

# Pharmacology of Autocoids

1) Know the physiologic effects of the selected autocoids on organ systems where we can pharmacologically modulate their action (histamine, serotonin, prostaglandins, thromboxanes, leukotrienes, prostacyclin).

2) Know the second messengers and signalling system employed by all receptor subtype.

3) For each therapeutic agent described, know:

- receptor subtype(s) the agent interacts with (be familiar with agents that interact with different receptor types and how this is used therapeutically, or contributes to toxicity)
- indications and toxicity

4) For eicosanoids:

- Know critical points in eicosanoid biosynthesis in particular, points and enzymes for synthesis of prostaglandins, prostacyclin, thromboxane, leukotrienes, LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>
- physiologic effects of eicosanoids in certain organs, role of eicosanoids in the pathology of certain disease states, and therapeutic strategies involving eicosanoid biosynthesis and action

Autocoids are substances with biologic activity that are synthesized at the site of action and exert primarily localized effects. They are not stored and released from glands, nor do they need to circulate to the site of action like "classical" hormones.

Receptors for serotonin, histamine, prostaglandins, leukotrienes consist of seven transmembrane domains, the typical structure of G-protein coupled receptors. Receptor subtypes are based on the signalling system utilized which include stimulation or inhibition of adenylate cyclase, or activation of phosphoinositide turnover. Some receptor subtypes are ligand-gated ion channels. The characterization of receptor subtypes and design of subtype-specific agents should be viewed as one of the most significant advances in the development of therapeutic agents.

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## INFLAMMATION

Factors involved in the inflammatory response

### A. Increased blood flow and vascular permeability

- produces redness, heat and swelling at the site of inflammation

### B. Production of Chemical Mediators

1) vasoactive amines - produce an immediate response to tissue damage; already synthesized

- histamine
- serotonin

2) the kinnin system

bradykinnin - the most potent vasodilator; increases permeability of venules, increases sensitivity to pain

B1 and B2 receptors; B2 receptors are constitutively expressed and B1 are induced by inflammation. The transcription factor NF-kappaB may be involved in the induction and mediator of B1 effects.

3) **Arachadonic acid derivatives** - products of cyclooxygenase and lipoxygenase pathways: prostaglandins, prostacyclin, thromboxane, leukotienes

4) **the Complement system** - complement can be directly involved in cell/tissue damage:

C3a - causes mast cell degranulation and histamine release

C5b - C9 - lysis of target cells

C. **Leukocyte chemotaxis/phagocytosis**

1) migration of large numbers of white blood cells to the site of the injury

2) release of lysosomal enzymes

- proteolytic enzymes such as elastase, collagenase, gelatinase cause tissue damage
- Oxygen radicals used to kill bacteria damage host tissues

superoxide anion ( $O_2^-$ ), hypochlorous acid (HOCl) produced by the  $H_2O_2$ - halide-myeloperoxidase system

D. **Nitric Oxide (NO) is produced by the conversion of arginine to citrulline by nitric oxide synthase (NOS)**

NO produced from endothelial cells causes vasodilation through interaction with guanylate cyclase. NO may have pro-inflammatory and anti-inflammatory effects. There is a constitutively active NOS and one induced by inflammation.

- NO may protect against inflammation by scavenging free radicals
- NO may mimic the cytoprotective effects of prostaglandins in the gastric mucosa
- inducible NOS produces NO that increases inflammatory cytokines; inhibition of iNOS ameliorates inflammation
- NO released during airway inflammation
- NO can react with  $O_2^-$  to produce peroxynitrate, which causes tissue damage

#### D. Immune Response

1) humoral - antigens produced to host tissues, antibody-complement interactions

2) cellular

- tissue toxicity from cytolytic T cells that recognize antigens on cells
- delayed hypersensitivity reactions

- production of cytokines that regulate immune response and promote inflammatory reactions. Cytokines (eg. IL-1, IL-6, TNF- alpha, alpha & beta-interferons) can increase prostglandin synthesis.

#### E. Regulation of immune activatable genes by nuclear transcription factors

1) **NFkappaB**- this protein exists in a dormant state in the cytoplasm. A variety of exogenous and endogenous stimuli (infectious agents, xenobiotics, heavy metals, radiation) activate the protein causing its translocation to the nucleus where it upregulates expression of immediate-early phase proinflammatory genes (eg. C-reactive protein, complement proteins, cytokine genes, endothelial surface proteins involved in leucocyte adhesion and chemotaxis).

Its levels have been found elevated in such inflammatory diseases as atherosclerotic disease, rheumatoid arthritis, experimental autoimmune encephalomyelitis, Alzheimer's disease neuronal plaques.

2) **AP-1** - in inflammatory conditions, this protein upregulates the expression of metalloproteinases that are involved in tissue damage (eg. collagenase) and intimately involved in tumor metastasis.

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#### Drugs that interact with Histaminergic Receptors

histamine (beta-aminoethylimidazole)

most compounds with histaminic activity contain the following structure

C C C N or C C C N

N N

Histamine, H<sub>1</sub> and H<sub>2</sub> agonists

#### Receptor-Effector coupling

- H<sub>1</sub> receptors stimulate phosphoinositide turnover and Ca<sup>++</sup> influx
- H<sub>2</sub> receptors stimulate adenylate cyclase resulting in increase cAMP
- H<sub>3</sub> receptors preseynaaptically regulate neurotransmitter release (ACH, dopamine,

GABA, glutamate, norepinephrine, 5-HT)

### Effects on Smooth muscle

- can contract (gut, bronchi), or relax (capillaries)
- hypotension from vasodilation is a combined H<sub>1</sub> and H<sub>2</sub> response
- effects on vasculature produce a flushing, decreased peripheral resistance
- H<sub>1</sub> effect is rapid and transient, H<sub>2</sub> response of slow onset and more sustained. H<sub>1</sub> receptors sensitive to lower histamine concentration
- Histamine can produce shock through hypotension, reduced blood volume by increased vascular permeability, and decreased venous return

### Bronchi

- H<sub>1</sub> contracts bronchi, predominant response; H<sub>2</sub> relaxes bronchi
- Histamine produces bronchospasm in asthmatics

### Heart

- H<sub>2</sub> : increases inotropic (by promoting Ca<sup>++</sup> flux) and chronotropic response (increase diastolic depolarization of the SA node)
- H<sub>1</sub> : slows AV conduction, increases automaticity

Histamine targeting parietal cells is a potent gastric secretagogue, along with acetylcholine and gastrin

activation of H<sub>2</sub> receptors drives a membrane-associated H<sup>+</sup>-K<sup>+</sup> ATPase pump that extrudes protons

Blockade of H<sub>2</sub> receptors **reduces the response to gastrin and Ach from vagal stimulation**

**histamine** causes intestinal muscle to contract

### Stimulation of sensory nerves

- cause pruritis in the epidermis; can produce pain coupled with pruritis in the dermis.

