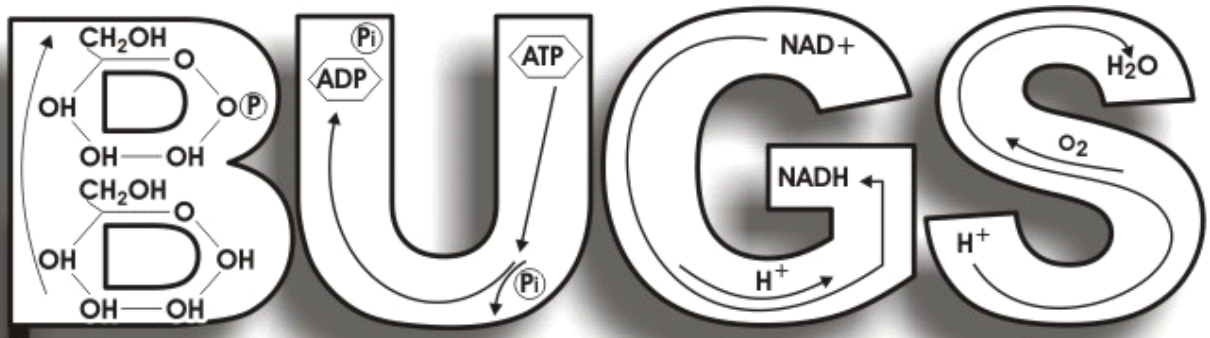
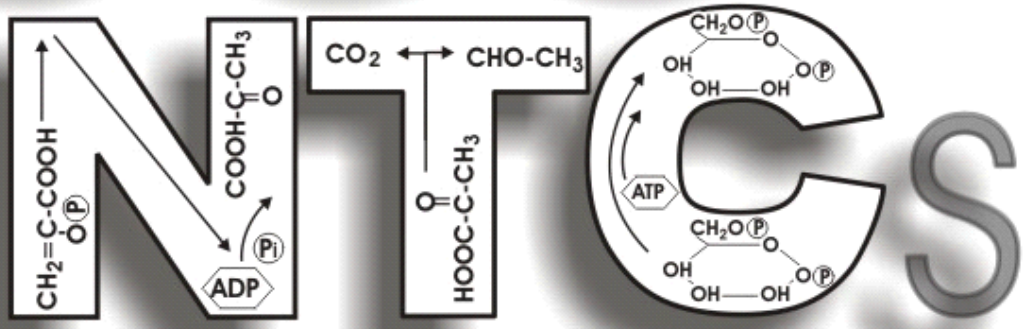




PHAR 301

SET #7 Lectures 17-19

ANNOUNCEMENTS

<u>BUGS Wine and Cheese</u>, April 2nd, from 2-5:30 at McIntyre Medical 6th Floor. Come meet the candidates of the next election over a nice assortment of cheese and cocktails.

The BUGS office will be *closing* <u>Thurs April 5th</u>. Pick up your NTCs, or anything else you need from B.U.G.S. BEFORE this date!

The Princeton Review

MERCK FROSST

< Biochemistry Undergraduate Society - 5th Floor McIntyre rm. 511 >
< bugs@sus.mcgill.ca - (514) 398-5247>

Thursday, March 15, 2007.
Dr. Clarke - Lecture #17

Migraines

Drugs and terms to know by name:

- Aura
- Caffeine, ergotamine
- Sumatriptan, triptans
- Prophylactic, abortive
- Photphobia, phonophobia
- Meninges, trigeminal nerve

Reading
Brody 4th edition does not cover migraine.

Instead, he recommends:
MA Moskowitz (1992) Trends in Pharmacol Sciences 13:307-311
- available online
- although now quite old, it is a useful general review of mechanisms

S Diamond (2001) A look at migraine therapy. Postgraduate Medicine 109 (1):49-54, 57-60
- available online at http://www.health.library.mcgill.ca/research/ejournals/
- Do NOT select "Postgraduate Medical Journal"
- Click on the "Issue Index" link towards the top of the screen
- Select January 2001
- No need to read about drug classes, he does not mention in the lecture

An ancient treatment to treat migraines was to fasten a crocodile on the patient head and pray for the migraine to go away…

2 types of migraine

Migraine without aura: (most common one)
- lasts 4-72 hours
- at least two of these primary symptoms:
  - unilateral (migraine comes from the Greek word *hemikranios* – half a head)
  - pulsating moderate or severe intensity
  - aggravated by physical activity
- at least one of these secondary symptoms:
  - nausea
  - vomiting
  - photophobia (sensitivity to light)
  - phonophobia (sensitivity to sound)

Migraine with aura: (known as "classic" migraine, affects about a third of patients)

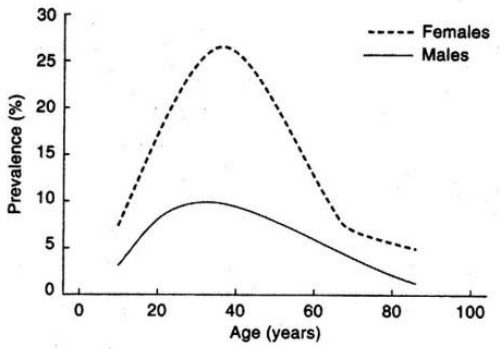
- two or more headaches preceded by aura
- aura symptoms, usual:
    - blurred vision
    - flashing lights or zig-zag lines around the margins
    - missing area of visual field (i.e. scotoma)
- aura symptoms:
    - fully reversible
    - last < 1 hour
    - typically start 5-30 min before pain (useful because tells you it's time to take medication)

- at the beginning of the aura, the visual field starts to get disturbed
- and with time the disturbance gets greater (a gap appears in visual field – scotoma)
- on the margins of scotoma, zig-zag lines appear
- something must happen in the visual region of cortex

What triggers migraine attacks?

- many distal (environmental) causes
- still some doubts about what triggers migraine at molecular or neuronal levels answers suggested by class:
- having periods (for women, this is a very common trigger!)
- physical activity
- reading too much, being in front of a computer for too long
- high altitude, change in temperature
- chocolate (for some people)
    - different for different people!

Migraine - more common in women



Migraine – more common in women than men

- it's about a 3:1 ratio

Migraine drugs

2 types:

- **prophylactic** (protection, taken chronically because you suffer so much from the migraine, that you need to maintain medication to prevent pain)
- **abortive** (taken only when you feel the aura or when the pain starts, taken as needed)

Drugs used to prevent migraine (i.e. prophylactic drugs):

1. **propranolol** (β-blocker, most common prophylactic drug for migraine)
2. **valproate** (from the epilepsy drugs)
3. **tricyclic "antidepressants"** (lethal if overdose)

