Autocoids

Chemicals produced by cells to produce effects in nearby cells

A look at the effects of biological mediators of inflammation and intercellular signaling – sometimes referred to as “slow-reacting” substances because they often initiate slow smooth muscle contractions.

What are autocoids?
(aka paracrine mediators)

In general, these chemicals are part of a **cell-signaling system**. They are locally produced and rapidly metabolized. All cells are capable of producing certain autocoids, like the prostaglandins, to carry out specific communications. Some cells, those with high communication needs, produce lots of autocoids. For instance, white blood cells produce dozens of different cytokines in addition to prostaglandins, leukotrienes, histamine and serotonin, depending upon the cell type and need. Cytokines include:

- Chemokines that are typically attractants for other WBCs,
- Lymphokines that are activating molecules for other WBCs,
- Interleukins and interferons that allow WBCs to talk to each other,
- Growth and “death” factors like tumor necrosis factor,
- And factors that control differentiation of stem cells, such as erythropoietin.

Autocoids play a role in inflammation, pain sensation, fever, blood pressure control, allergies & asthma, and cell communication, growth and death.
Blood Pressure Control: Angiotensin is the KING!

Think about how critical it is for the kidney to be able to filter blood properly – to remove wastes, to maintain salt and water balance, to keep you healthy. It is very important to maintain blood pressure high enough to properly filter the blood, so the body has a complicated and redundant system in place to ensure the kidneys can continue to function. The problem is that the system is thrown out of whack by our modern diet and behaviors.

Salt, sodium chloride, was once more precious than gold. It was rare and hard to obtain for most animals, so we have exquisitely fine tuned mechanisms to drive us to acquire salt. We crave its good taste. But, evolution hasn’t caught up with the fact that now, it’s easy to add grams of salt to our daily diet.

Angiotensin-2 (ANG-2) has direct effects on the heart and blood vessels as well as indirect effects on the sympathetic nervous system and Hypothalamus all leading to systematic and behavioral changes that elevate blood pressure.

How ANG-2 is made

The kidney juxtaglomerular cells secrete an enzyme called renin in response to several triggers: decreased renal perfusion (decreased blood pressure/volume), beta-1 receptor stimulation, and decreased levels of sodium at the kidney.

Renin activates a plasma protein (produced by the liver) that is subsequently activated to Ang-2 by Angiotensin Converting Enzyme (ACE - mostly produced by vascular endothelial cells in the lungs).

Ang-2 stimulates release of catecholamines from the adrenal medulla and sympathetic neurons. It stimulates the hypothalamus to activate the adrenal cortex to secrete cortisol and ALDOSTERONE, as well as to trigger thirst. It also triggers the release of growth factors leading to hypertrophy & hyperplasia of smooth & cardiac muscle.

Aldosterone acts on the kidney to increase water and sodium retention (excreting potassium while keeping sodium).
The thing about autocoids, they are not just autocoids

That may sound strange, but think about histamine. It is an autocoid when released by any cell other than a neuron, when it is a neurotransmitter. The same thing is true for serotonin. Some of the autocoids, like angiotensin, act more like a hormone, but are not secreted by a gland.

There are three classes of oral drugs (4 if you include beta blockers) with a role modifying the effects of angiotensin 2 (Ang2). They are:

1. Angiotensin Converting Enzyme Inhibitors (ACEI)
2. Angiotensin Receptor Blockers (ARBs)
3. Direct Renin Inhibitors (DRIs).

Problems with all the drugs that interrupt the renin-angiotensin-aldosterone system (RAAS) are: (1) serious fetotoxicity, (2) hypotension, (3) hyperkalemia and (4) angioedema. All drugs interfering with the RAAS, including ACEI, ARBs and DRIs, may cause kidney failure, especially if taken with an NSAID.

The ACEI are antihypertensive drugs that block the activity of ACE. This decreases the amount of Ang2, but increases the levels of bradykinin, because bradykinin is broken down by ACE. Bradykinin, another plasma protein, is a potent bronchoconstrictor, so in sensitive patients you may see a dry cough. Bradykinin is also a potent vasodilator, which may contribute to the beneficial effects of ACEI.

A problem with inhibiting ACE is that Ang2 provides negative feedback for the release of renin. Without Ang2, more renin is released.

Captopril (Capoten) is the prototype ACEI. It was developed based on a protein found in the spit of the Brazilian Pit Viper (Bothrops jararaca). Captopril is used to treat HTN, heart failure (HF), diabetic nephropathy, and left ventricular dysfunction following a myocardial infarction (MI).

Captopril is associated with agranulocytosis, especially a reduction in neutrophils. The risk is greatest in kidney dysfunction patients, in whom WCB and differential counts should be taken at baseline and then q2wks for at least 3 months.

Captopril, and other ACEI, can cause significant hypotension, especially in patients also taking a diuretic, so initial therapy should be started under close supervision for the 1st 2 weeks.