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### **Histamine agonists**

H<sub>2</sub> agonists used for diagnostic procedures in assessing gastric secretory response

Betazole - some residual H<sub>1</sub> activity

impromidine - 10,000 fold greater selectivity for H<sub>2</sub> receptors

### **Histamine Antagonists**

Most H<sub>1</sub> antihistaminics are substituted ethylamines with the following general formula:

R<sup>2</sup>

R<sup>1</sup>-X-C-C-N

R<sup>3</sup>

R<sup>1</sup> - an aromatic and/or heterocyclic group, may be separated from X by a methylene group. Halogen substitution in the para position of the phenyl or benzyl group increase antihistaminic activity.

terminal N of the ethylamine should be a tertiary amine with methyl groups or small cyclic moieties at R<sup>2</sup> and R<sup>3</sup>.

#### **A) Ethylenediamine derivatives**

Nitrogen in the X position

#### **B) Ethanolamine derivatives (aminoalkyl ethers)**

Oxygen in the X-position, substantial anticholinergic actions, sedative effects

**diphenhydramine** - commonly used as a sedative; its anticholinergic effects are of benefit in blocking dystonic reactions of certain antiemetics (phenothiazines); it also possesses antitussive activity

**doxylamine** - a hypnotic commonly used in OTC products

**clemastine** - common in allergy preparations

**dimenhydrinate** - OTC for motion sickness

### **C) Propylamine derivatives (alkylamines)**

Carbon in the X position, cause less sedation, commonly used in cold/allergy preparations

**brompheniramine, chlorpheniramine, triprolidine**

### **D) Phenothiazine derivatives**

Nitrogen as part of the phenothiazine nucleus is in the X position

principal usage as antipsychotic agents; also used as anti-emetics and antipruritics

**promethazine** - many diverse pharmacologic effects

anticholinergic,  $\alpha_1$  antagonist (can produce orthostatic hypotension), dopamine antagonist-increases prolactin release, effect on the CTZ, local anesthetic effect - antiarrhythmic action, decreased corticotropin and growth hormone release

Used as a sedative and an antiemetic in surgery and obstetrics, also in the treatment of hemolytic anemia in newborns

### **E) Piperazine derivatives**

Nitrogen as part of the piperazine nucleus is in the X-position

**bucizine, cyclizine and meclizine** are useful in motion sickness; this probably results from depression of labyrinth excitability, depression of conduction in vestibular-cerebellar pathways. These responses may be due to anticholinergic and CNS depressant effects.

**hydroxyzine** is a sedative, antipruritic, and has some anxiolytic effects

## **F) Second Generation Agents**

Many of the newer (2nd generation) antihistamines are more specific for histamine receptors and are primarily used for allergic rhinitis. They interact less with other receptors (less anti-cholinergic effects; less sedation) and have longer durations of action.

**terfenadine, astemizole, loratidine, cetirizine, acrivastine**, are highly effective but more expensive than older agent for allergic rhinitis. All of them require prescriptions.

**terfenadine and astemizole can cause arrhythmias, particularly with drugs that compete with their hepatic metabolism. Both drugs have been taken off the market.**

**levocabastine** - an H<sub>1</sub>-specific topical ophthalmic agent used to block histamine effects in allergic conjunctivitis

## **Inhibitors of mast cell degranulation and histamine release**

**Cromolyn sodium** - prophylaxis for asthma

- Believed to inhibit calcium influx required for histamine and leukotriene release by inhibiting mast cell degranulation, poor oral absorption, administered by inhalation
- available over-the-counter for allergic rhinitis

**Nedocromil** - mechanism similar to cromolyn; stabilizes other inflammatory cells such as eosinophils, macrophages, neutrophils, platelets

Both cromolyn and nedocromil are administered by inhalation for prophylaxis of asthma.

**Lodoxamide tromethamide** - prevents antigen-induced calcium influx into mast cells that causes histamine release; may also interfere leukotriene production.

Used topically for inflammatory diseases of the eye (eg. conjunctivitis)

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## **H<sub>2</sub> Receptor Antagonists**

A remarkable degree of specificity for Gastric H<sub>2</sub> receptors

### **H<sub>2</sub> antagonists can inhibit responses to all 3 gastric secretagogues**

- Initially these agents maintained the imidazole of histamine but with bulky subgroups attached (eg. cimetidine). The imidazole ring is not essential and other ring structures are found.
- Ranitidine has a substituted furan ring
- Famotidine has a guanidine substituted thiazole ring

Many drug interactions from cimetidine result from this drug's ability to bind to cytochrome P-450 and thereby inhibit the metabolism of drugs that use mixed-function oxidases (eg. theophylline, phenytoin, warfarin, lidocaine, some tricyclics and benzodiazepines). Newer H<sub>2</sub> blockers have reduced interactions with P-450.

**Zollinger Ellison syndrome** - a tumor of the pancreas producing excessive quantities of gastrin; beneficial response from high doses of H<sub>2</sub> antagonists

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### **Drugs that interact with the Serotonergic System**

- synthesis of serotonin from tryptophan
- storage and uptake mechanism
- Removal of serotonin

-high affinity re-uptake sites; **\*\*target for therapeutic agents**

### **Pharmacologic actions**

serotonin has profound effects on gastrointestinal, cardiovascular, respiratory, and central and peripheral nervous system function

#### **Pharmacologic actions includes:**

- effects respiratory minute volume and rate
- bronchoconstriction in asthmatics
- increase in motility of small intestine, variable effects on stomach and large intestine
- vasoconstriction in renal and splanchnic beds, placental, uterine, umbilical, and to a lesser degree, pulmonary vessels. This classical response accounts for the synonym "serotonin" for 5-HT
- vasodilation of skeletal muscle beds
- the positive inotropic and chronotropic effects of 5-HT are usually blunted by effects on the baroreceptors, chemoreceptors and vagal efferents that result in bradycardia
- stimulation of sensory nerves, can contribute to pain responses
- stimulation of Autonomic ganglia
- stimulation of catecholamine release from the Adrenal gland
- 5-HT is a neurotransmitter in the CNS and is responsible for diverse

## psychoneurologic effects

- 5-HT congeners (eg. tryptamines, LSD) have hallucinogenic effects
- cell bodies of serotonergic nerves found in the raphe nucleus involved in temperature regulation, sleep-wake cycles, blood pressure and various behaviors (normal and abnormal)
- HPA regulation; 5-HT can possibly regulate release of ACTH, growth hormone, prolactin, lutenizing hormone, FSH, TSH
- enterochromaffin cells in the gut release 5-HT. Tumors of these cells (carcinoid tumors) release large quantities of 5-HT producing severe diarrhea and abdominal cramps.