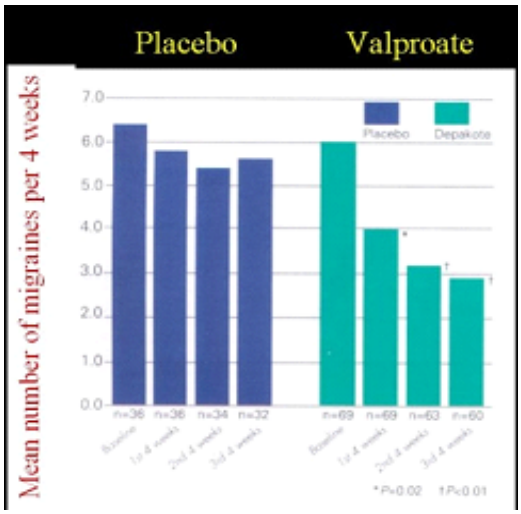
- none of these drugs works particularly well (they only reduce by half the migraine attacks, still not enough)
- all are considered "successful" since they prevent 50% of attacks
- none stand out as the best when you balance efficacy versus side effects (probably should try them all out and see which one works best for you)
- the safest are probably propranolol and valproate

Propranolol

- Advertisement : "Stops migraine before it starts" (prophylactic drug)

Valproate

- look at the mean number of migraine per three weeks
- test on patients suffering from migraines quite frequently (1.5/week)
- even at the end of study, the maximum reduction is only about half (still getting 3 attacks in 4 weeks)
- not perfect yet



Prophylactic drugs in more detail

Propranolol

- see Anxiety lecture
- most common prophylactic drug

Valproate

- see Epilepsy lecture
- multiple actions (GABA, Ca, Na channels)
- Which actions are anti-migraine? Not really known (We assume that it's its anti-GABA effect)

Tricyclic "antidepressants"

- see Depression lecture
- we don't really understand how they work either
- block monoamine transporters (likely works through this action)

Side effects of prophylactic drugs:

Propranolol – contraindicated where β block is a problem (see Anxiety lecture)
Valproate – thinning hair, fetal malformations (see Epilepsy lecture)
TCAs – e.g. alcohol interaction, O/D risk (see Antidepressant lecture)

Drugs used to acutely treat migraine attacks

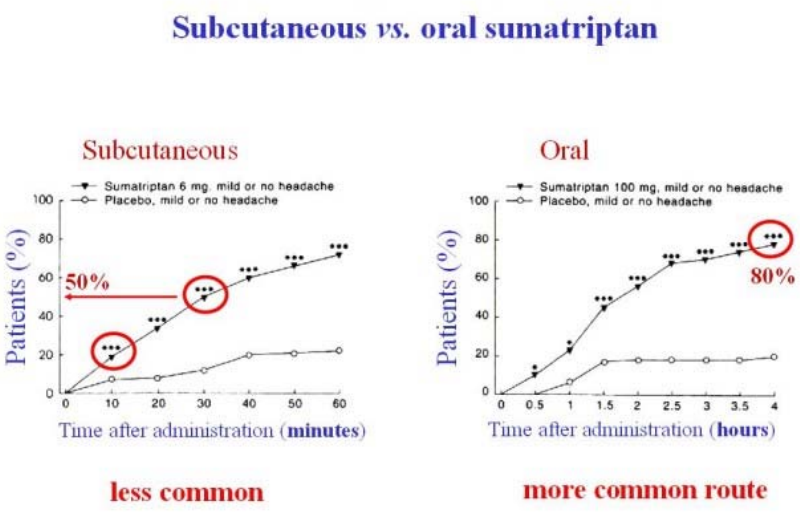
i.e. "abortive" drugs

- **anti-inflammatory drugs** (least effective ones, but commonly used)
  - inhibit cyclooxygenase, reduce prostaglandins synthesis
  - e.g. aspirin, ibuprofen
  - often taken with anti-emetic (drug to stop throwing up, can be injected or taken as suppository). Anti-emetic is used because a lot of people who suffer from migraines also suffer from nausea and we don't want people to throw up the medication they are taking!
- **narcotic analgesics** (opioid agonists – not used all that much)
  - easy to get addicted
  - abuse is not the only disadvantage - effect doesn't last very long (duration of action = few hours, compared to a median duration of a migraine attack = 24 hours)
  - e.g. codeine, morphine
- **5-HT agonists** (drugs of choice, should be used more against migraine)
  - Mainstay for moderate-severe migraine
  - There are 2 types of 5-HT agonists:
    - **ergot**amine, dihydro**ergot**amine (pharmacologically rich, they have multiple targets)
    - drugs ending with 'triptan' (e.g. sumatriptan – more effective and fewer side effects, more selective)

History (Case report)

43 year-old man

- intense pains in hands and feet started one week ago
- has been taking ergotamine 2 mg 1-6 pills/day for 20 years (can assume that he suffers from migraines)
- **intermittent claudication** (this term can mean intense limb pain in leg, but here it means limping) – last 2 years
- 1 week ago he acquired febrile disease (chills, cough) – treated with amoxicillin (antibiotic)
- pains started shortly after



At admission

- intense pain at extremities
- normal temperature (37.6°C)
- extremities cold, cyanotic (blue, suggesting deficient oxygen circulation), no measurable pulse
- carotid and femoral pulses detected
- infiltration of lower right lobe of lung

Treatment

- stop ergotamine
- give captopril (inhibits ACE - angiotensin converting enzyme, thus produces peripheral vasodilation)
- within 6 hours, peripheral pulses, skin colour, less pain

What caused the symptoms in this patient?

- When you have a fever, you get dehydrated (might have an effect on circulation)
- Ergotamine is a vasoconstrictor.
    - Leading to high pressure
- St. Anthony's Fire:
    - See link with summary of story
        - http://www.medicinenet.com/script/main/art.asp?articlekey=14891
        - Rye grain, contaminated with a fungus (ergot – aka rust), was used to bake bread in Middle Ages
        - People eating that bread were suffering from hallucinations, vomiting, craziness and intense pain in limbs (vasoconstriction, dropping off of their limbs)
        - Ergot, related to LSD (lys**erg**ic acid diethylamide)
        - Treatment: St-Anthony's Fire (the area where he lived was contaminated with that fungus). People would go on pilgrimages to the shrine of St. Anthony in France and they would get better because that was an area that wasn't affected by this fungus!

Subcutaneous *vs.* oral sumatriptan

- Subcutaneous injection: rapid improvement in headache treatment with sumatriptan (reaches max within an hour)
- Oral: it takes longer to get the max effect (about 4 hours) even though the max effect is approximately the same for the subcutaneous vs. oral routes (80% peoples pain improved)

Monosodium glutamate (MSG)

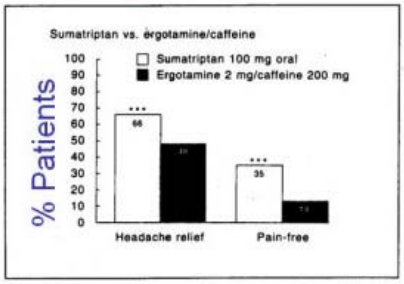
- in some people it triggers migraine
- so caffeine combined with ergotamine treats migraine (caffeine increases ergotamine absorption), discovered by patients

Sumatriptan *vs.* other migraine-abortive remedies

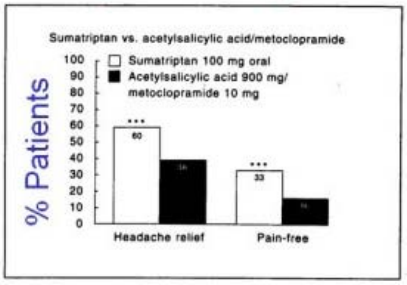
Sumatriptan is the most effective abortive drug for migraine

