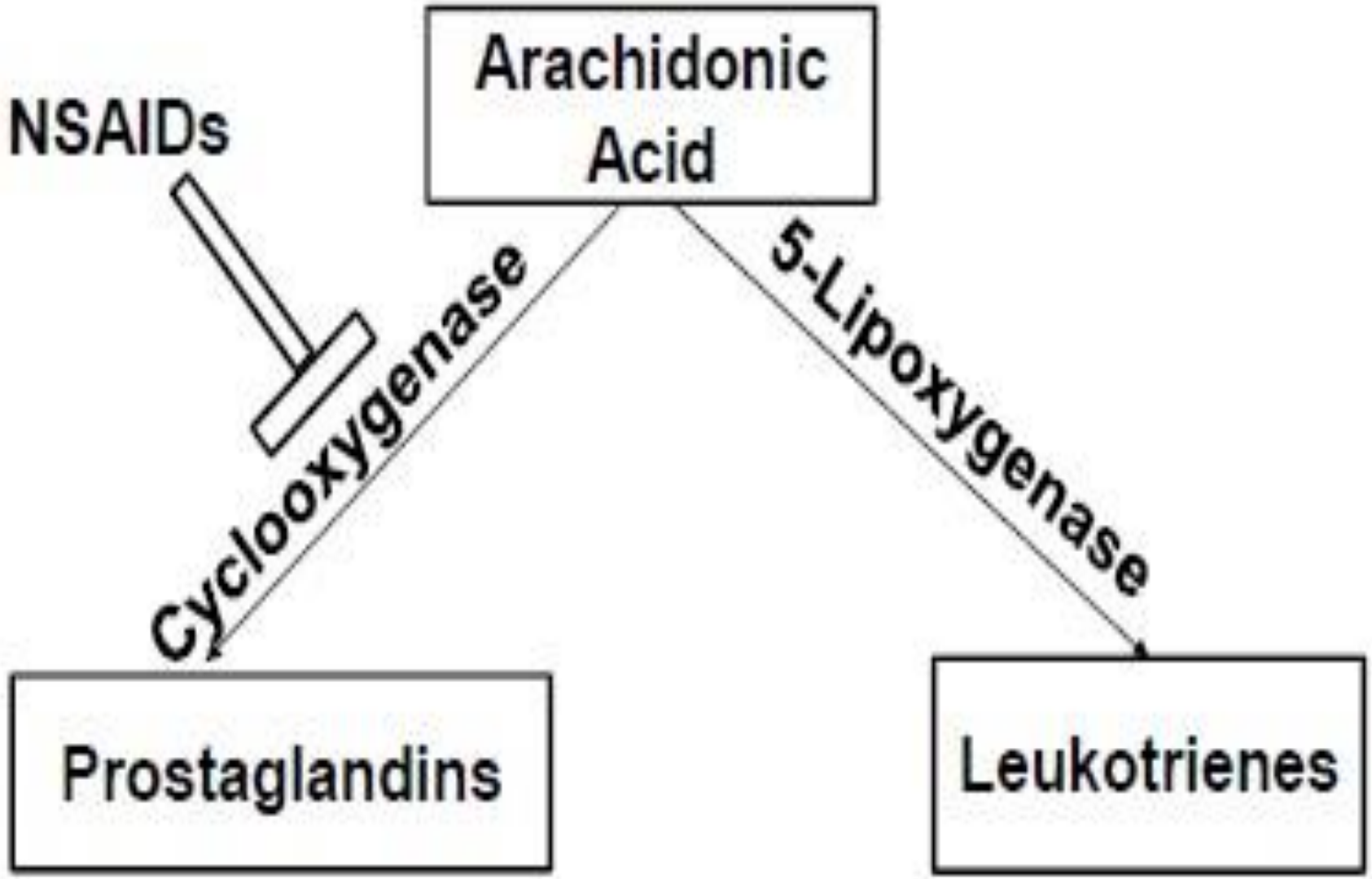
Effects of NSAIDs

- Analgesia
- Antiinflammatory
- Antipyresis
- Antiplatelet
- inhibit COX-1 thus preventing thromboxane A2 (TXA2) production to decrease platelet aggregation