## **Serotonin receptor subtype pharmacology and therapeutic agents**

The identification of serotonin-subtypes and their actions has had a tremendous effect on expanding therapeutic agents that are pharmacologically specific with reduced non-specific adverse effects.

### **5-HT<sub>1</sub> Receptors**

- Agonist binding to these receptors results in the inhibition of adenylate cyclase via the inhibitory GTP-binding protein (G<sub>i</sub>).

### **5-HT<sub>1A</sub> receptors**

- These receptors also regulate K<sup>+</sup> channels via a G-protein.
- Effects in generalized anxiety

**Buspirone** - partial-agonist for 5-HT<sub>1A</sub> receptor, the first specific non-benzodiazepine anxiolytic

Agonists of this receptor subtype may be useful in depression, alcohol consumption, substance abuse craving, appetite regulation and hypertension

**Ibogaine** - an indol alkaloid from the African herb *Tabernathe iboga* a serotonin antagonist, a hallucinogen in high doses used in religious ritual by certain ethnic groups in Gabon.

- The drug is in clinical trials in the U.S. for alleviating the craving of abused substances (eg. cocaine, amphetamine, etc.). May have utility in alcohol and nicotine addiction. Some studies suggest neurotoxicity as a possible adverse effect with repeated use.

### **5-HT<sub>1B</sub> receptor subtype**

- species specific; has not been identified in the human brain. The 5-HT<sub>1D</sub> receptor may be the analogue of the 5-HT<sub>1B</sub> subtype in humans

### **5-HT<sub>1D</sub> Receptor**

**Sumatriptan** - used in acute treatment of migraine headaches

- a highly selective agonist of the 5-HT<sub>1D</sub> subtype receptor located on peripheral trigeminal nerve terminals that supply pain-sensitive vascular and meningeal structures. Produces contraction of the large intracranial arteries.

Actions related to anti-migraine efficacy

- Sumatriptan blocks the neuropeptide-mediated inflammatory response after trigeminal stimulation and may block trigeminal neurotransmission.
- vasoconstriction of intracranial arteries

**Zolmetriptan, Naratriptan** - Chemically related to sumatriptan, these agents have increased bioavailability, longer half-lives, and cross the blood-brain barrier.

**Rizatriptan** is the most recently introduced member of this class.

### 5-HT<sub>2</sub> and 5-HT<sub>1C</sub> receptors

These receptors share a common mechanism whereby agonist stimulation leads to turnover of phosphoinositides and production of arachidonic acid and its metabolites. These receptors also regulate Cl<sup>-</sup> channels via a G-protein.

5-HT<sub>1C</sub> receptor identified by molecular biological techniques; no receptor-specific ligands yet.

### 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors

These receptors are present in smooth muscle (vasculature, gut, uterus) and there appear to be site in the cerebral cortex and the caudate nucleus

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### Ergot Alkaloids and derivatives

from the fungus *Claviceps purpurea* that grows on rye and other grains, ergot alkaloids are derivatives of the tetracyclic compound 6-methylergoline. Ergot alkaloids have long been recorded for their toxic effects throughout the world. They has long been recognized as an abortifacient and poisonings produced an intense burning sensation and grangrenous condition in the limbs as a result of persistent peripheral vasoconstriction. In general, these drugs are not specific for serotonin-receptor subtypes, and this may contribute to some of their adverse effects.

The interaction of ergot alkaloids with serotonergic receptor systems is variable and complex, with some compounds acting as partial agonists in some tissues and as antagonists in others. Interaction with other receptor types such as alpha adrenergic and dopaminergic can contribute to both therapeutic and adverse effects of ergot.

**Ergotamine and dihydroergotamine** have high affinity but poor selectivity for antagonizing 5-HT<sub>1</sub> receptors. Notably, they have a biphasic effect on alpha<sub>1</sub> receptors stimulating them at low concentrations and competitively blocking them at

higher concentrations. They also block the reuptake of norepinephrine which contributes to vasoconstrictor response. They are used for the **treatment** of migraine. Ergotamine is can be administered orally, sublingually, and nasally, but is best absorbed rectally. Dihydroergotamine is administered intravenously, can be given subcutaneously. Dihydroergotamine stimulates the chemoreceptor trigger zone (CTZ) and may require an antiemetic (usually a phenothiazide).

**Methysergide** a semi-synthetic ergot alkaloid is a 5-HT<sub>2</sub> antagonist with greater potency than ergotamine and dihydroergotamine that is used for migraine **prophallaxis**.

**Ergonovine and methyl ergonovine** produce uterine contractions and contraactions of other smooth muscles. Have partial-agonist and/or antagonistic actions depending on the tissue type. Used for the prevention and treatment of postpartum and postabortion hemorrhage.

### **Ergot poisoning**

- acute poisoning - vomiting, diarrhea, thirst, tingling, itching, coldness of the skin, weak pulse, confusion, unconsciousness
- chronic poisoning - cold, numb extremities, circulatory disturbances, gangrene, headache, nausea, vomiting, diarrhea, confusion, drowsiness

**Ketanserin** - the first selective 5-HT<sub>2</sub> antagonist, a prototype for a series of serotonin-antagonists

also recognizes alpha<sub>1</sub>, histamine H<sub>1</sub> and dopaminergic receptors

Can lower BP by inhibition of 5-HT-induced vasoconstriction, but antagonism of other receptor systems are probably involved in this response as well. May inhibit central adrenergic outflow.

Ketanserin is available for BP therapy outside of the U.S. and is in phase III clinical trials here. It is also being tested in trials for peripheral vascular disease.

**Cyproheptadine** - antagonist of 5-HT<sub>2</sub> receptors; also produces histamine H<sub>1</sub> receptor blockade (structurally similar to phenothiazines), and weak anticholinergic effects

used to treat Carcinoid tumors.

### 5-HT<sub>2</sub> receptors have a role in depression and anxiety

**Risperidone**, a new antipsychotic blocks 5-HT<sub>2</sub> receptors; it also has significant activity antagonizing D<sub>2</sub>-Dopaminergic receptors (but less than Haldol). Also, there is weak interaction with alpha 1 and 2 adrenergic receptors, and H<sub>1</sub>-Histaminergic receptors. It improves positive (unusual thoughts, hallucinations, conceptual disorientation, paranoia) and negative (blunted affect, emotional and social withdrawal, poverty of speech) symptoms. Its weaker affinity for D<sub>2</sub>-dopaminergic receptors may account for the lower incidence of extrapyramidal symptoms.

