Nonsteroidal Anti-Inflammatory Drugs
analgesic, anti-inflammation, antipyretic

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Peripheral mechanisms of pain
Drugs for the Relief of Pain

Analgesics

- Non-Opioid
- Opioid
- Adjuvant
Non-steroidal anti-inflammatory drugs (NSAIDs) are just that - drugs that act to relieve inflammation, but are not structurally related to the corticosteroids.
Cyclooxygenases: COX 1, COX 2

- PGs, mostly by COX-1, are constitutively expressed in almost all tissues; COX-2 appears to only be constitutively expressed in the brain, kidney, bones, reproductive organs, and some neoplasms.

- Under normal physiologic conditions, PGs play an essential homeostatic role in cytoprotection of gastric mucosa, hemostasis, renal physiology, gestation, and parturition.

- Only COX-1 in platelets converts arachidonic acid to TXA₂.
- COX-1 predominant in gastric mucosa is a source of cytoprotective PGs.

- The production of PGs (inducible COX-2 activity >> COX-1) at sites of inflammation propagate pain, fever.
NSAID Therapy

- NSAID inhibition of PGs production alleviates most of the pathologic effects associated with inflammation, but it also interferes with the physiologic role of these molecules.

- Consequently, long-term therapy with nonspecific NSAIDs is frequently limited by their adverse effects, particularly those caused by erosion of gastric mucosal protection.
Pharmacodynamic Effects of NSAIDs

Positive

analgesic - refers to the relief of pain by a mechanism other than the reduction of inflammation (for example, headache);
- produce a mild degree of analgesia which is much less than the analgesia produced by opioid analgesics such as morphine

anti-inflammatory - these drugs are used to treat inflammatory diseases and injuries, and with larger doses - rheumatoid disorders

antipyretic - reduce fever; lower elevated body temperature by their action on the hypothalamus; normal body temperature is not reduced

Anti-platelet - inhibit platelet aggregation, prolong bleeding time; have anticoagulant effects
## Analgesic: compared with Opioids

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects</strong></td>
<td>Inhibit PGs and TXA&lt;sub&gt;2&lt;/sub&gt; synthesis by inhibiting COX</td>
<td>Stimulate opioid receptors</td>
</tr>
<tr>
<td><strong>Clinical usage</strong></td>
<td>Headache, toothache, neuralgia, arthronalgia, courbature(肌肉痛), menalgia(痛经)</td>
<td>Various pain including severe pain</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>GI reactions, no addiction</td>
<td>Addiction</td>
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## Anti-inflammatory: compared with glucocorticoid

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs</th>
<th>Glucocorticoid</th>
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<tbody>
<tr>
<td><strong>Effects</strong></td>
<td>Inhibit PGs and TXA&lt;sub&gt;2&lt;/sub&gt; synthesis by inhibiting COX</td>
<td>Various effects including inhibition of PLA&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Clinical usage</strong></td>
<td>Rheumatic, rheumatoid, trauma</td>
<td>Various inflammation</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>GI reactions</td>
<td>Various side effects, such as metabolism disturbance, damage of defense etc.</td>
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antipyretic: compared with chlorpromazine

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs</th>
<th>Chlorpromazine(氯丙嗪)</th>
</tr>
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<tbody>
<tr>
<td><strong>Effects</strong></td>
<td>Inhibit PGs synthesis and enhance thermolysis</td>
<td>Inhibit thermotaxic center in hypothalamus, induce the body temperature change according to that of environment.</td>
</tr>
<tr>
<td><strong>Clinical usage</strong></td>
<td>Lower the abnormal high temperature to normal. Used for various fever.</td>
<td>artificial hibernation(人工冬眠), Hypothermic anesthesia</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>GI reactions, no addiction</td>
<td>Extrapyramidal effects (锥体外系反应)</td>
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</table>
Pharmacodynamic Effects of NSAIDs

**Negative**

- Gastric irritant
- Decreased renal perfusion
- Bleeding
- (CNS effects)
Gastrointestinal Adverse Effects associated with NSAIDs

- NSAID-associated dyspepsia(消化不良) occurs in up to 50% of patients who use these drugs

- no relationship, however, between NSAID-associated dyspeptic symptoms and the presence of erosions or ulceration

- appears to be an inverse relationship: those who have ulceration are more likely to be free of symptoms. As a result, neither the patient nor his or her physician may be aware that the patient harbors an ulcer and is at risk for serious gastrointestinal complications.

- up to 100% of patients taking nonselective NSAIDs - subepithelial hemorrhage,
  ~ 50% have erosions (small, shallow breaks in the GI mucosa)
  ~ 20% have ulceration (injury extending through the muscular mucosa)

- unless the ulcer results in symptoms or becomes complicated (eg, causes bleeding or perforation), it is not clinically relevant. Only 1 - 3% of patients develop serious GI side effects while taking NSAIDs.
For patients presenting to hospital with upper gastrointestinal (UGI) bleeding - a significant percent were using NSAIDs.