- Graph shows the percentage of patients that are relieved or pain-free
- Sumatriptan (white bars) significantly better than ergotamine with caffeine or aspirin/metoclopramide
- this experiment is missing a placebo group – therefore we don't know whether the ergotamine/caffeine mixture had a significant effect since in the course of time people do get spontaneously better

vs. ergotamine/caffeine

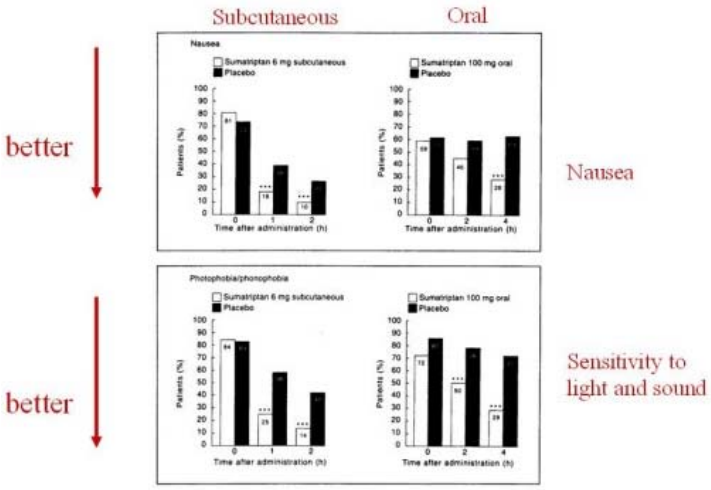


vs. aspirin/metoclopramide



Sumatriptan works on non-headache symptoms too

AJ Pilgrim 1994 Eur Neurol 34 (Suppl 2):26 Fig 5



There's one thing that sumatriptan does not prevent; doesn't inhibit aura, but it does stop the headache.

Placebo (black columns)

- probably placebo effect happening, not just spontaneous recovery because the placebo group behaves differently when the patients are receiving the placebo subcutaneously vs. orally

Adverse effects of ergot-derived drugs and triptans

Ergotamine, DHE

- peripheral vasoconstriction
- mental disturbance (if excess)

Triptans

- chest "tightness" (constricts coronary arteries, heart blood supply)
- myocardial ischemia, so contraindicated in
  - ischemic heart disease
  - cerebrovascular disease

What is migraine headache caused by?

Vasodilation hypothesis (Wolff 1940)

- trigger for migraine (pain) is vasodilation of meningeal blood vessels
- it's the dilation that is painful
- Evidence:
  - Pain pulsates like vessels (he claimed that he could see the temporal artery pulsate in migraine patients)

- Vascular disease (can have frequent painful headaches)
- If you stimulate meningeal vessels on the surface of the brain (= painful)
- Nitroglycerin (used as vasodilator, produces headache = painful)
- Angioplasty (painful)

Meninges = **membranes that cover the brain (and spinal cord) and help to shock absorb the brain and protect it in other ways**

- You can make a parallel with the kidney; the kidney has a capsule around it (membranes that are highly innervated by sensory nerve fibers). If you were to get a punch in the kidney (like as in the case of a boxer) it can be very painful.

But, some cracks in the evidence…

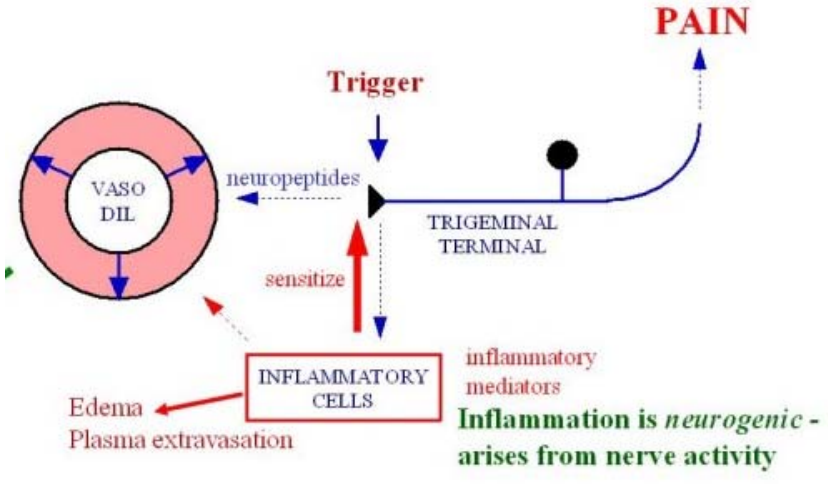
- vessel does *not* pulsate (temporal artery) – this happened in SOME patients, but was not at all consistent in all patients
- vascular disease –affects more than vessels (also has effects on brain and other areas of the body)
- Can have vaso*constriction* in migraine!
- Nitroglycerine vasodilation outlasts the pain (don't correlate very well)
- Angioplasty dilates the vessel but also *scrapes*, and is usually not painful anyway

Neurogenic inflammation hypothesis (Moskowitz 1990)

- neurogenic = caused by neural activity
- the trigger causes pain directly, and vasodilation is kind of a side effect (pain is not due to vasodilation)

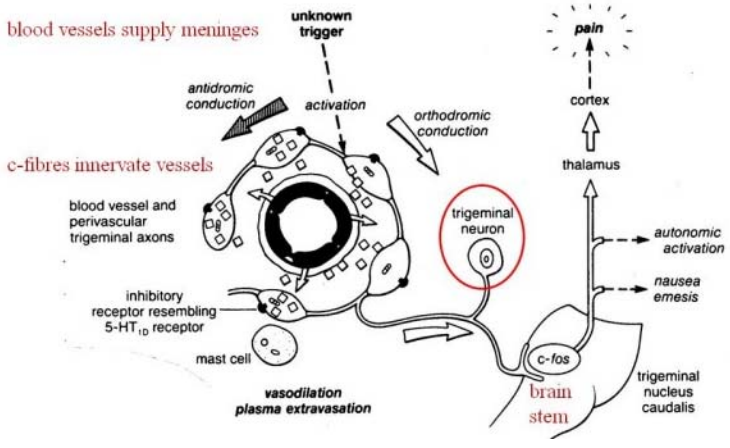
Neurogenic inflammation hypothesis

- the trigger stimulates the trigeminal nerve directly and this causes pain by transmitting up to the brain
- on the other hand, the release of neuropeptides from the terminals of C-fibres causes vasodilation
- the nerve terminals also activate inflammatory cells that act back on C-nerve terminals (they sensitize them) through inflammatory mediators and cause vasodilation
- Inflammatory cells cause EDEMA (passage of fluid from the vessel into the surround) and plasma extravasations (proteins leaking through the vessel wall into the extravascular space)



Proposed mechanism underlying vascular headaches

- c-fibre wraps around blood vessel, from the trigeminal neuron (is a unipolar primary sensory cell, with two processes, one around blood vessel, the other going up to the brainstem)
- in the brainstem, we have the trigeminal nucleus caudalis (the inflammatory cells in this area are mast cells)



Mediators released by electrical stimulation of the trigeminal nerve

- upon electrical stimulation, the nerve terminal releases *neuropeptides* (CGRP, a vasodilator, is detected in plasma as in migraine sufferers when they are having an attack)
- the neuropeptides act on inflammatory cells (mast cells), which in turn will release cytokines, Eicosanoids, histamine, 5-HT, etc. These inflammatory mediators act back on nerve terminals (become sensitized).