### 5-HT<sub>3</sub> Receptors

This receptor subtype is an ligand-gated ion channel for K<sup>+</sup> and Na<sup>+</sup>.

5-HT<sub>3</sub> receptors are located peripherally on vagal nerve terminals and centrally at the Chemoreceptor Trigger zone (CTZ). Antagonists of these receptors are potent inhibitors of chemotherapy and radiation -induced emesis. **Ondansetron and Granisetron** are currently available in the U.S. as anti-emetics. These drugs are very specific for the serotonin receptor subtype and therefore do not produce the adverse effects of other anti-emetics that interact with other receptors (serotonergic, dopaminergic, adrenergic, histaminergic, etc.)

### 5-HT<sub>4</sub> receptors

These receptors are positively coupled to adenylate cyclase, opposite of 5-HT<sub>1</sub> receptors; they can also modulate voltage sensitive potassium channels via a G-protein.

Found in high density in the myenteric plexus

**Cisapride** is a specific 5-HT<sub>4</sub> receptor agonist, similar to metoclopramide but with much weaker dopaminergic action. It also enhances release of Ach from nerve terminals in the myenteric plexus. It is a prokinetic agent that enhances and promote motility in the GI tract. It relieves Gastroesophageal reflux disease by increasing lower esophageal sphincter pressure.

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### 5-HT Reuptake Inhibitors

Many drug useful ass antidepressant block the reuptake of serotonin. These include many tricyclic agents (eg. amitrytilline, nortritylline, imipramine) which may also inhibit catecholamine reuptake. Newer agents include **fluoxetine, sertraline, fluvoxamine, paroxetine, venlafaxine, and citalopram**. These drugs have no effect on norepinephrine uptake, and interact minimally with cholinergic, dopaminergic and adrenergic systems.

**Fenfluramine, dexfenfluramine** - a halogenated amphetamine that may have a toxic effect on serotonergic-neurons. Brain serotonin is depleted and enzymes involved in synthesis and transport of serotonin are also depleted. The drug promotes weight loss by suppressing appetite. These drugs were removed from the market primarily for their cardiovascular toxicity and pulmonary hypertension. **Sibutramine**, a congener of the halogenated amphetamines recently approved for obesity, inhibits the reuptake of both serotonin, norepinephrine and to some degree, dopamine.

## **Arachidonic Acid Metabolites: Prostaglandins, Prostacyclin, Thromboxane A<sub>2</sub>, Leukotrienes**

Eicosanoids - derived from 20 carbon essential fatty acids

arachidonic acid is the most common precursor of eicosanoids, derived from linoleic acid, hormone-regulated biosynthesis of eicosanoids involves receptor-G-protein mediated activation of phospholipase A<sub>2</sub>.

prostaglandins - cyclopentane ring

thromboxane - six-membered oxane ring

**PGH synthase** - this enzyme has two catalytic activities; a cyclooxygenase function that converts arachidonic acid to the cyclic endoperoxide-hydroperoxide, PGG<sub>2</sub> and a peroxidase activity that converts the hydroperoxide to the PGH<sub>2</sub>. PGH<sub>2</sub> is the direct precursor of prostaglandins, thromboxane, and prostacyclin. Inhibition of cyclooxygenase inhibits production of all these metabolites. Since these compounds often produce opposite clinical responses, specific inhibition of their synthesis has obvious clinical advantages. Thromboxanes are produced by **thromboxane synthase**; prostacyclin produced by **prostacyclin synthase**.

Non-steroidal anti-inflammatory drugs (NSAID) inhibit cyclooxygenase

**5-lipoxygenase** - catalyzes the production of hydroxylated straight chain fatty acid derivatives of arachidonic acid. HPETE metabolized to LTA<sub>4</sub>, precursor for LTB<sub>4</sub>. LTA<sub>4</sub> also the substrate for **LTC<sub>4</sub> synthase** (glutathione-S-transferase) catalysis to cysteinyl derivatives LTC<sub>4</sub> and LTD<sub>4</sub>, first described as the "slow reacting substance of anaphylaxis".

- 5-lipoxygenase requires the presence of 5-lipoxygenase activating protein (FLAP) to become catalytically active
- inhibition of cyclooxygenase can lead to increased production of leukotrienes

### **Classification of Prostanoid Receptors (IUPHAR)**

PGD<sub>2</sub> stimulates adenylate cyclase inhibits platelet aggregation

- vasodilatation
- myometrial relaxation

PGE<sub>2</sub> phosphoinositide hydrolysis (EP1) smooth muscle relaxation

- stimulation of adenylate cyclase (EP2) stabilization of mast cells
- smooth muscle relaxation
- inhibitors of granulocytes
- inhibition of adenylate cyclase/ smooth muscle contraction

phosphoinositide hydrolysis (EP3) inhibition of gastric secretion

- stimulation of adenylate cyclase (EP4) inhibition of lipolysis
- vasodilatation
- inhibition of T-lymphocytes

PGF<sub>2a</sub> phosphoinositide hydrolysis smooth muscle contraction(uterus)

PGI<sub>2</sub> stimulation of adenylate cyclase vasodilatation

- (prostacyclin) inhibits platelet aggregation
- sensitization of sensory neurons

TBX phosphoinositide hydrolysis vasoconstriction

- (thromboxane) bronchoconstriction
- platelet aggregation

Some pharmacologic properties of eicosanoids - These compounds show a remarkable degree of diversity in biologic activity with some responses being tissue and species dependent. Effectors of eicosanoid action may target their receptors (antagonists) or inhibit their synthesis.

### **Vasculature**

Most PGEs are potent vasodilators, Prostacyclin (PGI<sub>2</sub>) is a potent vasodilator producing hypotension (leading to reflex tachycardia). Angiogenesis in tumors and increased vascularity in rheumatoid joints appears to be mediated by COX2 (discussed below). Thromboxane A<sub>2</sub> is a potent vasoconstrictor. Leukotrienes LTC<sub>4</sub> and LTD<sub>4</sub> cause capillary leakiness.

**Alprostadil** (PGE<sub>1</sub>) dilates the ductus arteriosus improving pulmonary blood flow in neonates with heart defects. It has recently been approved for use in impotence.