Captopril has a number of significant drug interactions, especially in sensitive populations.

Because all the ACEI, including captopril, inhibit the release of aldosterone (by decreasing Ang2), an elevation of serum potassium should be seen. So care should be taken to ensure the patient doesn’t develop hyperkalemia.

Benazepril (Lotensin) and Enalapril (Vasotec) are both Prodrugs but otherwise very similar to captopril.

ARBs block the receptor for angiotensin on vascular smooth muscle, reducing vasoconstriction, and in the adrenal gland, reducing aldosterone release.

The indications and issues are pretty much the same as the ACEI. All seven of the ARBs are on the top 200 sales list. They are extremely popular.

You should know Irbesartan (Avapro) and Valsartan (Diovan). Note the “sartan” stem for ARBs and the “pril” stem for ACEI.

Aliskiren (Tekturna) is a DRI. DRIs cannot be used in patients with diabetes who are also on either an ARB or an ACEI due to increased risk of kidney damage, hyperkalemia and hypotension. Kidney patients may have trouble with a DRI. It should NOT be taken with fatty food.
Serotonergic Drugs

Serotonin is one of the odd chemicals in the body that acts in many capacities. While we are going to mention a number of serotonergic drugs here, note that these drugs are mainly interacting with 5-HT receptors related to the nervous system where 5-HT is acting as a neurotransmitter. There are lots of different 5-HT receptors, many of which are not enervated.

**Buspirone** (Buspar) is a non-sedating anxiolytic. It interacts with several receptors in the CNS including acting as a partial agonist at the 5-HT<sub>1a</sub> receptor. This is the most widespread of the 5-HT receptors in the brain. The Selective Serotonin Reuptake Inhibitors, like **Fluoxetine** (Prozac) and **Sertraline** (Zoloft), seem to relieve anxiety and depression by preventing the reuptake of 5-HT at neurons expressing these receptors (thus they also are 5-HT<sub>1a</sub> agonists). Many antidepressants and antipsychotics activate this receptor.

One interesting fact about the 5-HT<sub>1a</sub> receptor, is that it is also an **Autoreceptor** that inhibits serotonin release. This may be why there is such a long lag time between starting an antidepressant and seeing a benefit, because the Autoreceptor needs to be down regulated. Some people have a genetic variant that produces Autoreceptors that don’t desensitize and SSRIs don’t work well in those people.

**Sumatriptan** (Imitrex) is a triptan antimigraine drug. It stimulates a 5-HT receptor that causes vasoconstriction in the vasculature of the brain. This may alleviate migraine, but is not for prophylaxis, nor is it for cluster headaches.

**Trazodone** (Desyrel) blocks several 5-HT receptors. This is interesting because it is also effective as an anti migraine drug, although its indication is to treat depression. It is also occasionally used off label to treat schizophrenia symptoms.

**Ondansetron** (Zofran) and other 5-HT<sub>3</sub> antagonists are very important anti emetics. The 5-HT<sub>3</sub> receptor is common in the gastrointestinal tract (GIT) and on the Chemoreceptor Trigger Zone (CTZ) of the brain. The CTZ has many types of receptors, but the 5-HT<sub>3</sub> receptors are there to detect elevations in serum serotonin. The GIT produces 5-HT as an autocoid to stimulate GIT smooth muscle (causing peristalsis). When an irritant gets into the GIT, these cells produce lots of 5-HT to increase peristalsis to help rid the body of the irritant. This leads to gut cramping and diarrhea. Excess serotonin is absorbed into the blood, where platelets soak up as much serotonin as they can. They will use it in the event they are activated to trigger the activation of additional platelets to form a clot. Any serotonin that is left over will make it to the brain and the CTZ, which triggers vomiting.

**Leukotriene Inhibitors**

The leukotrienes (LTs) are lipid-based autocoids produced by white blood cells. The feedstock is Arachidonic acid fed into two pathways: (1) cyclooxygenase, COX produces prostaglandins, etc. and (2) lipoxygenase, LOX produces the LTs. LTs do many things. They are potent bronchoconstrictors and stimulate the lung to produce mucous.

Zileuton (Zyflo) directly inhibits LOX, reducing the synthesis of LTs, but potentially increasing the synthesis of prostaglandins. **Montelukast** (Singulair) and **Zafirlukast** (Accolate) block the LT receptors.

All three are indicated for asthma, Montelukast is also used for allergies. All three have been associated with psychiatric effects including aggression, agitation, anxiety, sleeplessness, vivid dreams and suicidal ideation.
Other drugs that inhibit the 5-HT_3 receptor nearly as well as the “setron” antiemetics include the antidepressant **Mirtazapine** *(Remeron)* and the antipsychotic **Olanzapine** *(Zyprexa)*.

### Antihistamines

Histamine, like serotonin, acts as both an autocoid and as a neurotransmitter. In this lecture we talk about the H₁ antagonists, what we normally call antihistamines. The H₂ antagonists, block gastric acid release, and will be covered with GI drugs.