Sensitization of meningeal sensory neurons to mechanical stimuli – the origin of migraine headaches?

Patients having a migraine don't want to move their head because it is painful.

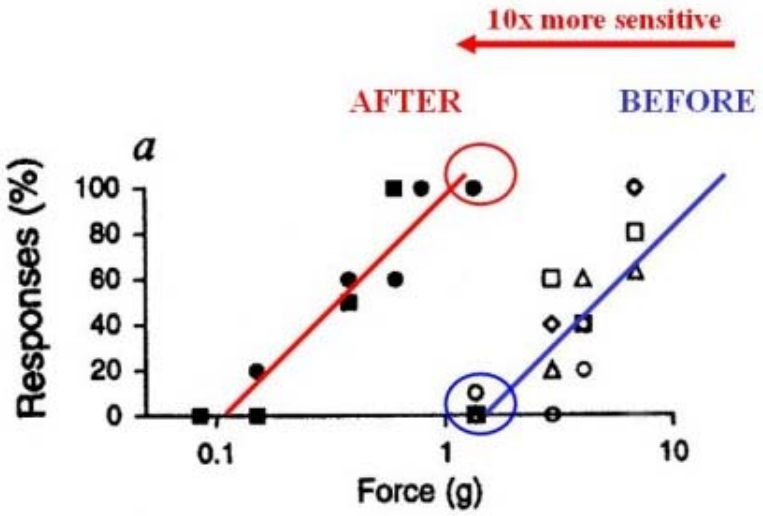
- Idea is that maybe C-fibres during a migraine attack might become abnormally sensitive to mechanical disturbance
  - experiment in rat, meninges still in place:
  - stimulate the meninges with fine paint brush (stroke transverse sinus) and record the trigeminal nerves (sensory neuron)
  - when stroke meninges on the same side, you increase the firing rate of the sensory neurons, but not when stimulating the other side. This is as expected, i.e. normal.

Trigeminal ganglion cells respond to "inflammatory soup"

- if replace the paint brush stimuli with an "inflammatory soup", you also increase the firing rate of sensory nerve cells
- Conclusion: maybe the inflammation itself can cause pain!

Sensitization to mechanical stimulation after application of inflammatory soup to dura

- before the combination of both stimuli, the force applied with the brush needed to be high to reach a maximal response (cell firing)
- after adding the inflammatory soup, the brush could stroke the nerve softer (force about 10x lower) and reach the same response level.
- the force that didn't use to create a response is now causing a maximum response



Conclusion from this experiment: it looks like inflammation can sensitize the nerve endings so that they become more sensitive to mechanical stimulation

Human 5-HT Receptors subtypes

- major target for prophylactic drugs

3 families:

- 5-HT1 family
  - (1A), 1B, and 1D, interested in the latter two, are important target for abortive drugs (agonists)
    - inhibit cAMP
- 5-HT2 family
- 5-HT3 family

Sumatriptan binds selectively to 5-HT_{1B} and 5-HT_{1D} receptors

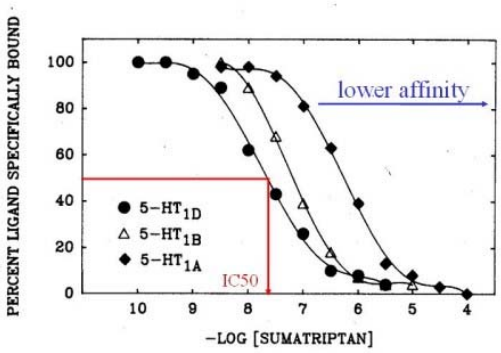
- the more you add sumatriptan, the less the drug binds to receptors
- the lower the IC50 value, the higher the affinity

5-HT1D receptor affinity predicts antimigraine efficacy

- abortive (i.e. treat acutely) all have low Ki (Ki ~ IC50) and therefore a high affinity
- prophylactic (i.e. used chronically to prevent) have high Ki and so low affinity for these receptors

Sumatriptan binds selectively to 5-HT_{1B} and 5-HT_{1D} receptors

Peroutka and McCarthy 1989 Eur J Pharmacol 163: 133



Does this prove that 5-HT1D receptors are the therapeutic target for the abortive drugs?
It could be coincidence, there's no proof. We know they're agonists rather than antagonists, but we also need to know what is the conequence of stimulating those receptors.

Do abortive drugs act on other receptors?

- Comparing DHE (ergotamine analog) and sumatriptan: act selectively on 5-HT1B and 5-HT1D (highest affinity)
- DHE has very high affinity for α adrenergic receptors whereas sumatriptan is ineffective on these adrenergic receptors. DHE has a richer pharmacology than sumatriptan.
- The starting point of sumatriptan was 5-HT (chemically very similar)

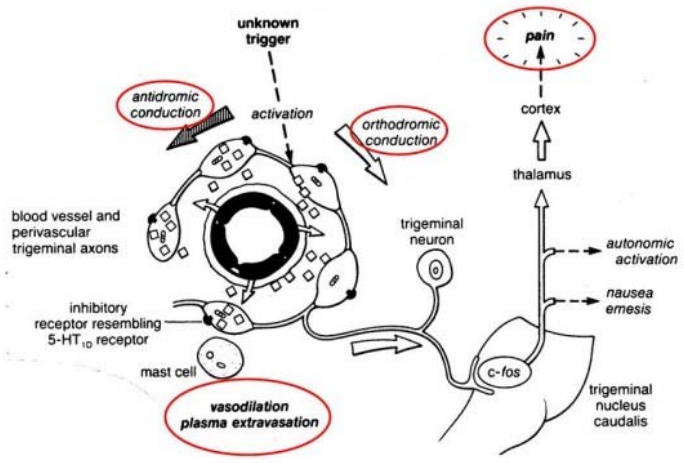
Do abortive drugs act on other receptors?

Receptor	K_i values (nM) DHE	Sumatriptan
Serotonergic		
5-HT_{1D}	19	17
5-HT_{1B}	0.74	27
5-HT_{1A}	1.2	100
5-HT_{1C}	39	>10,000
5-HT_2	78	>10,000
5-HT_3	>10,000	>10,000
Adrenergic		
α_1-	6.6	>10,000
α_2-	3.4	>10,000
β-	960	>10,000
Dopaminergic		
$Dopamine_1$	700	>10,000
$Dopamine_2$	98	>10,000
Other sites		
Muscarinic	>10,000	>10,000
Benzodiazepine	>10,000	>10,000

DHE = ergotamine analog

RECAP: Proposed mechanism underlying vascular headaches

MA Moskowitz 1992 TIPS 13: 307



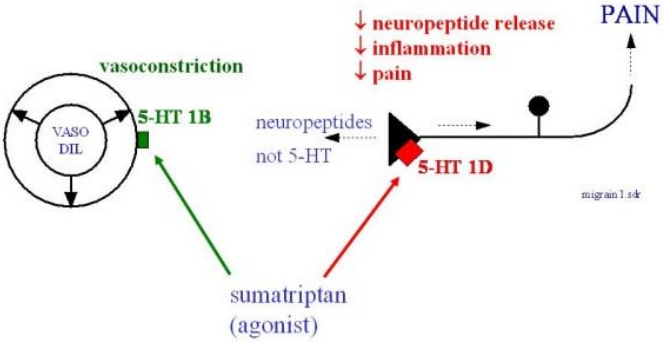
Sumatriptan

- pharmacologically selective
- does not get through the blood brain barrier (this narrows the search for sites of action)