### **Platelets**

- PGI<sub>2</sub> inhibits platelet aggregation, TXA<sub>2</sub> is a platelet activator
- LTB<sub>4</sub> chemotaxis of PMN, eosinophils, monocytes, neutrophils
- prostaglandins generally inhibit cellular and humoral immunity

### **Lung**

- prostaglandins have mixed effects on bronchial muscle
- TXA<sub>2</sub> constricts bronchial muscle, **TXA<sub>2</sub> receptor antagonists in asthma**
- inhibitors of thromboxane synthase block production of thromboxane and reduce the early and late allergic and bronchoconstrictive response to allergen-induced asthma. Studies confirm the clinical efficacy of thromboxane synthase inhibitors. Inhibition of thromboxane synthase has the additional benefit of increasing the production of the vasodilator prostacyclin.
- LTC<sub>4</sub> and LTD<sub>4</sub> potent bronchoconstrictors; 1000 x > histamine
- They also produce mucosal edema, and increase microvascular permeability which contribute to the pathology of airway disease.
- LTB<sub>4</sub> causes neutrophil chemotaxis/aggregation and the release of enzymes and inflammatory mediators.
- 5-lipoxygenase inhibitors - should be the best approach since the production of both bronchoconstrictors and leukokines is blocked.

**Zileuton (Zyflo)**- a 5-lipoxygenase inhibitor for use in asthma

Inhibition of CYP3A4 may result in drug interactions. Monitor hepatic transaminases particularly during the first two months of therapy.

Peptidyl leukotriene receptor antagonists - **Zafirlukast (Accolate), Montelukast (Singulair)**

Zafirlakust should be administered on an empty stomach; potential for drug interactions due to inhibition of CYP2C9 and CYP3A4.

Montelukast doesn't causes inhibition of p450's and can be taken with or without food. It can be used in patients as young as six years.

## **Uterus**

Certain Prostaglandins cause uterine contraction in pregnancy

clinically used as abortifacients or to induce labor

**Dinaprostone (PGE<sub>2</sub>) and Carboprost (15-methyl-PGF<sub>2a</sub>)**

## **GIT**

PGEs and PGI<sub>2</sub> inhibit gastric acid secretion, stimulated by feeding, histamine or gastrin

Maintainance of the gastric mucosa - stimulation of mucus secretion

**misoprostol** (substituted PGE<sub>1</sub>) used for NSAID-induced gastritis; administered intra-vaginally with methotrexate (oral) for non-surgical abortion

In inflammatory bowel disease, neutrophil infiltration and degranulation in injured colonic mucosa contribute to the pathology. Clinical trial have shown the efficacy of LTB<sub>4</sub> receptor antagonists.

**Dermatologic** - neutrophil infiltration of epidermal skin lesions contribute to the pathology of psoriasis. LTB<sub>4</sub> receptor antagonists, and 5-lipoxygenase inhibitors have shown efficacy in clinical trials in psoriasis.

PGE<sub>2</sub> and PGI<sub>2</sub> increase renal blood flow, inhibition of their synthesis (eg. NSAIDs) can compromise renal blood

### **Plasma Kinnins**

- Bradykinin named for its ability to produce a slow ("brady") contraction of the gut. Also observed to lower blood pressure.
- Bradykinnin - Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg
- lysyl-Bradykinnin (kallidin)
- kinnins are released from high molecular weight protein precursors by proteolytic enzymes called kallikrein
- kinnins degraded by kinninase II, angiotensin converting enzyme

### **Pharmacologic effects of kinnins**

- Plasma kinins are the most potent vasodilator autacoids
- 10X more potent than histamine
- large arteries and most veins are contracted by bradykinnin
- - increase capillary permeability, produce edema
- - involved in pain responses
- Contract bronchioles in asthmatics, involved in the late bronchoconstrictor response which may be important to the etiology of chronic asthma. In animal models, bradykinnin receptor peptide antagonist reduce the late bronchial responses and additionally reduced levels of leukotrienes, TXA and PGs
- Because of the extremely short half-life, kinins are not used clinically
- Augmenting kinnin responses
- prevent their degradation, ACEI can do this (Kinninase II) but this produces minimal clinical response

Blocking kinnin action

- receptor antagonists
- inhibitors of kallikrein - no kinnin production

*aprotinin* - a protease inhibitor, used in treating acute pancreatitis, carcinoid syndrome and other inflammatory states with excessive kinnin production



## **INHIBITORS OF CYCLOXYGENASE**

- Non-steroidal Anti-inflammatory Drugs (NSAIDs)
- Inhibit the production of eicosanoids by inhibiting cyclooxygenase

### Two isoforms of cyclooxygenase (COX):

COX-1 - present in blood vessels, platelets, stomach and kidney

COX-2 - induced by inflammatory cytokines and mediators; expressed in tumors and regulates angiogenesis, vascular proliferation in rheumatic joints

### **Common Pharmacologic Actions of NSAIDs**

With some variations, many of the NSAID's possess all of the pharmacologic actions

- Analgesia - prostaglandins sensitize pain receptors

to mechanical stimuli and chemical mediators

- Anti-inflammatory - primarily through effect on cyclooxygenase but some NSAIDs have additional actions as well

- Inhibition of Platelet Aggregation - inhibition of platelet cyclooxygenase blocks the production of thromboxane A<sub>2</sub>. Aspirin irreversibly acetylates platelet cyclooxygenase. The platelet has little capacity to synthesize new cyclooxygenase, so a single dose can inhibit activity for the life of the platelet (8-11 days).

- Anti-pyretic - prostaglandins that mediate effect of endogenous pyrogen

- Uricosuric - these drugs are organic acids, they have dose dependent effects on urate excretion. Low doses may decrease excretion and enhance plasma urate, large doses produce uricosuria.

### **Indications**

These drugs relieve inflammation and pain associated with inflammatory disease but do not alter the course or progression of the disease.

### **Common Toxicities of NSAIDs/Salicylates**

#### **Gastrointestinal**

- constipation, heartburn, abdominal pain, colitis, GI bleeding, gastritis. NSAID-induced GI complications may be life-threatening.
- Drugs that predominantly inhibit COX-2, with little activity on COX-1 cause less GI effects (eg. nabumetone, celecoxib, rofecoxib).
- NO-aspirins - can inhibit COX but also release NO, which mimics prostaglandins in their cytoprotective effects of the GI mucosa.
- monitor for GI complaints, occult blood in stool (guaiac test), anemia suggesting GI bleeding

## Renal

In patients where there is a decrease in renal blood flow (decrease in blood volume or primary renal disease), there is a compensatory activation of Angiotensin II and sympathetic systems which produce vasoconstriction. PGE2 and PGI2 are required to maintain adequate renal perfusion and natriuresis.