Note: Over-the-counter (OTC) use of NSAIDs was more prevalent than was prescribed NSAID usage.
NSAIDs - Gastric Irritant Effects: Molecular Mechanisms

PGs reduce H⁺ secretion and increase mucous production. Consequently, NSAIDs cause some degree of gastric upset due to inhibition of PG synthesis.

- **Misoprostol**, a synthetic prostaglandin analogue, can also decrease the risk of NSAID-induced ulceration and complications.

- **PPIs** can reduce the risk of peptic ulcer formation.
NSAIDs and Platelet Function

Physiology:
- **TXA2 is mainly produced in platelets**: upon platelet activation; promotes platelet aggregation, vasoconstriction, and vascular proliferation

- **platelets do not have a nucleus and cannot synthesize new COX molecules** to replace those that have been irreversibly inactivated.

Pharmacology:
- **apart from aspirin (irreversible COX inhibition), all NSAIDs inhibit COX competitively**, and inhibitory effects on platelet aggregation depend on the pharmacokinetic profiles of the agents.
  After administration of a single dose of aspirin, platelet aggregation is impaired for up to 4 days, until new platelets enter the circulation in sufficient numbers.

- as thrombotic events can occur at any time and for a prolonged period after rupture of a vulnerable plaque, sustained inhibition of platelet activity is needed in order to provide cardioprotection.
1. Healthy, intact endothelium releases prostacyclin into plasma.
   - Prostacyclin binds to platelet membrane receptors causing synthesis of cAMP.
   - cAMP inhibits release of granules containing aggregating agents.

2. Thrombin, thromboxane A$_2$ and exposed collagen cause release of arachidonic acid from platelet membrane.
   - Thromboxane A$_2$ is synthesized from arachidonic acid and released from the platelet.
   - This pathway is inhibited by aspirin.

3. Thromboxane A$_2$ binds to receptors on other platelets thereby initiating release of additional aggregating agents.

4. Balance between levels of prostacyclin and thromboxane A$_2$ influences whether platelet aggregates or circulates freely.

- **Diagram Notes**
  - Serotonin, ADP, Prostaglandin H$_2$, Prostacyclin (PGI$_2$), Thromboxane A$_2$, Aspirin, Arachidonic acid, and DAG/IPC are key components in the interaction.
  - ATP, cAMP, IP$_3$, 5'-AMP, and Dipyridamole influence platelet aggregation.
- small doses (40~80 mg/d): inhibiting TXA₂ synthesis, preventing thrombosis.
- larger doses: inhibiting PGI₂ synthesis, promoting thrombosis. PGI₂: vasodilation and platelet depolymerization (血管小板解聚).

- Most of these drugs will potentiate the action of oral anticoagulants such as coumadin, by their effects on platelet aggregation.
NSAIDs and Platelets/Endothelial Cells

Note: Selective inhibition of COX-2 will inhibit the production of PGI₂ but not of thromboxane A2, which is produced by COX-1. SO?
NSAIDs – Effects on Renal Function

- In healthy hydrated individuals, renal PGs do not play a major role in sodium and water homeostasis

- Under certain conditions of localized circulatory stress associated with elevated levels of angiotensin II and catecholamines resulting in decreased renal perfusion, renal blood flow is dependent upon prostaglandin synthesis

- thus, NSAID-induced inhibition of PG synthesis can result in significant decreases in renal blood flow and GFR, leading to acute renal failure in kidney function-compromised individuals

- Patients at most risk include those with congestive heart failure, volume depletion, chronic renal disease, liver disease and those patients receiving diuretics
Salicylates (水杨酸类) – aspirin (阿司匹林)
History - Salicylates

- Salicylates were first discovered when the observation was made that chewing willow bark could relieve pain
- Hippocrates: Willow bark as a pain killer during childbirth
- Stone (1700) Extract of willow bark to reduce fever
- Piria (1838) Isolation of salicin (水杨苷) from willow bark
- Kolbe (1853) Synthesis of salicylate from salicin
- Von Gerhardt at Beyer Pharmaceutical Co. synthesized acetyl SA (ASA) in 1850
- Hoffman, at Beyer gave ASA to his rheumatoid father
- Beyer started sales of Aspirin in 1899
- **Acetylsalicylic acid (aspirin)** was introduced as a pain reliever in 1899, at that time it was used in doses of 650 mg every 4 hours
History - Salicylates

