► Molecular Mimicry

Anterior (Head) Kidney

This is the front part of fish kidney with immune functions comparable to mammalian bone marrow, i. e. it performs hematopoiesis.
► Fish Immune System

Anthracene

► Polycyclic Aromatic Hydrocarbons (PAHs) and the Immune System

Anti-Cancer Antibodies

Antibodies directed against tumor-specific antigens, used as therapeutic and/or diagnostic agents.
► Antibodies, Antigenicity of

Anti-DNA Antibodies

► Antinuclear Antibodies

Anti-Double Stranded (ds) DNA Antibodies

► Antinuclear Antibodies

Anti-Histone Antibodies

► Antinuclear Antibodies

Anti-Inflammatory Antibodies

Antibodies directed against pro-inflammatory molecules, such as cytokines, cell adhesion molecules and leukotrienes, used to suppress inflammation.
► Antibodies, Antigenicity of

Anti-Inflammatory Cytokine

A cytokine (e.g. interleukin-10) that downregulates an inflammatory process by reducing expression of proinflammatory cytokines.
► Cytokines

Anti-Inflammatory (Nonsteroidal) Drugs

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Synonyms

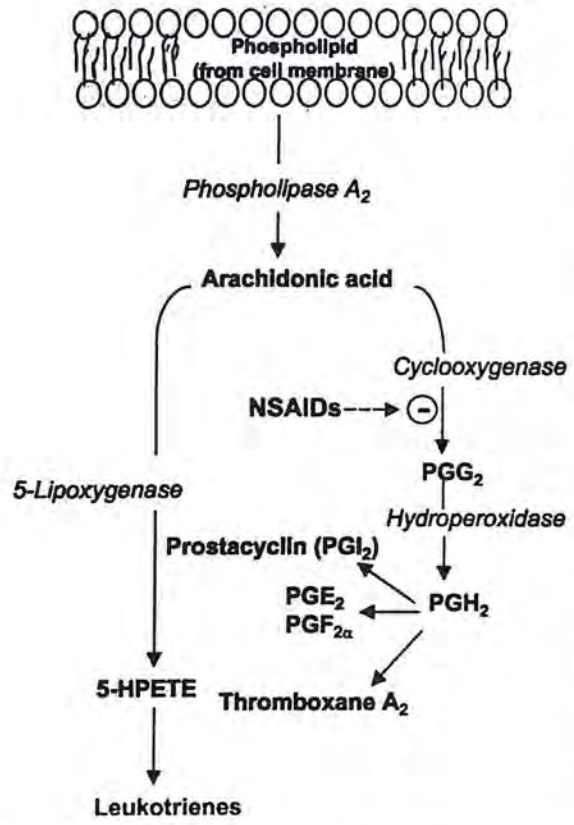
Nonsteroidal antiinflammatory drugs, NSAIDs, aspirin, aspirin-like drugs, cyclooxygenase inhibitors, COX inhibitors.

Definition

NSAIDs are a group of chemically dissimilar agents, other than steroids, commonly used to treat a variety of conditions because of their analgesic, antiinflammatory, and antipyretic properties. They are widely used to reduce inflammation and pain in musculoskeletal disorders including osteoarthritis, rheumatoid arthritis, gout, tendonitis, and muscle strains. They are also used for treatment of headaches, fever, dental and other common painful conditions. Recently, the use of aspirin for prevention of diseases such as myocardial infarction, stroke and cancer has gained attention.

Characteristics

The mechanism of action of NSAIDs is primarily related to inhibition of prostaglandin synthesis (Figure 1).
Arachidonic acid, a 20-carbon fatty acid, is the precursor of the eicosanoids including prostaglandins. Enzymatic action of phospholipase A_2 on cell membrane phospholipids triggers the arachidonic acid cascade. There are two major pathways in the synthesis of eicosanoids. All eicosanoids with ring structures (including prostaglandins, thromboxanes, and prostacyclins) are synthesized through cyclooxygenase pathways. Cyclooxygenase exists in two isoforms, COX-1 and COX-2. Despite structural similarities, they are encoded by different genes and are distinct in their distribution and expression in various tissues. COX-1 is the constitutive isoform; its responsibilities include maintaining gastrointestinal mucosal integrity,



Anti-Inflammatory (Nonsteroidal) Drugs.
Figure 1 Synthesis of prostagandins (PGs) and leukotrienes.

platelet aggregation, and renal blood flow. COX-2 is the inducible isoform involved in inflammation, mitogenesis, and signaling pathways. Alternatively, several lipoxygenases act on arachidonic acid to form leukotrienes and related products. The NSAIDs act primarily by inhibiting the cyclooxygenase enzymes but not the lipoxygenase enzymes. Based on their specificity for the isoforms of the cyclooxygenase, the NSAIDs can be classified in four major groups: highly COX-1, equally COX-1/COX-2, relatively COX-2 and highly COX-2 selective (Table 1).