1st Generation antihistamines, such as **Chlorpheniramine** *(Chlor-Trimeton)*, **Diphenhydramine** *(Benadryl)* and **Promethazine** *(Phenergan)* are older drugs with many side effects. Because of this, they may be useful to treat conditions other than allergy, including motion sickness, other causes of emesis (promethazine only), or sleeplessness (since most are very sedating). Most of the 1st generation side effects (sedation, anti-emesis) are related to their anticholinergic effects. Promethazine is also a phenothiazine. We’ll learn more about phenothiazines when we cover the antipsychotics.

The 2nd generation antihistamines better target the H₁ receptor. They have a longer duration, but also fewer side effects (and other uses) – they really only help with allergic rhinitis or hay fever. Fexofenadine also helps relieve the symptoms of urticaria, including drug-induced dermatitis.

**Loratadine** *(Claritin)*, **Fexofenadine** *(Allegra)* and **Azelastine** *(Astelin)* are all 2nd generation drugs.

### Others...

**Aprotinin** *(Trasylol)* is a potent inhibitor of an enzyme found in the blood that is involved in the production of bradykinin. It is actually a naturally occurring chemical isolated from the lungs of cows at the slaughterhouse. It is used to reduce blood loss during coronary artery surgery, but because it is a protein, it can cause fatal, 1st dose, anaphylaxis. Though Aprotinin was discontinued in 2007, it is still available, and still used.

**Sildenafil** *(Viagra, Revatio)* is a 5-phosphodiesterase (5-PDE) inhibitor. This enzyme is part of a complex pathway that regulates the production of nitric oxide by endothelial cells. Nitric oxide is a potent vasodilator. Sildenafil was originally developed to treat a serious condition called Pulmonary Arterial Hypertension (PAH), and it still carries that indication. It was subsequently discovered to have the ability to treat erectile dysfunction (ED, or PED). The “afil” drugs cannot be taken with any nitrate/nitrite as they can cause severe hypotension. They are also associated with priapism.

**Ibuprofen** *(Advil)* is a non-steroidal anti-inflammatory (NSAID). It acts by inhibiting an enzyme called cyclooxygenase (COX) that is involved in the synthesis of prostaglandins. We will cover the NSAIDs more completely in the PAIN lecture.

**Dexamethasone** *(Dexasone)* is a synthetic corticosteroid. It is mimicking the activity of the hormone cortisol (produced by the adrenal cortex). Corticosteroids like dexamethasone have an unbelievable variety of uses to treat inflammation, pain, cancer, allergy, and even, importantly, chemically induced emesis (both CINV and PONV). Cortisol inhibits the production of prostaglandins and leukotrienes.

**Misoprostol** *(Cytotec)* is a prostaglandin E₁ (PGE₁) analog. PGE₁ is an autocoid with many functions (see some of these listed on slide 34), two important functions are that (1) it protects the stomach against ulceration by decreasing the secretion of stomach acid and increasing the secretion of mucous in the stomach, and (2) it stimulates uterine contractions. It used to be used as an abortifacient. Now it is only used to protect against NSAID induced gastric ulcers (NSAIDS block the synthesis of PGE₁) or to help heal existing gastric ulcers.
Asthma and COPD

We’ve looked at antimuscarinic and beta-2 agonist bronchodilator drugs used to treat asthma and COPD. In the autocoid chapter, we look at the use of Leukotriene receptor blockers like Montelukast and Lipoxygenase (LOX) inhibitors like Zileuton that approach this issue from another direction.

Because Zileuton is blocking the enzyme that produces leukotrienes, that means there is more precursor available to make into prostaglandins, which have issues of their own (they may be pro-inflammatory).

Regardless of the approach, it is important to note that controlling asthma is a balancing act requiring sensitivity on the part of the patient to understand their triggers.

All images, except the Tekturna product display panel and the photo of the author with her much beloved dog, are from the National Library of Medicine image collection.

Homework and Exercises

1. Read the “START HERE” announcement in Laulima for updates and instructions.
2. There is not an “Autocoid” chapter in your textbook. Read about body defenses in Chapter 43 and Chapter 44, Pharmacology of Inflammation and Fever. In Chapter 48, read about allergies. Adams & Urban, PHARMACOLOGY Connections to Nursing Practice.
3. Review the Powerpoints and listen to the audio from the face-to-face lecture. You may opt to watch the appropriate videos for this lecture. Review any handouts available for this lecture in the Course Index.
4. Complete the SLO practice set for Autocoids in Tasks, Tests and Surveys.
5. Use “Chat,” “Discussions and Private Messages” or the lecture “Forum” to ask questions and find answers or to seek assistance.
6. Complete the online quiz in Laulima, Tasks, Tests and Surveys.

If you have any questions, email me at abeale@hawaii.edu