- ASA developed
- ASPIRIN distributed to doctors, becomes #1 drug worldwide
- ASPIRIN recognized for preventing second heart attacks
- ASPIRIN 81mg launched
- ASPIRIN used within 1st 4 hours of heart attack can reduce risk of fatality by up to 25%
- ASPIRIN recognized by Health Canada as preventing first, non-fatal heart attacks
Aspirin-Mechanism of Action: Covalent Binding to COX

ASA covalently and irreversibly modifies both COX-1 and COX-2 by acetylating serine-530 in the active site

Acetylation results in a steric block, preventing arachidonic acid from binding

Note: Acetylation of COX-2 retains the COX activity although the reaction produces a different product, 15-R-HETE
Aspirin Metabolism Pathways
acetylsalicylic acid (ASA)

ASA: $t_{1/2} \sim 20$ min

irreversible acetylation of COX

Salicylate $t_{1/2} \sim 3-5$ hrs

- Salicylate elimination is 1st order at low and moderate doses;
- When total body salicylate $> 600$mg ($>3.5$g/d), elimination is zero order
Uses of Aspirin

Dose-Dependent Effects:
Low: < 300mg  
blocks platelet aggregation

Intermediate: 300-2400mg/day  
antipyretic and analgesic effects

High: 2400-4000mg/day  
anti-inflammatory effects
Side effects of aspirin

- Gastrointestinal symptoms
- CNS toxicity / Salicylate reaction
- Anaphylaxis (asthma)
- Metabolic acidosis, respiratory alkalosis
- Hepatic damage / Reye’s syndrome
- Renal damage
- Hematologic effects
NSAIDs: Classification by Plasma Elimination Half Lives

Short Half Life (< 6 hours):
more rapid effect and clearance
• Aspirin (0.25-0.33 hrs),
• Diclofenac (双氯酚酸，1.1 ± 0.2 hrs)
• Ketoprofen (酮洛芬，1.8 ± 0.4 hrs),
• Ibuprofen (2.1 ± 0.3 hrs)
• Indomethacin (4.6 ± 0.7 hrs)

Long Half Life (> 10 hours):
slower onset of effect and slower clearance
• Naproxen (14 ± 2 hrs)
• Sulindac (舒林酸，14 ± 8 hrs),
• Piroxicam (吡罗昔康，57 ± 22 hrs)
**NSAIDs**

Reversible Non-Selective COX inhibitors  
(for mild to moderate pain)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>dose (mg)</th>
<th>interval</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Ibuprofen (布洛芬)</td>
<td>400 PO</td>
<td>q 4-6 h</td>
<td>Available without prescription</td>
</tr>
<tr>
<td>Naproxen (萘普生)</td>
<td>250-500 PO</td>
<td>q 12 h</td>
<td>Delayed effects may be due to long half-life</td>
</tr>
<tr>
<td>Fenoprofen (非诺洛芬)</td>
<td>200 PO</td>
<td>q 4-6 h</td>
<td>Contraindicated in renal disease</td>
</tr>
<tr>
<td>Indomethacin (吲哚美辛)</td>
<td>25-50 PO</td>
<td>q 8 h</td>
<td>Gastrointestinal side effects common</td>
</tr>
<tr>
<td>Ketorolac (酮咯酸)</td>
<td>15-60 IM, 4-6 h</td>
<td>Available for parenteral use (IM, IV)</td>
<td></td>
</tr>
</tbody>
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*Ketorolac* is indicated for the short-term (up to 5 days) management of moderately severe, acute pain, that requires analgesia at the opioid level. It is NOT indicated for minor or chronic painful conditions.
NSAIDs: Classification by COX selection

In vitro assessment of COX-1 – COX-2 activity

Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed., Copyright © 2006 Saunders, An Imprint of Elsevier
Summary of COX-1 vs COX-2 Inhibition

Prostaglandin Synthesis

Membrane Phospholipids

Phospholipase A2

Arachidonic Acid

Lipooxygenase

Leukotrienes

Physiological Regulation by COX-1

Non-Selective Cox Inhibitors

Cox-2 Selective NSAID's

Inflammatory response by newly expressed COX-2

<table>
<thead>
<tr>
<th>PGE₂</th>
<th>PGI₂</th>
<th>TXA₂</th>
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<tbody>
<tr>
<td>GI Protection</td>
<td>GI Protection</td>
<td>Platelet function</td>
</tr>
<tr>
<td>Platelet Function</td>
<td>Regulation of blood flow</td>
<td>Regulation of blood flow</td>
</tr>
<tr>
<td>Kidney Function</td>
<td></td>
<td></td>
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PGE₂ PGI₂ Other Chemical Mediators