Aspirin is the most commonly used NSAID and the drug with which all other antiinflammatory drugs are compared. Aspirin is unique among the NSAIDs because it irreversibly and nonselectively inactivates (by acetylating) cyclooxygenase enzymes. The inhibition of cyclooxygenase activity diminishes the formation of prostaglandins at the peripheral target sites and at the thermoregulatory centers in the hypothalamus resulting in strong antiinflammatory and antipyretic effects. Furthermore, reduction of prostaglandin levels results in diminished sensitization of pain receptors to both mechanical and chemical stimuli. Low doses (60–80 mg daily) of aspirin used over many days can irreversibly inhibit thromboxane production in platelets, resulting in reduced platelet aggregation without markedly affecting the prostaglandin synthesis by most tissue.

The therapeutic use of aspirin and other NSAIDs is limited by their significant gastrointestinal and renal toxicity. Normally, prostacyclin (PGI_2) inhibits gastric acid secretion, whereas prostaglandins PGE_2 and $PGF_2\alpha$ stimulate synthesis of protective mucus in both the stomach and small intestine. Inhibition of COX-1 leads to increased gastric acid secretion and diminished mucus protection. The consequences might be epigastric distress, ulceration, and/or hemorrhage. Renal complications of NSAIDs are also related to inhibition of basal COX activity, particularly in the presence of vasoconstrictors such as angiotensin, norepinephrine, and vasopressin. The prostaglandins PGE_2 and PGI_2 are responsible for maintaining renal blood flow under these conditions. A reduction of these can result in retention of sodium and water or hyperkalemia in some patients.

The recently introduced selective inhibitors of COX-2 have strong antiinflammatory properties and reduced gastrointestinal toxicity. However, selective COX-2 inhibitors seem to have the same degree of renal toxicity and increased risk for thrombosis and myocardial infarction as the traditional NSAIDs. Selective COX-2 inhibition suppresses the synthesis of PGI_2 and has no effect on thromboxane(Tx)A_2, shifting the hemostatic balance toward the prothrombotic state. The original paradigm regarding COX-1 and COX-2 might be simplistic as they might share more complex physiologi-

Anti-Inflammatory (Nonsteroidal) Drugs. Table 1 Cyclooxygenase isoform selectivity of NSAIDs (adapted from Cryer and Dubois (1))

Selectivity			
Highly COX-1	Equally COX-1/COX-2	Relatively COX-2	Highly COX-2
Flurbiprofen	Aspirin	Meloxicam	Celecoxib
Ketoprofen	Ibuprofen	Nimesulide	Rofecoxib
Aspirin (low dose)	Indomethacin		
	Naproxen		

cal and pathophysiological roles. A new approach for reducing gastrointestinal and renal toxicity of NSAIDs is by the use of NSAIDs containing nitric oxide (NO) —for example NO-Aspirin. NO has a critical role in intaining the integrity of the gastroduodenal muco- In theory, the NO-NSAIDs have the potential to ıvide the same or better therapeutic effects, includ- ; prophylaxis against myocardial and cerebrovascu- ischemia, with lower level of toxicity.

Immunotoxicity of NSAIDs

Other adverse effects of NSAIDs are associated with sensitivity reactions. The prevalence of NSAID sensitivity ranges from 0.3% to 2.5% in the general population to around 10% in asthmatic patients. Two types of mechanism may account for the induction of NSAIDs sensitivity: allergic reactions (hypersensitivity) and pseudoallergic (idiosyncratic) reactions (Table 2). Allergic reactions are rare and could be cell-mediated or IgE-mediated. They can range from acute ▸ urticaria/angioedema to anaphylactic shock. Usually they are induced by a single drug and starting an alternative NSAID is helpful.

The most common NSAID-related sensitivity is a pseudoallergic (idiosyncratic) reaction, Such reactions mimic allergic reactions, but do not include immune recognition. They are associated with underlying allergic disease, for example asthma or urticaria and excessive production of leukotrienes. They are characterized by cross-reactions to different NSAIDs. Enhanced activity of key synthetic enzymes, perhaps genetically determined, has been implicated in affected people. Furthermore, a trigger event in the pathogenesis is NSAID-induced COX-1 inhibition. The subsequent decrease in the synthesis of prostaglandins, such as PGE_2, an inhibitor of 5-lipooxygenase, results in shifting the balance of the pathway in the direction of excessive leukotriene production. Most of the proinflammatory actions of the leukotrienes are mediated by binding to one of their high-affinity receptors, termed $CysLT_1$. Overexpression of this receptor on inflammatory cells has been proposed as an additional contributory mechanism in NSAID sensitivity. The leukotrienes can produce bronchospasm, increased bronchial hyperresponsiveness, mucus production, mucosal oedema, airway smooth-muscle cell proliferation, and eosinophil recruitment to the airways.

Aspirin-exacerbated respiratory disease (AERD), formerly referred to as aspirin-induced asthma or aspirin intolerant asthma, is the most well characterized and common example of NSAID-related pseudoallergic sensitivity. It is associated with progressive sinusitis, nasal polyposis, and asthma. Small single doses of aspirin, or other nonselective COX inhibitors, may cause rhinorrhea, bronchospasm, and shock symptoms. AERD is seen only in adulthood with higher prevalences in females.