Mechanism of Action

Roles of COX-1 and COX-2




Arachidonic Acid
NSAIDs
Cyclooxygenase
5-Lipoxygenase
Prostaglandins
Leukotrienes

Perception of Pain

Phospholipids

PLA_2

Arachidonic acid

– COX

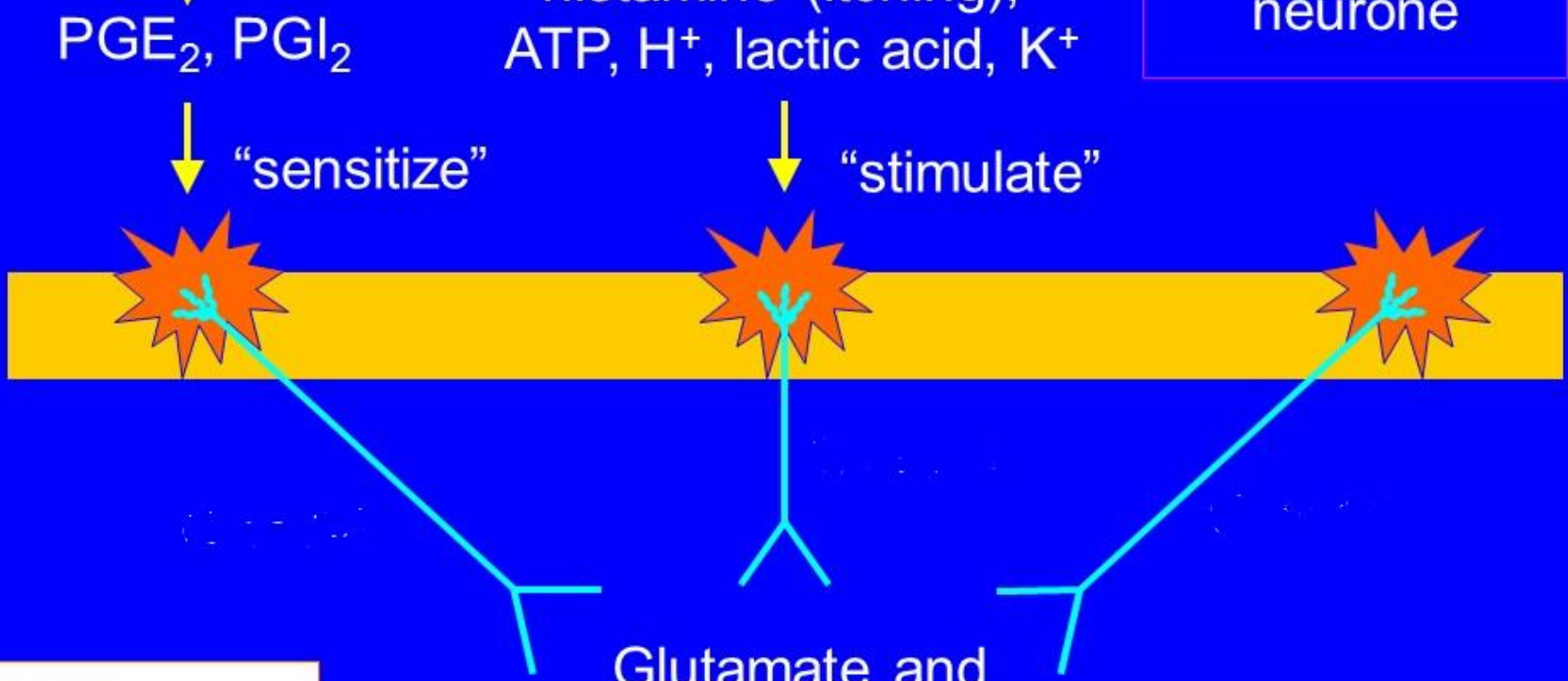
PGE_2, PGI_2

"sensitize"