Decreased renal blood flow, decreased glomerular filtration rate -fluid retention and weight gain, sodium and potassium retention, increased BUN and creatinine

Analgesic nephropathy - papillary necrosis with subsequent interstitial nephritis

## Neurologic

- tinnitus and hearing loss (this is a dose related effect with aspirin and an indicator of toxicity). usually reversible
- cholestasis, jaundice, hepatitis, elevations in liver function tests (borderline elevations may occur in up to 15% of patients treated with NSAID's)
- dermatologic reactions
- thrombocytopenia, leukopenia, anemia
- headache, dizziness, nervousness, drowsiness, irritability, fatigue

## Common drug-drug interactions of NSAIDS

- displacement of other highly protein bound drugs
  - eg. anticoagulants, hypoglycemics
- effects on renal excretion
  - eg. uricosurics, methotrexate
- Drugs that potentiate NSAID adverse effects
  - eg. nephrotoxins, GI irritants

## Salicylates

- esters or salts of salicylic acid
- Salicylic acid from the bark of the Willow tree

In aspirin, pharmacologic activity results from both the salicylate moiety and the acetate component.

Aspirin, but not other salicylates, irreversibly acetylates platelet cyclooxygenase and inhibits platelet aggregation.

In addition to inhibitory effects on cyclooxygenase, other mechanisms may include:

- inhibition of leukocyte migration
- stabilization of lysosomal enzymes
- interference of antigen-antibody interactions

Salicylate and acetylsalicylate (aspirin) inhibit the activation of NK-kappaB proinflammatory genes at higher concentrations than they inhibit cyclooxygenase. This may explain why higher concentrations of salicylates are required for their anti-inflammatory effects (in addition to the relatively low selectivity for COX-2).

### **Metabolism**

glycine conjugate, phenolic glucuronide, acyl glucuronide, gentesic acid. The liver has a limited ability to form the glycine conjugate, and the phenolic glucuronide. At high doses a greater percentage of the drug is excreted unchanged.

### **Elimination**

At low doses, elimination is first order; T<sub>1/2</sub> about 3 hr.

at higher doses, metabolism is saturable, therefore with increasing doses there is a greater than proportional increase in steady-state serum concentrations. The serum half-life also increases and correspondingly, the time to reach steady state is increased.

### **Salicylate Toxicity**

- neurologic symptoms - tinnitus and hearing loss, impaired vision, headache, vertigo, confusion, drowsiness
- increased heart rate
- hyperventilation

metabolic acidosis - due to salicylate interference with carbohydrate and amino acid metabolism, also as a result of phosphoric and sulfuric acids accumulating secondarily to salicylate-induced renal impairment

respiratory alkalosis - due to respiratory stimulation and hyperventilation

Treatment is symptomatic and supportive. Further absorption of the drug should be blocked. Fluid, electrolyte and acid-base disturbance should be corrected, and the elimination of the drug should be enhanced (alkalinization of the urine).

### **Dosing of Aspirin**

- anti-platelet effects 81 mg (baby aspirin) - 365 mg
- analgesia and anti-pyretic effects 650 mg - 1000 mg
- anti-inflammatory effects 3 g - 6 g

buffered aspirin - buffering may enhance dissolution and reduced GI irritation due to local effects

enteric coated aspirin - absorption may be erratic but once steady-state is achieved, regular dosing maintains steady blood levels

### Other Salicylates

**methyl salicylate, diflunisal, salsalate, sulfasalazine**

**Amino-salicylates - they are poorly absorbed but are active for treatment of inflammatory bowel disease**

**- 5-aminosalicylic acid**

**- sulfasalazine - metabolism by gut bacteria releases 5-amino salicylic acid; used for inflammatory bowel disease and rheumatoid arthritis**

**Non-salicylate NSAIDS - reversible, competitive inhibitors of COX**

**Propionic acid derivatives Indole derivatives**

- ibuprofen indomethacin
- naproxen sulindac
- fenoprofen
- flubiprofen **fenamates**
- ketoprofen mefenamic acid
- meclofenamate
- bromfenac

**Pyrazalone derivative pyrrole acetic acid derivative**

- phenylbutazone tolmetin
- oxphenbutazone
- **oxicams**
- **cyclic propionic acid derivative** piroxicam
- ketorolac

Selection of NSAIDS is largely empirical. Unless there are special considerations or contraindications, almost any agent can be tried. If no response is obtained, or if the drug loses activity later in therapy, switch to another agent. NSAID's can be used in combination often providing an increased response, but toxicities may be increased.

**Special features**

**Sulindac** - a prodrug that is metabolized to the active compound, sulindac sulfide. An enzyme in the kidney converts the drug back to the inactive parent compound. It has therefore been suggested that sulindac has a sparing effect on renal prostaglandins. In patients with renal disease, some studies show sulindac not compromising renal function, but many studies fail to show this effect. There is still the possibility that sulindac may effect kidney function less than other NSAID's, the drug should be used with caution in at-risk patients.

Sulindac and its metabolites (the sulfide and sulfone) inhibit the nuclear translocation of NF-kappaB, which contribute to anti-neoplastic effects and promote apoptosis in colon and other tumor cells.

## NSAIDS with relative selectivity for COX-2

These drugs seem to produce relatively fewer adverse GI and renal effects as a result of their selectivity

**meloxicam** - an agent with clinical anti-inflammatory activity available in Europe

**nabumetone** - a COX-2 selective agent recently approved for use in the U.S

**celecoxib** - in addition to very good effects in Rheumatoid arthritis, this drug has also been used in cancer trials due to its anti-angiogenic action.

**rofecoxib** - greater COX-2 selectivity

special indications

**In Neoplastic disease** - Epidermal Growth Factor (EGF) involved in pathogenesis of tumors in epithelial tissues causes increased production of PGE2 through activation of COX2. PGE2 stimulates growth of epithelial tumors. NSAIDS are being used both in prevention and treatment of certain tumors (colon cancer, small-cell lung carcinoma, breast carcinoma)

## Patent ductus arteriosus

indomethacin

phenylbutazone, oxphenylbutazone - high risk for aplastic anemia, safer agents used more frequently

Over-the counter products

- aspirin
- ketoprofen - orudis
- naproxen - aleve
- ibuprofen - advil, nuprin

## Analgesics

### Coal Tar derivatives

Acetanilide introduced into medicine for treating fevers, but very toxic. Para-aminophenol, believed to be the active metabolite of acetanilide was tried but toxicities weren't lessened. Two derivatives of p-aminophenol were found useful, phenacetin (DC'd in the U.S. because it was implicated in analgesic abuse nephropathy) and acetaminophen (paracetamol; N-acetyl-p-aminophenol, tylenol).

