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THE BIOCHEMISTRY OF PAIN: HOW IBUPROFEN AND ASPIRIN WORK

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Relevance. Understanding the molecular mechanisms of pain and the action of NSAIDs like ibuprofen and aspirin is essential for improving pain management strategies and minimizing side effects in clinical practice.

Aim. To analyze the biochemical pathways of prostaglandin synthesis and explain how NSAIDs modulate pain through their interaction with COX enzymes.

Results and discussion. Pain functions as an essential biological alert system, signaling potential tissue damage. At the molecular scale, pain perception is initiated by nociceptors—specialized sensory neurons attuned to harmful stimuli. Their activation sets off complex biochemical pathways, prominently involving prostaglandins, which sensitize these neurons and lower the threshold for pain, intensifying the response.

Prostaglandins in Pain Signaling. These bioactive lipids, synthesized from arachidonic acid, possess a cyclopentane ring and diverse functional groups. Prostaglandin E2 (PGE_2), in particular, binds to EP receptors on sensory neurons, triggering intracellular cAMP elevation and ion channel phosphorylation, thereby amplifying pain sensitivity. Synthesis begins with phospholipase A_2-mediated liberation of arachidonic acid, followed by COX-mediated conversion to prostaglandin H_2 (PGH_2), the precursor of various active prostaglandins.

Cyclooxygenase (COX) Enzymes. Two primary COX isoforms—COX-1 and COX-2—mediate prostaglandin synthesis. COX-1, expressed constitutively, maintains homeostatic functions such as gastric protection, renal blood flow regulation, and platelet aggregation. COX-2, predominantly inducible by pro-inflammatory stimuli, is also constitutively active in select tissues like the brain and kidneys. Structurally, both are membrane-bound homodimeric glycoproteins with catalytic domains. A key difference lies in the binding site: COX-2's larger channel arises from a valine substitution, allowing selective inhibition.

Mechanism of Action of NSAIDs. Ibuprofen and Aspirin. Ibuprofen and aspirin represent two distinct molecular approaches to COX inhibition, with profound implications for their clinical use and side effect profiles.

Ibuprofen (2-(4-isobutylphenyl)propionic acid) interacts with COX enzymes through reversible competitive inhibition. The S-enantiomer, which is pharmacologically active, features a carboxylic acid group that forms ionic bonds with Arginine 120 at the entrance of the COX enzyme's hydrophobic channel. Hydrogen bonding between ibuprofen's carboxyl oxygen and Tyrosine 355 further stabilizes this interaction, while its aromatic ring engages in π-stacking with phenylalanine residues. The isobutyl side chain forms van der Waals interactions with hydrophobic residues including Val349 and Leu531, completing a complex network of non-covalent bonds. X-ray crystallography confirms that ibuprofen physically occupies the upper portion of the channel, directly competing with arachidonic acid for access to the catalytic site.

The interaction follows classical competitive inhibition kinetics, with ibuprofen increasing the Km for arachidonic acid without affecting Vmax. With an inhibition constant (Ki) of approximately 12-15 μM for COX-1 and 20-30 μM for COX-2, ibuprofen demonstrates modest selectivity (1.5-3 fold) for COX-1 at therapeutic concentrations. Critically, this binding is entirely non-covalent and therefore reversible—the inhibition persists only while sufficient drug concentration remains in proximity to the enzyme. Once plasma levels decline, ibuprofen dissociates from the binding site due to thermodynamic equilibrium, and the enzyme immediately regains catalytic activity. This reversibility explains ibuprofen's relatively short half-life (1.8-2.5 hours) and the requirement for repeated dosing to maintain analgesia.

Aspirin (acetylsalicylic acid), in contrast, employs a fundamentally different mechanism representing a unique case among NSAIDs. Its structure contains a salicylic acid core with an acetyl group esterified to the phenolic hydroxyl group—this acetyl moiety is essential for its distinctive mechanism. Rather than simply competing

for the active site, aspirin modifies COX through an irreversible covalent interaction. The process begins with aspirin binding non-covalently near the catalytic site. Once positioned, a transacetylation reaction occurs where the acetyl group transfers from aspirin to a specific serine residue (Ser530 in COX-1, Ser516 in COX-2). This reaction hydrolyzes the ester bond in aspirin, releasing salicylic acid while forming a new ester bond between the acetyl group and the serine's hydroxyl oxygen.

The molecular consequences of this acetylation are dramatic—the added acetyl group creates significant steric hindrance at a critical position in the hydrophobic channel. X-ray crystallography reveals that the acetylated serine protrudes into the channel, physically obstructing substrate binding and disrupting hydrogen bonding networks essential for catalysis. Importantly, the reaction rate of acetylation is approximately 10-100 times faster with COX-1 compared to COX-2, explaining aspirin's greater selectivity for COX-1. In COX-2, the acetylation still occurs but can redirect the enzyme to produce anti-inflammatory lipoxins rather than completely inhibiting activity.

Once acetylated, the enzyme remains permanently inactive, with restoration of COX activity requiring de novo protein synthesis. In most tissues, new enzyme production rapidly restores function. However, in platelets, which lack nuclei and cannot synthesize new proteins, the inhibition persists for the entire platelet lifespan (7-10 days). This prolonged effect forms the basis for aspirin's use in cardiovascular disease prevention at doses as low as 75-100 mg daily. The uniqueness of this mechanism is highlighted by the fact that other salicylates lacking the acetyl group (e.g., sodium salicylate) cannot acetylate COX and have substantially weaker anti-inflammatory properties.

These distinct molecular mechanisms – reversible competitive inhibition for ibuprofen versus irreversible covalent modification for aspirin—explain their different pharmacological profiles, including aspirin's prolonged antiplatelet effect, effectiveness at low doses for cardiovascular protection, and its higher gastrointestinal toxicity due to greater COX-1 selectivity.

Clinical Implications. Therapeutic Benefits. NSAID-induced COX inhibition yields analgesia (via reduced PGE_2), anti-inflammatory action (through dampened vasodilation and leukocyte recruitment), fever reduction (by modulating hypothalamic thermoregulation), and antiplatelet effects (notably from aspirin via thromboxane A_2 suppression).

Adverse Effects. However, side effects result from disrupted prostaglandin synthesis: gastrointestinal injury due to diminished mucosal protection, renal complications from altered vasodilation, increased cardiovascular risks (especially with COX-2 selectivity), and respiratory issues due to leukotriene pathway activation.

Future Directions. Research targets safer COX-2 inhibitors, dual COX/lipoxygenase blockers, prostaglandin receptor antagonists for precision therapy, and nanocarrier systems to enhance drug delivery and reduce systemic exposure.

Conclusion. NSAIDs like ibuprofen and aspirin remain foundational in analgesia, acting via distinct molecular engagements with COX enzymes. Deeper understanding of these mechanisms fosters the advancement of safer, more effective pain management strategies.

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PREECLAMPSIA AND ECLAMPSIA: CURRENT APPROACHES TO DIAGNOSIS AND MANAGEMENT (A Literature review)

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Introduction

Preeclampsia and eclampsia are among the most severe pregnancy complications and remain leading causes of maternal and perinatal morbidity and mortality worldwide. According to the WHO, more than 70,000 women die annually from preeclampsia or eclampsia, with significant associated fetal complications [1]. Despite progress in understanding the pathogenesis and implementing screening protocols, these conditions still present clinical challenges, especially in low-resource settings.

Modern understanding of preeclampsia extends beyond classical definitions based on hypertension and proteinuria, focusing on multisystem involvement and endothelial