Mechanism of pain:

- unknown trigger activates nerve = release of neuropeptides (leads to orthodromic conduction = towards the brain) and produces pain, it can also cause nausea and vomiting.
- Also activates cells in antidromic direction (interacting with inflammatory cells)

- Sumatriptan works in the periphery
- the receptors that sumatriptan works on are:
  - on the blood vessels (1B)
  - on the terminal (1D)
- when the nerve is excited, there is a release of neuropeptides, and incidentally, NOT 5-HT
- sumatriptan can inhibit the release of neuropeptides



Evidence that Sumatriptan stops release of neuropeptides:

- if electrically stimulate the trigeminal nerve, you get release of CGRP - vasodilator which goes in plasma (measurable)
- that effect is reduced by sumatriptan treatment

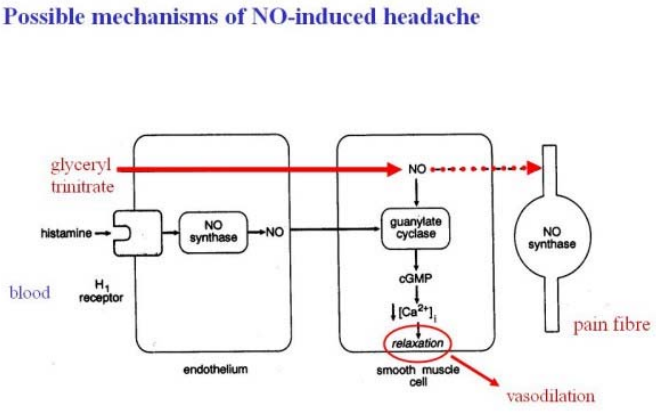
Pain-associated neuronal activation in spinal cord is reduced by sumatriptan

- can measure pain using c-fos immunohistochemistry (index of neuronal activity). Fos is an immediate early gene, expressed in activated neurons within a few minutes (can be detected with antibody).
  - Can do immuno-staining in brain or spinal cord sections
  - commonly used as a marker for neuronal activity
- anesthetized rats given sumatriptan or vehicle (control)
- give the stimulus: painful, vasoconstrictor substance applied to meninges
- rats killed soon after and analyze look for presence of fos in nucleus of cells.
  - Animals treated with sumatriptan had much less fos activation
- conclusion: SUMA reduced generation of nerve impulses originating from trigeminal terminals

Can be neurogenic inflammation hypothesis explain how how nitric oxide (NO) causes migraine headache (i.e. if we accept that the NO-induced vasodilation itself does not cause pain)?

Glyceryl trinitrate (NO donor) produces headaches in normal subjects.

- Low dose = headache
- High dose = headache (rapid onset)
- Headache lasts for 30 minutes
- Vasodilation is known to outlast headache



Possible mechanisms of NO-induced headache

- glyceryl trinitrate comes from the blood circulation, it readily diffuses through endothelium, gets into the smooth muscle cells where it produces NO (highly diffusible since it is a soluble gas). NO then goes to c-fibre and it stimulates it (unknown mechanism).
- NO is smooth muscle cells produces relaxation (vasodilation)

Progression of a migraine attack

- trigger (e.g. in visual cortex) → aura → migraine attack
- 1/3 of patients suffer from aura (typically visual)
- Scotoma starts in center of visual field.
- Cortical spreading depression (3 mm/min), there's a wave of excitation that starts in visual cortex and spread forward.
- Excessive glutamate is released and the neurons are very active.
- Right behind, cells behind wave become silent - the nerves stop functioning (become so depolarized that they can't fire anymore).
- ↑↑ K+ and H+ released from these neurons → stimulates nociceptive fibers (= pain), local inflammatory reaction.

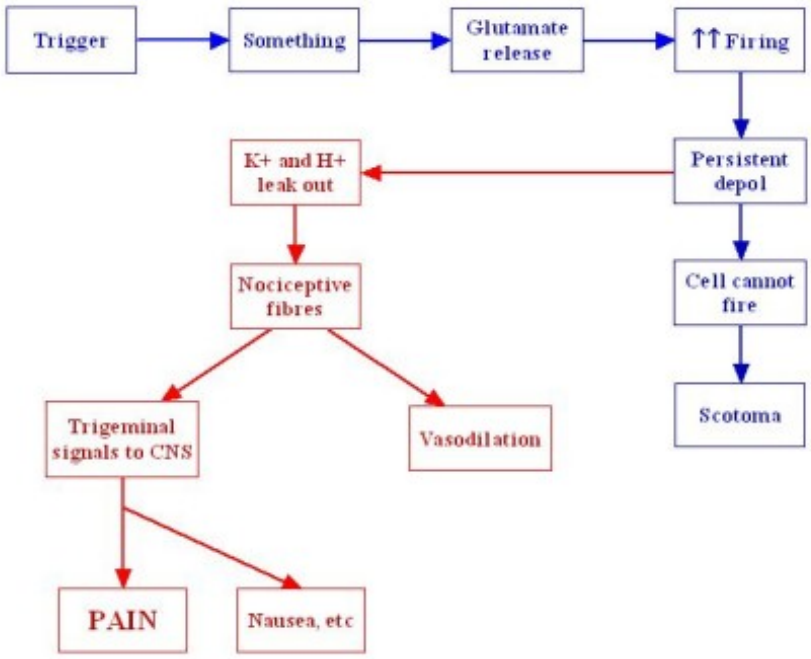
Something makes neurons fire abnormally.

- Extracellular K^+ and H^+ will stimulate the trigeminal nerve to release things that will cause a local inflammation of the blood vessels
- At the same time, the nerve will be conducting orthodromically action potentials that go up to the brainstem and then cause the headache

Cortical Spreading Depression (CSD) can be visualized in humans

- 16 sec checkerboard visual stimulus
- Visual cortex - functional MRI
- Index of neuronal activity
- Normal state is constant in both hemisphere; in migraine attack, the brain activity is clearly abnormal (visual cortex shows reduced response to visual stimuli).
- Spreading depression corresponds anatomically to the visual location of aura in humans.
- The scotoma increases in size at the same time of spreading. (at Fovea (fixation point) – early, at periphery – late)

Possible basis of migraine attack



Tuesday, March 20th, 2007.
Dr. Szyf – Lecture #18

GI Drugs

-the material for this lecture can be found in chapter 55 of Brody, pages 711-734.