**Acetaminophen** - anti-pyretic and analgesic activity equivalent to aspirin

- no anti-inflammatory activity of clinical utility, no anti-thrombotic effects
- less side-effects than aspirin

**metabolism** - the drug undergoes hepatic conjugation with glucuronate (60%), sulfate (35%), or cysteine (3%).

A small amount undergoes N-hydroxylation by P-450 producing N-acetylbenzoquinoneimine. This reactive species normally targets sulfhydryl groups of glutathione. In acetaminophen overdose, elevated levels of the reactive species deplete the pools of glutathione and the compound reacts with sulfhydryl groups of hepatic proteins producing necrosis. Administration of N-acetyl cysteine replenishes glutathione.

## **Osteoarthritis**

Etiology is complex but inflammation plays a minor role. A recent hypothesis suggests that mitochondrial degeneration lead to chondrocyte death in the synovium. This is the major form of arthritis and the major risk factor is increased age.

Appears to involve an imbalance between cartilage degradation and repair by chondrocytes. Normally, cartilage degradation results in increased synthesis of proteoglycans and collagen. Components of proteoglycans include keratin sulfate, chondroitin sulfate, and hyaluronic acid.

## **Pharmacologic management**

- acetaminophen - drug of choice
- also NSAIDS (including COX-2 selective)
- intra-articular steroids (methylprednisolone, triamcinolone acetonide)

### Topical agents

- Capsaicin - selective desensitization of sensory neurons
- methyl salicylate
- tolamine salicylate

Capsaicin, derived from chili peppers, has been recently shown to bind to vanilloid receptors (VR-1) on nociceptive nerve fibers, inducing the influx of cations. The receptors also respond to heat and protons from low pH, both being conditions characteristic of inflamed tissues.

### Dietary supplements that may have substantiated efficacy

1. chondroitin sulfate- involved in hydration of proteoglycan complex and shock-absorbing properties of cartilage. Orally administered supplements concentrate in cartilage tissue
2. glucosamine - rate limiting agent in glycosaminoglycan synthesis. May be superior or at least comparable to some NSAIDS for pain relief in long term-therapy. Oral bioavailability is about 25%

Exercise, weight loss and physical therapy when necessary should be part of the regimen for managing the disease.

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## **Disease-Modifying Drugs in Inflammatory/Autoimmune Disorders**

These agents can slow progressive joint destruction to varying degrees. In most cases, their therapeutic effects may require weeks to months. Patients should be maintained on NSAIDs.

### **Antimalarials**

#### **chloroquine, hydroxychloroquine, quinacrine**

These drugs have the ability to slow the progression of inflammatory diseases. In some instances, they can induce remission of disease.

#### **Mechanism of action**

The precise mechanism of the anti-inflammatory effect is unknown.

Possible mechanisms include:

1. inhibition of chemotaxis of polymorphonuclear phagocytes, macrophages, eosinophils
2. may inhibit conversion of arachidonic acid to prostaglandin F<sub>2</sub>
3. may antagonize histamine and serotonin
4. may inhibit production of inflammatory cytokines
5. may interfere with immunoglobulin production/interactions
6. binding to nucleoproteins which can suppress LE cell factor
7. inhibits production of rheumatoid factor and acute phase reactants
8. stabilizes lysosomal membranes

#### **Indications**

- Rheumatoid arthritis
- Systemic Lupus Erythematosus
- Discoid lupus erythematosus
- Polymyositis
- Dermatomyositis - combination anti-malarials

#### **Toxicities**

1. Ophthalmic - visual disturbances such as blurred vision, difficulty in focusing or accommodation, reversible after discontinuing drug. Retinopathy is most serious effect, dose-related; seldom becomes a problem if dosage maximum isn't exceeded. Pts. should have fundoscopic exam every 4-6 months. Hydroxychloroquine is produced as a racemic mixture and only the R-isomer is responsible for toxicity.
2. GI upset - usually reduced by administering the drug with food.
3. Disturbances in conduction - more common with chloroquine

- peripheral neuropathy
- EKG changes (T wave depression, widening of the QRS complex)
- dermatologic

### **Organic Gold Compounds**

Gold compounds are used to induce remission or slow progression in rheumatoid arthritis. They should be used early in the course of progressive disease; not in mild disease or advanced disease.

### **Mechanism of Action**

The actual mechanism of action is unknown, but related to suppression monocyte phagocytic function and T-cell function.

The high affinity that gold has for sulfur suggests that it might inhibit sulfhydryl enzyme systems.

Other possibilities include:

- inhibition of leukocyte migration
- decreased antibody-cellular toxicity/antibody-complement interactions
- interference with cell-mediated responses
- inhibition of phagocytosis

Injectable Preparations

### **aurothioglucose, gold sodium thiomalate**

Oral preparations

### **auranofin**

### **Toxicities**

- Dermatologic manifestations - a variety of reactions involving skin and mucous membranes. Often if the drug is discontinued, it can be restarted later without further complications.
- Nephrotoxicity - damage to the proximal tubules causes proteinuria; membranous glomerulonephritis. Most renal toxicity is reversible after discontinuing the drug.
- Hematologic - thrombocytopenia, leukopenia, agranulocytosis

Oral gold produces less severe and less frequent toxicities (dermatologic, hematologic and renal) than the parenteral preparations, but there is a high concentration of GI upset that sometimes necessitate discontinuing therapy.

### **Azathioprine**

A purine antagonist antimetabolite with immunosuppressive activity.

It is used in therapy for severe active and erosive rheumatoid arthritis after anti-malarials and or gold have been tried. The drug's anti-inflammatory effect is probably related to suppression of cell-mediated responses from T-lymphocytes and possible suppression of antibody responses.

In patients on steroid therapy, azathioprine reduces steroid requirements. Patients should be closely monitored for toxicity.

### **Toxicities**

- leukopenia, macrocytic anemia, pancytopenia, thrombocytopenia
- GI upset - diarrhea, nausea and vomiting, anorexia
- hepatotoxicity may develop especially in allograft recipients

### **Methotrexate**

Inhibits dihydrofolate reductase. Mechanism of action in inflammatory disease is not known but may involve inhibition of lymphocyte multiplication.

Oftentimes, patients can be maintained on intermittent dosing (eg. 7.5 mg for three doses, once a week). The response to methotrexate may wane after one-two years of therapy.