Inflammation

Pain

Fever
## COX-1 compared to COX-2

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<thead>
<tr>
<th></th>
<th>COX-1</th>
<th>COX-2</th>
</tr>
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<tbody>
<tr>
<td><strong>Expression</strong></td>
<td>Constitutive (activated by physiologic stimuli)</td>
<td>Inducible by pro-inflammatory stimuli (LPS, TNF$\alpha$, IL-2, IFN$\gamma$ etc)</td>
</tr>
<tr>
<td><strong>Tissue localization</strong></td>
<td>Ubiquitous</td>
<td>Inflammatory and neoplastic sites (small amounts in kidney, uterus, ovary, CNS [neocortex, hippocampus])</td>
</tr>
<tr>
<td><strong>Role</strong></td>
<td>“Housekeeping” and maintenance</td>
<td>Pro-inflammatory and mitogenic functions (?) neuronal plasticity</td>
</tr>
</tbody>
</table>
COX-2 Selective Drugs

COX-2 is also up-regulated in the CNS and plays an essential role in the mediation of pain and the febrile response.

COX-2 is also up-regulated in colorectal polyps and adenocarcinomas.

COX-2 selective inhibitors are generally larger molecules than NSAIDs and therefore preferentially inhibit COX-2 compared to COX-1 because the hydrophobic channel of COX-2 is larger. That is, COX-2 selective inhibitors are too bulky to access the binding pocket of the COX-1 enzyme.
Patients with rheumatoid arthritis were treated with celecoxib (100, 200, or 400 mg twice daily), naproxen 500 mg twice daily, or a placebo for 12 weeks. **Rates of gastroduodenal ulceration with naproxen were statistically higher** (*, *P* < .01) than rates with celecoxib or a placebo. (Data from Simon LS, Weaver AL, Graham DY, et al: Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis. JAMA 282:1921–1928, 1999.)
After 6 months of treatment, approximately 43% of the patients discontinued the study.

After 6 months of therapy, the annualized rate of UGI ulcer complications was 0.76% (11 events/1441 patient-years) among patients treated with celecoxib and 1.45% (20 events/1384 patient-years) among those treated with NSAIDs.

Similar incidence of the primary end point of ulcer complications among patients treated with celecoxib or with nonspecific NSAIDs.
Celecoxib is now the only selective COX-2 inhibitor available in the US
- withdrawal of rofecoxib (Vioxx, Merck & Co) Sept 2004
- suspension of valdecoxib (Bextra, Pfizer) Apr 2005

A black box warning by FDA

Celecoxib includes a boxed warning, highlighting the potential for increased risk of cardiovascular events and the well described, serious, potential life-threatening gastrointestinal bleeding associated with their use.

Note: The fact that it now carries exactly the same warning for gastrointestinal risk as the older nonselective NSAIDs is quite remarkable, new drugs—were supposedly less risky to the gastrointestinal tract than the older nonselective agents
Risk of Cardiovascular Events in Patients Receiving *Celecoxib*: A Meta-Analysis of Randomized Clinical Trials

- 7,462 patients exposed to celecoxib 200 to 800 mg/day for 1,268 patient-years compared with 4,057 patients treated with placebo for 585 patient-years.

- 19,773 patients treated with celecoxib 200 to 800 mg/day for 5,651 patient-years compared with 13,990 patients treated with nonselective NSAIDs (diclofenac, ibuprofen, naproxen, ketoprofen, and loxoprofen) for 4,386 patient-years.

*Am J Cardiol* 2007;99:91–98
Risk of Cardiovascular Events in Patients Receiving Celecoxib: A Meta-Analysis of Randomized Clinical Trials

Am J Cardiol 2007;99:91–98
Celecoxib: cardiovascular events

- Celecoxib compared with placebo is not associated with an increased risk for cardiovascular events for duration of use from 12 to 52 weeks.

- Celecoxib compared with nonselective NSAIDs is not associated with increased cardiovascular endpoints.
Celecoxib: cardiovascular events

- The results are controversial.
- Currently a large trial enrolled 20,000 patients is going on, which is supported by Pfizer. And hopefully can be finished in 2010.
Acetaminophen (对乙酰氨基酚)

Pharmacology

- produces analgesia
- antipyretic
- no significant anti-inflammatory effects
- no gastric irritation
- no platelet function interference
- half life 2–3 h
- weak inhibitor of COX-1, -2; some evidence for COX 3 inhibition
- not contraindicated for asthma
- not associated with Reye’s Syndrome
Acetaminophen

- equipotent with aspirin in relieving mild to moderate pain and reducing fever; (no significant anti-inflammatory effects)

- The major concern regarding the use of acetaminophen is the potential for high doses to cause liver toxicity

- Concurrent use of alcohol can cause toxicity at lower doses of acetaminophen. Also, the use of multiple products that each contain acetaminophen can inadvertently cause a toxic dose of acetaminophen

- The FDA recommendation is that patients who consume more than three alcoholic drinks per day should consult their physician before using acetaminophen
References


• Goodman & Gilman’s
  the pharmacological basis of therapeutics (11th edition), 2006.