THE GI TRACT AND ITS FUNCTIONS

-food comes in the mouth, travels through the esophagus and into the stomach
-the stomach is a very acidic environment…this can lead to **heartburn**
- ▪if the sphincter between the stomach and the esophagus isn't working properly, acid goes up into the esophagus, giving the feeling of heartburn

-digestion occurs in the stomach by way of proteases
- ▪these proteases are activated by acid
- ▪this provides a challenge to drugs that are administered orally

-the stomach has to protect itself from the acid…if it doesn't, you can get an ulcer, or heartburn
-after the stomach, the food goes through the intestine for further digestion and absorption
-the bad material exits as feces
-should food get stuck = constipation
-should the food go too fast (with water) = diarrhea

-laxatives can cause a tremendous amount of dependence…they are a serious health issue

-the GI tract is highly controlled by nervous inputs from the **myenteric plexus** as well as centrally

-the intestine is controlled by both **longitudinal** and **circular** muscles
- ▪the circular muscles constrict, and keep everything in
- ▪the longitudinal muscles push the stuff out
- ▪the coordination of the activity between the circular and longitudinal muscles are essential for overall activity

-the GI tract is highly influenced by our central moods
- ▪this is because of the **vagal parasympathetic input (preganglionic)** as well as the **sympathetic input (postganglionic)**

GASTROINTESTINAL DRUGS

GI Tract:
- ▪stores, digests and absorbs nutrients
- ▪eliminates waste - *you want to eliminate waste and NOT nutrients!*

Regulated by:
- ▪Enteric (local) nervous system
- ▪CNS
- ▪GI hormones

TREATABLE CONDITIONS

1. **Reflux Esophagitis-** *also known as heartburn*
2. **Peptic Ulcers-** *acid in the stomach attacks the mucosal layers of stomach*
3. **Delayed Gastric Emptying-** *food etc. stays in the stomach and doesn't empty into small intestine*
4. **Inadequate Propulsion of Chyme-** *stuff doesn't move fast enough in the intestines*
5. **Infections and Inflammation-** *treating with anti-diarrheals doesn't help…makes it worse! -the diarrhea is present to rid the infection*

PEPTIC ULCERS

-in the normal situation, there is a balance between the **acid pepsin aggression** (pepsin=protease that cleaves food) and **mucosal defense** (layer on mucosal that protects it from peptidic attack)

▪with an ulcer, the balance is tipped…the aggression overwhelms the defense

-there are different types of ulcers:

(a) Duodenal Ulcers

-increased mass of gastric **parietal cells**

- These are the cells that secrete gastric acid (therefore we get an increase)

(b) Gastric (peptic) Ulcers

-acid secretion is normal

-there is a mucosal defect that is caused by bacteria that leads to the ulcer

-**Helobacter Pylori** is the bacteria that causes ulcers

▪in the normal situation, there is a balance between the secretion of acid and the hormones that regulate the secretion…this is through a negative feedback mechanism

▪the hormone that controls this is called **Gastrin**

- The acid secretion is secreted by a pump in parietal cells; the more acid there is, the less gastrin there is
- The less gastrin there is, the less secretion of HCl there is

▪when infected with helicobacter pylori, the feedback loop is disrupted

- The cells keep pumping acid without getting the feedback inhibition

▪the easiest way to treat this is with antibiotics - kill the bacteria

▪also want to treat the symptoms, the **acid** – use a chemical neutralization

▪you can also block the machinery that pumps acid into the lumen

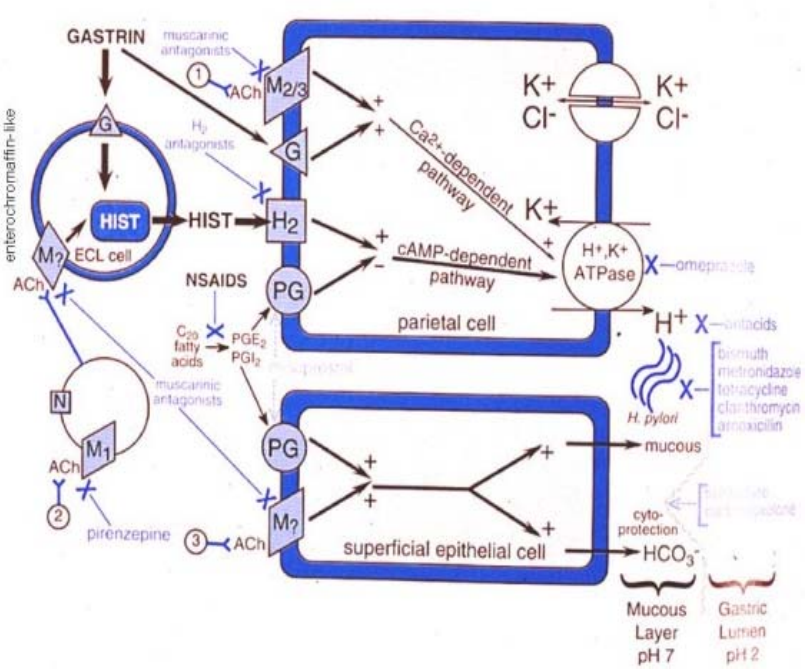
-in addition, the **exotoxin** (toxin secreted by bacteria) also damages the gastric mucosa by itself…this reduces the defense of the mucosa against the bacteria

Therefore, the bacteria disrupts:
1-The feedback mechanism
2-The mucosa (damages)

-the **parietal cells** pump out the H^+ ions that create the acid

▪this pump = energy dependent - it is an **ATPase –** creates energy by cleaving ATP so can pump out AGAINST the gradient (stomach is already very acidic to begin with)

▪this pump is regulated by a Ca^{2+} dependent pathway which is activated by **muscarinic receptors** ($M_{2/3}$)
▪so, a vagal input from the para-sympathetic system will activate these receptors
▪this pump can ALSO be activated by receptors for the hormone gastrin (whose secretion is triggered by food, since food increase the pH of the stomach)
-there are also **histamine (H_2)** receptors that can activate the pump through a cAMP dependent pathway
-finally, there is a **prostaglandin receptor** that has a negative effect



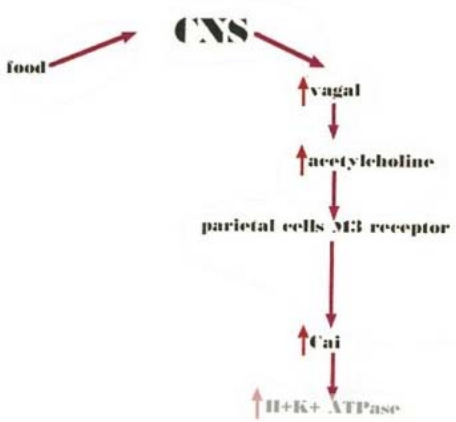
▪this is why aspirin causes ulcers; aspirin inhibits prostaglandins, which usually control acid secretion
▪it is best to thing of PGs as a negative control on the secretion of acid

-**enterochromffin-like** cells can control the parietal cells (release of acid) through histamine
▪these cells will release histamine in the presence of food, leading to acid secretion
▪ food talks to these cells through gastrin
▪gastrin can act on these cells!