5-HT, bradykinin,
kallidin,
histamine (itching),
ATP, H^+, lactic acid, K^+

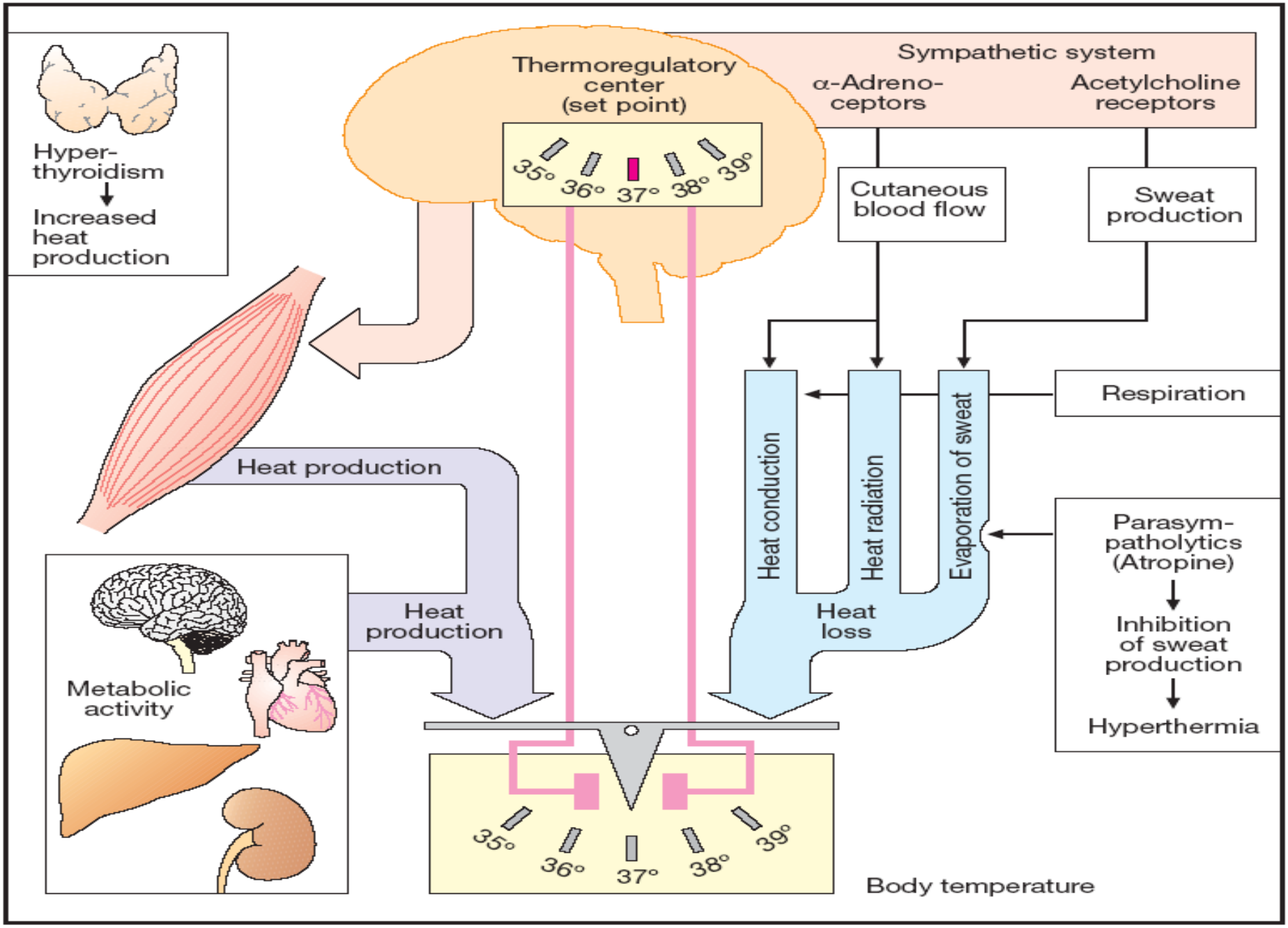
"stimulate"