People with NSAID sensitivity can be diagnosed definitively only through provocative tests. NSAID challenge can be by oral, bronchial, or nasal routes. The oral provocation test is one of the most commonly used methods and is the only one available in the USA. If 650 mg is administered without reaction, and the patient is not taking > 10 mg of prednisone or a leukotriene modifier drug, the challenge test is determined to be negative.

The treatment of NSAID sensitivity includes desensitization by repeated administration of increasing doses of the drug until all reactions have disappeared. NSAIDs share the phenomena of cross-desensitization. Acetaminophen (paracetamol), a weak peripheral COX-1 and COX-2 inhibitor (not included in the group of NSAIDs) can be used for analgesic and antipyretic treatment in patients with NSAID sensitivity. However, cross-reactions have been reported at high concentrations of this drug. The selective COX-2 inhibitors and new types of antiinflammatory drugs, including phospholipase A2 inhibitors (benzydamine) and leukotriene modifiers (zileuton and montelukast), might provide an alternative antiinflammatory approach in NSAID sensitive patients.

Aspirin given during viral infections, especially in children, has been associated with increased incidence of ▸ Reye's syndrome, an often fatal, fulminating hepatitis with cerebral edema. Although the pathogenesis of this fatal disease is not well understood, acetamin-

Anti-Inflammatory (Nonsteroidal) Drugs. Table 2 Classification of NSAID sensitivity (adapted from Stevenson et al (2))

Allergic reactions	Cross-reactions after first exposure
Single drug-induced urticaria/angioedema	No
Multiple drug-induced urticaria/angioedema	Yes
Single drug-induced anaphylaxis	No
Pseudoallergic reactions	
NSAID-induced rhinitis and asthma	Yes
NSAID-induced urticaria/angioedema	Yes

ophen is recommended instead of aspirin for children who need medication.

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Anti-Single Stranded (ss) DNA Antibodies

► Antinuclear Antibodies

Anti-Tumor Immunity

► Tumor, Immune Response to

Antibodies, Antigenicity of

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Synonyms

Antibodies, monoclonal antibodies, recombinant antibodies, immunoglobulins.

Definition

Antibodies used for treatment and/or diagnosis of human disease are immunoglobulin molecules of variable origin and structure.

Characteristics

Currently, there are many different types of therapeutic and/or diagnostic antibodies in various stages of clinical use (1,2). Chimeric mouse to human antibodies are recombinant immunoglobulin molecules composed of murine variable and human constant domains. Humanized antibodies are recombinant molecules comprising murine complementarity determining regions (CDRs) grafted onto human immunoglobulin framework. Fully human antibodies produced by recombinant technology or by hybridoma technology in transgenic mice are also in clinical use. Additional variants of therapeutic and/or diagnostic antibodies are represented by recombinant constructs such as monovalent and multivalent antigen binding fragments, single-chain variable fragments, antibodies conjugated with toxins, enzymes, prodrugs and viruses, as well as radiolabeled antibodies or fragments thereof. There are also purified animal and human serum antibodies directed against specific targets or just plain ► immunoglobulins used for various clinical applications.

Major Indications and Efficacy

Thus far, the major therapeutic applications of recombinant antibodies are in oncology and inflammation. There has been successful treatment of breast cancer, colon cancer, and lymphoma by humanized and chimeric antibodies. Chimeric, humanized, and fully human antibodies with anti-inflammatory activity are effective in the treatment of rheumatoid arthritis and psoriasis. Most recently, a humanized anti-IgE antibody has been approved for allergic asthma. Transplantation is another important therapeutic area where a spectrum of antibodies, including mouse ► monoclonal antibodies, human serum antibodies, and recombinant humanized antibodies directed against lymphocytes are used to inhibit graft rejection. Animal antisera against venoms, as well as antibodies that provide passive immunity against microorganisms and/or their toxic products, have been in use for decades. Diagnostic applications of antibodies primarily include detection cancer by the use of radiolabeled ► recombinant antibodies directed against tumor antigens.

Antigenicity

Antigenicity of antibodies depends on several factors that apply to all therapeutic proteins. These include species differences, route of administration, dosing regimen, concomitant therapy, formulation, purity, presence of immunogenic epitope(s) as well as the overall complexity of the molecule (3).

Obviously, the greater the species divergence, the more antigenic are injected antibodies. For example, animal antibodies such as horse anti-venom immunoglobulins or mouse monoclonal antibodies invariably cause a high incidence of antibodies in humans. Conversely, human antibodies cause a strong antibody response in rodents and a less pronounced, but still present, antibody response in non-human primates. It should be pointed out that antigenicity of therapeutic antibodies can be diminished in a number of ways. Recently, horse anti-venom preparations have been replaced by ovine affinity-purified Fab anti-venom

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