-therefore, gastrin can act directly (through its receptor and the Ca^{++} pathway) or indirectly (through receptors on the enterochromaffin-like cells, secreting histamine)

-there are two sites where muscarinic receptors are present: on the parietal cells itself (directly) or on the enterochromaffin-like cells, leading to the secretion of histamine (main activator of the secretion of acid) and the eventual acid secretion by the parietal cells

-because of the great numbers of receptors, and cells, there are many different pharmacological targets
e.g. **Omeprazole** covalently binds the H^+ ATPase pump
▪you can also use: -muscarinic antagonists
-H_2 antagonists



-**cholinergic** regulation of acid secretion (see diagram on right)

- normally, the stomach is very acidic and has a low pH - when food comes in, the pH increases
▪this triggers **gastrin release** (gastrin release is sensitive to pH)
- increasing pH = more gastrin released
- low pH = gastrin not released

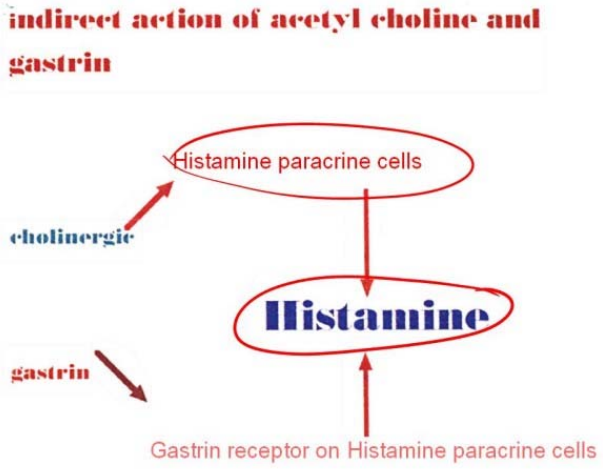
▪as gastrin receptors increase in activity, the Ca^{++} levels also increase, leading to secretion by the parietal cells

-the **histamine** pathway is the <u>most important one!</u>

- ▪histamine acts on **H_2 receptors**, which through G_s coupled receptors, increase adenylate cyclase
- ▪adenylate cyclase then increases the amount of cAMP, which is part of a path that works on the ATPase (H^+ pump)

-acetyl choline and gastrin also have INDIRECT effects

- ▪these can work on **histamine paracrine cells** (chromaffin-like cells that secrete histamine, located next to parietal cells) to increase histamine, and thus, increase the activity of the ATPase (H^+ pump)
- gastrin can also act on these cells to increase histamine
- ▪this is why histamine is so important - it is a meeting point of all the inputs from the brain, pH, etc.



DRUGS FOR PEPTIC ULCERS: POTENTIAL SITES OF ACTION

1. **Antacids neutralize pH-** *e.g. magnesium oxide, magnesium hydroxide*
   -these are not even drugs! Just chemicals, not pharmacological agents since they do not act on receptors. These are just chemicals that change the chemistry in the gut.
2. **H_2 Receptor Blockers** *-cimetidine*
3. **M_1 or M_3 Blockage** *-propantheline*
4. **Adenylate Cyclase Inhibitors**
5. **Inhibitors of H^+ ATPase** *-omeprazole*

<u>*H_2 RECEPTOR BLOCKERS*</u>

-e.g. **cimetidine, famotidine, rantidine, nizatidine**

-cimetidine suppresses acid secretion

- ▪to prove this works, you do experiments with **betazole**, a histalog (analog of histamine, stimulates acid secretion)
- ▪comparing cimetidine to placebo, you see that the peak of acid secretion is much lower or non-existent (depending on dose)
- ▪because pepsin secretion follows acid secretion, you can do the same with pepsin levels (see that cimetidine suppresses this when compared to the placebo)

Disadvantages of Cimetidine

- ▪short duration of action (since it is just a competitor)
- ▪interference with p450s (slow clearance of other drugs such as diazepam, phenytoin)
- ▪antiadrogenic effects- *makes you appear female (bad for males!)*

-because of the disadvantages of cimetidine, **ranitidine** was created

- ▪longer duration of action
- ▪doesn't interfere with p450s as much
- ▪less antiadrogenic effects

PROTON PUMP INHIBITORS

-**omeprazole** is an irreversible inactivator of the H^+/K^+ pump (ATPase)
- ▪irreversible drugs stay persistent as long as the protein is present
- ▪the protein turnover rate determines how long the drugs is effective for

-this drug is activated by acid, meaning it is only activated in situations of high acid (a pro-drug)
-the drug works by forming a covalent cysteine-cysteine (S-S) bond between itself and the enzyme
-this can be measured by comparing omeprazole with a placebo and acid secretion
- ▪the acid secretion level only reaches the original level after 14 days

Side Effects of Omeprazole:
- ▪gastric mucosal hyperplasia- *overgrowth that could lead to tumorigenesis*
  - -this could be a result of excessive gastrin secretion; gastrin is also a hormone that can stimulate cells
  - -omeprazole blocks the pump, reducing the pH, resulting in gastrin release which causes the formation of more parietal cells leading to hypertrophy

-it was one of the most common treatments of peptic ulcers (until antibiotics were starting to be used)
-there is chronic treatment of some patients with antacids and pump inhibitors, as it is very difficult to completely rid the stomach of all the bacteria causing the problem

ANTACIDS

-responsible for neutralizing intragastric HCl
-NaCl and other salts created are not absorbed and are excreted in the feces
-by increasing pH of the intragastric region, pepsin (a protease) activity decreases, meaning less breakdown of the stomach

-you can take **systemic antacids** such as **sodium bicarbonate** that work everywhere
= can lead to increased blood pH and alkalinized urine (problematic!)

-you can also take **non-systemic antacids** such as **calcium, magnesium** and **aluminum salts**
= these are poorly absorbed and remain within the system they are found in

-there are both therapeutic effects and side effects associated with antacids
- this is an effective management of peptic ulcers…no acid = less problems!

Disadvantages:
- ▪frequent dosing required
- ▪disagreeable taste

-different antacids have different properties, based on the chemistry

Mechanism of action of antacids

(1) $Al(OH)_3 + 3HCl \rightleftharpoons Al Cl_3 + 3H_2O$

(2) $Mg(OH)_2 + 2HCl \rightleftharpoons Mg Cl_2 + 2H_2O$

Interaction of soluble $MgCl_2$ with sodium carbonate in the lumen to form insoluble $MgCO_3$

(3) $Mg Cl_2 + Na_2 CO_3 \rightleftharpoons MgCO_3 (PPT) + 2NaCl$

Interaction of soluble $MgCl_2$ with fatty acid salts in the lumen to form insoluble $MgCO_3$

(4) $MgCl_2 + 2R—COONa \rightleftharpoons Mg (R—COO)_2 (PPT) + 2NaCl$

(a)Sodium and Potassium→ rapid onset, short duration of action
(b)Calcium→ rapid onset, pH raised to only 1.5, longer duration of action
(c)Magnesium→ rapid onset, pH raised to high values, acts as a laxative (diarrhea)
(d)Aluminum→ slow onset, constipative

-antacids available in stores are MIXTURES of the above

- ▪usually involves = **rapid onset + long duration + constipative/laxative**

- ▪low sodium preparation are used for patients on restricted sodium intakes
  - -e.g. common with patients that have high blood pressure

MUCOSA PROTECTORS

-another method of drug administration can be through increasing the protection of the mucosa

- ▪this drug is called **Sucralfate**

-this drug is an aluminum salt of sucrose
-it DOES NOT decrease acid concentration

- ▪this is important because the acid serves a vital role in digestion

-complexes with protein at ulcer site to form a protective layer
-sucralfate can also bind to pepsin and slow back diffusion of H^+ ions