### **Toxicities**

Hematologic - leukopenia, thrombocytopenia

GI - stomatitis, glossitis, gingivitis, pharyngitis are among the most common adverse effects. Folate can be administered without interfering with therapeutic response. Topical vitamin E has been used and mouthwashes containing local anesthetics and a cytoprotective agents (dissolved sucralfate) provide immediate relief and help the healing.

Pneumonitis manifesting initially as a persistent dry cough can be fatal. It can occur at any dose.

Liver Toxicity - Transient elevations in aminotransferases are not uncommon and do not necessitate discontinuance of the drug. Fatal hepatotoxicity can occur. Some clinicians recommend regular biopsies since progression to fatty infiltration, portal inflammation or fibrosis are often not preceded by changes in liver function tests.

**Cyclophosphamide** - antineoplastic alkylating agent, drug of choice for the treatment of SLE Nephritis. May be combined with steroid, reducing dosage.

### **Laboratory monitoring**

- dsDNA levels
- active urinary sediment

- urinary protein and renal function
- complement levels

### **Penicillamine**

A degradation product of penicillins that can chelate copper, iron, mercury and lead and the complex is renally excreted. It can also chelate cystine and can reduce cystine stones. In arthritis the drug may interfere with collagen formation and also T-cell mediated responses.

### **Toxicities**

Dermatologic - these reactions are very common and are mostly pruritic, erythematous, or macolopapular rashes.

The drug can produce

- proteinuria
- Bone marrow depression and blood dyscrasias
- GI upset
- liver dysfunction
- changes in taste perception

**Leflunomide** - metabolized to a product that inhibits dihydroorotate dehydrogenase involved in the upregulation of *de novo* pyrimidine synthesis in activated lymphocytes. This effect is selective for lymphocytes involved in disease pathology and not those involved in normal immune regulation. It has a safer profile than methotrexate.

### **Drugs that interfere with tumor necrosis factor**

**Etanercept (Enbrel)/ Infliximab (Remicade)** - Two TNFalpha receptors (ligand binding domains) are linked to the Fc fragment of Human IgG and expressed as a recombinant protein. It can bind TNF and reduce tissue levels of the cytokine. Etanercept is approved for RA; Infliximab for Crohn's disease

## **Hyperuricemia and Gout**

### **Acute Therapy**

#### **Colchicine**

An alkaloid of *Colchicum autumnale* (autumn crocus), its anti-inflammatory actions have been exploited for centuries. Uric acid crystals in the synovium elicit an inflammatory response. Phagocytosis of sodium urate crystals by granulocytes release lactic acid which decreases synovial pH and facilitates deposition of urate crystals. The exact mode of action isn't clearly understood but the drug probably interferes with chemotaxis and mobility of polymorphonuclear cells. It decreases phagocytosis of the crystals. The drug is known to interact with cytoskeletal tubules. The drug has an anti-

mitotic effect which may contribute to its toxicity in rapidly dividing tissue (eg. marrow).

The drug is useful during acute attacks and for prophylaxis of attacks.

Toxicities involve GI tract, bone marrow toxicity (leukopenia, thrombocytopenia, etc.), renal and hepatic toxicity may ensue. There may be CNS involvement.

### **Dosing**

Oral - 0.6 - 1.3 mg every 1-2 hours until pain is relieved or diarrhea/GI upset appears, I.V. 1-2 mg followed by 0.5 mg every 6 hrs.

Prophylactic therapy - 0.6 mg a daily or intermittently

Other indications include familial Mediterranean fever, liver cirrhosis, primary biliary cirrhosis

**NSAIDS - can be used for acute gouty attacks**, not as effective as colchicine for prophylaxis

- indomethacin
- naprosyn
- aspirin should not be used based on its variable effects on urate excretion

### **Inhibition of Uric Acid Production**

**Allopurinol** - a structural analog of hypoxanthine

Allopurinol and its metabolite oxypurinol (alloxanthine) inhibit xanthine oxidase blocking the conversion of hypoxanthine to xanthine and xanthine to urate. Allopurinol competitively inhibits xanthine oxidase and is converted to oxypurinol, which non-competitively inactivates the enzyme.

De novo purine synthesis is inhibited by:

- a reaction with PRPP reduces the available pools for purine synthesis
- allopurinol inhibits conversion of PRPP to phosphoribosyl amine

Increased hypoxanthine levels from allopurinol use lead to increased synthesis to purines via HGPRTase (hypoxanthine-guanine phosphoribosyl transferase) which feedback inhibit de novo purine synthesis.

### **Uricosurics**

In humans, uric acid is 90% reabsorbed. Urate-anion exchanger in the luminal side of the proximal tubule. Many drugs that are uricosurics enhance urate excretion at higher doses whereas they promote urate retention at lower doses.

## **Probenecid**

Originally designed to increase plasma levels of penicillins by blocking tubular secretion. The drug enhances uric acid secretion by inhibiting its reabsorption.

**Sulfinpyrazone** - a congener of phenylbutazone with no anti-inflammatory effects. The drug also inhibits platelet function. It is a potent inhibitor of the renal tubular reabsorption of uric acid.

1) Prepare a table where you list 1) serotonin receptor subtype 2) signalling system used by the receptor (eg. K<sup>+</sup> efflux channel, phosphoinositide turnover) 3) anatomical location of receptors 4) Drugs that act at these receptors, pharmacologic actions (eg. antagonist, partial agonist) and clinical indications.

2) Non-specific interactions with receptor/enzyme systems by therapeutic agents often results in toxicities that are not seen in specific agents. Identify two examples of agents with non-specific actions on a receptor/enzyme system where newer specific agents are reducing toxicities and improving clinical management.

3) In certain clinical situations, NSAIDs can precipitate adverse gastrointestinal and renal effects, but the drugs are not usually withdrawn unless the toxicities are serious. What pharmacologic options are available for clinical management in a) a renal compromised pt. that requires an NSAID b) a pt. with NSAID-induced gastritis whose arthritis pain and swelling is significantly improved by an NSAID.

4) Many drugs with anti-histaminic activity can also act at other receptors including dopamine receptors, cholinergic receptors, alpha-receptors. Their clinical activity may be correlated with the degree to which they act at a particular system. For each drug and indication, list the most likely receptor system responsible for the clinical effect or adverse effect:

- a. use of diphenhydramine to block dystonic reaction
- b. orthostatic hypotension from a promethazine
- c. elimination of pruritis with hydroxyzine
- d. antiemetic effect of phenthiazines
- e. hypnotic effect of doxylamine

5) Overdose toxicity from acetaminophen and aspirin are the result of certain pharmacokinetic and/or metabolic features of the compounds. Discuss how these features contribute to the development of toxicity from these agents. Describe clinical manifestations of acute toxicity from these agents.