Primary afferent neurone

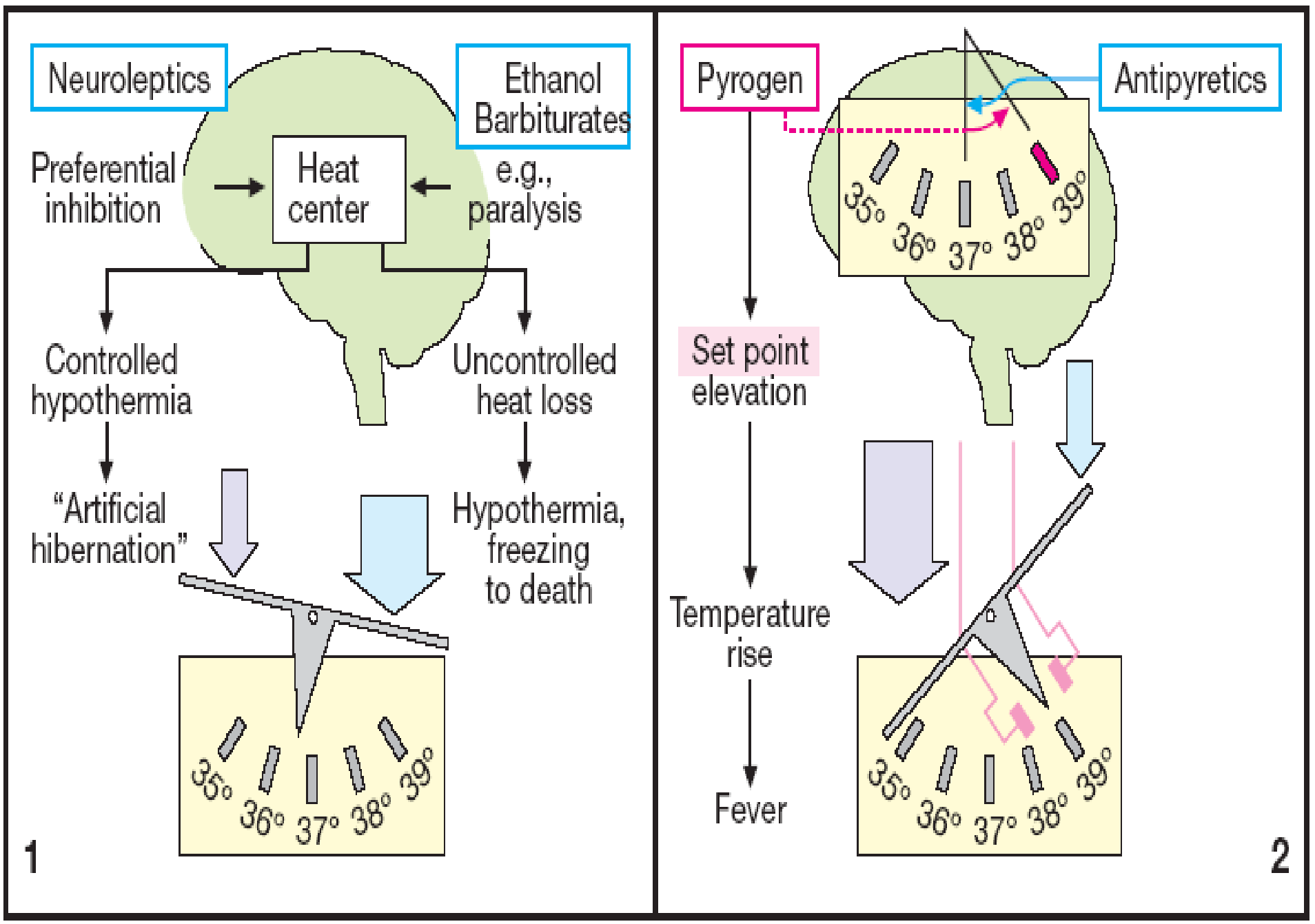


NSAIDs
e.g. ibuprofen

Glutamate and
Substance P release in
dorsal horn of spinal cord



A. Thermoregulation

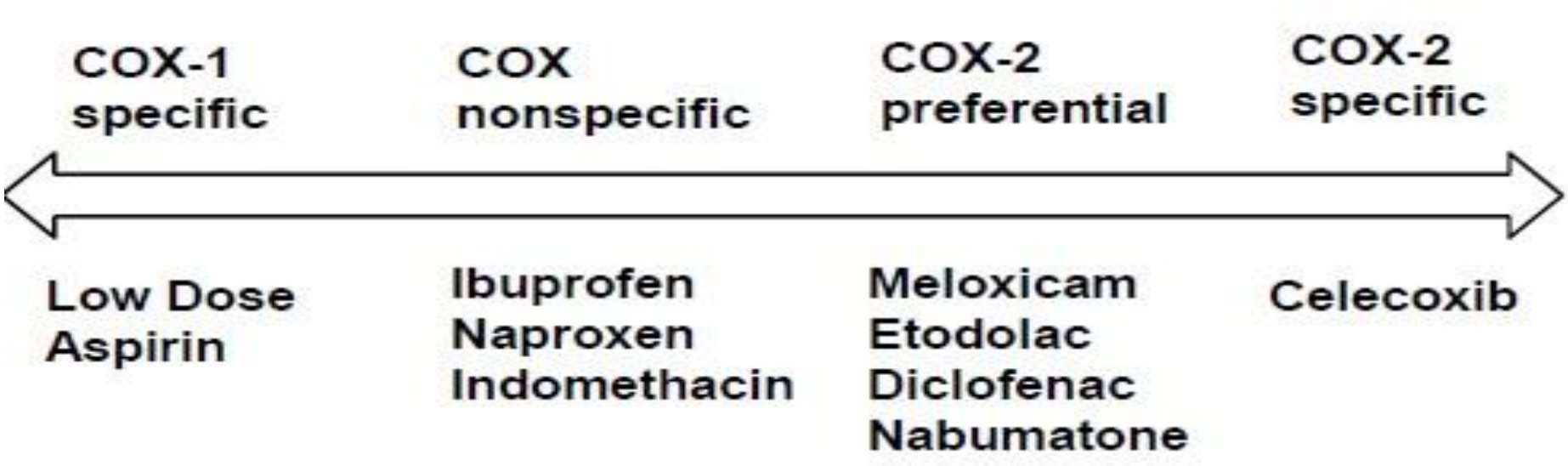


B. Disturbances of thermoregulation

NSAID Classes

Class	Drugs
Salicylate acetylated	Aspirin
Salicylate non-acetylated	Diflunisal
Propionic Acids	Ketoprofen, Flubiprofen, Oxaprozin, Naproxen, Ibuprofen
Enolic Acids	Meloxicam, Piroxicam
Acetic Acids	Diclofenac, Etodolac, Indomethacin, Sulindac, Tolmetin
Anthranilic Acids	Meclofenamate, Mefanamic acid
Nonacidic	nabumatone
Selective Cox 2 inhibitors	Celecoxib, Etorcoxib

COX selectivity



PGE2 Inihbition by NSAIDs

- PGE2 is the most abundant Prostaglandin(PG) at sites of inflammation1
- Microsomal PGE synthase-1 (mPGES-1)acts in concert with COX-2 to produce high levels of PGE2 during inflammation2
- NSAIDs block mPGES-1

cAMP & NSAIDs

- Can inhibit phosphodiesterases which lead to increased cAMP levels resulting in inhibition of:
  - peripheral blood lymphocyte response to mitogen stimulation
  - Monocyte and neutrophil migration
  - Neutrophil aggregation

More NSAID actions

- Scavenge free radicals
- Reduce mononuclear cell phospholipase C activity
- Inhibit inducible nitic oxide synthase activity
- Aspirin and salicylate inhibit NFKB activation

NSAID Complications

Big 3 complications

A. Gastrointestinal

B. Renal

C. Cardiovascular

GI Complications

Injuries to Gastric mucosa

- **NSAIDs may disrupt the gastric epithelial cell barrier causing mucosal erosions**
- **PG depletion perpetuates the development of clinically significant ulcerations**

- pKa important in determining risk of topical injury
- Aspirin prone to mucosal injury
- Nonacidic NSAIDs (nabumatone, etodolac, celexcoxib) not prone to acute mucosal lesions

Dyspepsia

- 10-20% of NSAID users
- Present even amongst COX-2 selective NSAIDs
- Improved with Proton pump inhibitors (PPI)
- Improved with histamine-2-receptor antagonists (H2RAs)

Outliers in GI risks

Renal Complications

Renal effects

- PGs important to solute and renovascular homeostasis.
- COX-1 expressed in renal vasculature, glomerular mesangial cells, and collecting duct
- COX-2 expressed in vasculature, cortical thick ascending limb (cells in macula densa), medullary interstitial cells.
- COX-2 inhibition may result in apoptosis of medullary interstitial cells and result in papillary necrosis.

Sodium Excretion

- PGs inhibit active transport of sodium in the thick ascending limb and the collecting ducts and increase renal water excretion by blunting the actions of vasopressin1
- Sodium retention reported in up to 25% of NSAID treated patients
- More likely in those with heart failure or liver disease
- Consider if weight gain or peripheral edema

Acute Renal Failure

- Due to vasoconstrictive effects of NSAIDs
- More common in those with:
- CHF
- Cirrhosis
- Renal insufficiency

Cardiovascular Risks

- COX-1 isoform generates platelet TXA2 which effects platelet aggregation and thrombus formation1
- PGI2 is antithrombotic and blocked by COX-2 inhibition2

- NSAIDs effect:
- Blood pressure
- Endothelial function
- Nitric oxide production
- May interfere with Aspirin (particularly ibuprofen and naproxen)

Drug Interactions

Plasma binding interactions

- **NSAIDs may displace other drugs from binding to plasma binding sites thereby increasing drug toxicity:**
- **Sulfonylurea**
- **Hypoglycemic agents**
- **Oral anticoagulant**
- **Phenytoin**
- **Sulfonamides**
- **Methotrexate**

Methotrexate	Increases plasma levels of methotrexate
ACE inhibitors	Lowers effects
Aspirin	Both block COX-1 but Aspirin is irreversible, so offers cardioprotective effects
Glucocorticoids	Increase GI risks
Anticoagulants	Inhibit platelet function and increase bleeding
SSRI	Increase GI risks

Take Aspirin 2 hours before other NSAIDs

NSAID Overdose

- ❑ Aspirin/salicylate intoxication Signs/symptoms
- ❑ Tachypnea
- ❑ Confusion
- ❑ Ataxia
- ❑ Oliguria
- ❑ Increased BUN/Cr

- ❑ Non-Aspirin/salicylate NSAID overdose Signs/symptoms
- ❑ CNS depression
- ❑ Seizures
- ❑ Nystagmus
- ❑ Blurred vision
- ❑ Headache
- ❑ Tinnitus
- ❑ Bradycardia & Hypotension
- ❑ Abnormal renal function
- ❑ Coma
- ❑ Cardiac arrest

- ❑ Evacuation of the stomach
- ❑ Observation
- ❑ Administration of fluids
- ❑ NSAIDs are not dialyzable


Thank
You