REFLUX ESOPHAGITIS

= inappropriate relaxation of lower esophageal sphincter

- ▪this means that things can leave the stomach and enter the esophagus

-if there is a flow of gastric contents into the esophagus, you get an irritation and inflammation of esophageal mucosa

-to remedy this, you can increase the tone of the sphincter or you can use antacids to reduce the acids

- ▪by increasing the tone, you increase the contractility (prevents the backflow)
- ▪you can also treat the backflow chemically with antacids

GASTROPARESIS

= damage to gastric nerves or smooth muscle (e.g. in diabetes)

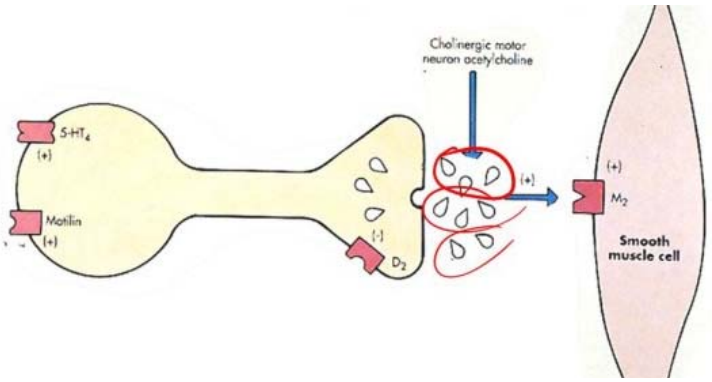
-this results in a paralysis in the smooth muscle of the gastric cells

-this leads to a delay in gastric emptying

-to remedy this, you use pro-kinetic drugs, drugs that will increase the emptying rate

- ▪these drugs increase the kinetics of the muscles (e.g. increase general contractility)

PRO-KINETIC DRUGS



-in the normal situation, Ach leaves nerve terminals and acts on receptors (e.g. M_2) on smooth muscle cells

-by acting on these muscarinic receptors, the contractility of the muscle is increased (very similar to asthma)

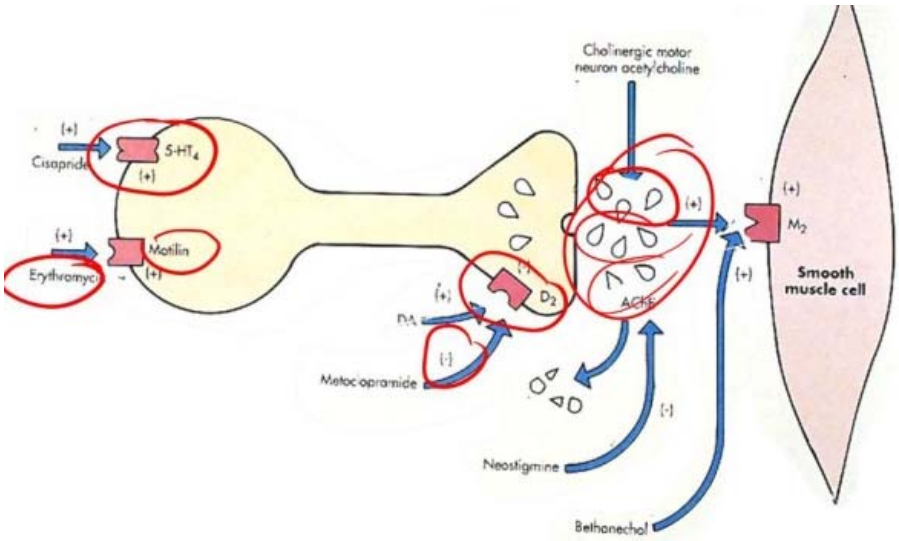
-because of this action, you have different pharmacological targets for drugs

-for example, you can use **cholinesterase inhibitors**, which will increase the concentration of Ach leading to an increased firing rate of the smooth muscle cells

-you can also have pre-synaptic targets

- there is a NEGATIVE dopamine (D_2) receptor that is inhibitory…when activated, release of Ach is blocked
- there is a POSITIVE serotonergic (5-HT) receptor
- there is a hormonal receptor for the hormone **Motilin** (think: Motilin = motion) which causes secretion of acetyl choline (a positive receptor)
  - -this can be activated with **Erythromycin**

-therefore, with pro-kinetics, you can either target the synapse, or positive/negative receptors pre-synaptically
-as indicated in the diagram, there are many different drugs that can act pro-kinetically…



-ALL of these drugs serve to INCREASE Ach levels, thereby increasing the amount of contraction in the smooth muscle

- **Neostigmine**=cholinesterase inhibitor
- **Metaclopramide**=D_2 inhibitor
- **Cisopride-** 5-HT agonist etc.

Side Effects of Cholinergic Drugs (remember, Ach is part of the cholinergic system)

- increased cholinergic stimulation of salivary, gastric, pancreatic and intestinal secretory cells
- no coordination of gastroduodenal contraction
  - -muscles don't contract on their own…controlled by pre-synaptic nerve
  - -by just adding Ach, you lose coordination as the nerve inputs are no longer the only things causing contraction

-because of the potential for a loss of coordination, it is best to work at the pre-synaptic inputs, as this allows for nerve impulses to still come into play

- cardiac conditions and asthma could be exacerbated as a result of cholinergic drugs
  - -the nerves that trigger smooth muscle in the stomach also trigger the bronchii

-an example of a cholinergic drug is **metoclopramide**, a dopamine antagonist that is a pro-kinetic drug

- this acts pre-synaptically, preventing inhibition
- because it is pre-synaptic, coordination is maintained to a higher degree

D_2 Receptor Antagonists:

- ▪increase lower sphincter tone
- ▪increase force of gastric contraction
- ▪increase coordination of gastrodudenal contraction (compared to other drugs)
- ▪increase gastric emptying

-as such, these drugs can fix both problems with the sphincter and problems with gastric emptying
-the most important differentiation between cholinergic drugs and D_2 antagonists is coordination
-there are also different side effects

Side Effects:

- ▪Parkinson like side effects- **dystonia**
- ▪Increased prolactin- **gynecomastia, galactorrhea** (increase breast in males, increase lactation)

-some prokinetic drugs can suppress **emesis** (a positive side effect)
-it is important to note the differences in side effects between cholinergic drugs and D_2 antagonists…also remember that they are BOTH pro-kinetic drugs!

5-HT4 Agonists

- ▪increase lower sphincter tone
- ▪increase gastroduodenal coordination
- ▪increase gastric contractions

-**ondansteron** has 5-HT3 antagonistic activity as well as **anti-emetic activity**
(emesis = vomiting etc.)

CONSTIPATION

-there are many causes of constipation:

- ▪functional disorders
- ▪drug treatment-*e.g. magnesium*
- ▪low residue diets - *diets that are low in fiber, and don't absorb a lot of water*

-to deal with constipation, you use laxatives

DIARRHEA

-can be **acute** or **chronic**

- ▪the acute condition is caused by either viral or bacterial infection
  - -to treat, treat the infection
- ▪the chronic condition is inflammatory and can be a result of **functional bowel disease**
  - -to treat, use **antidiarrheal agents**

LAXATIVES

-pharmacologically act and trigger secretion of water in the GI tract

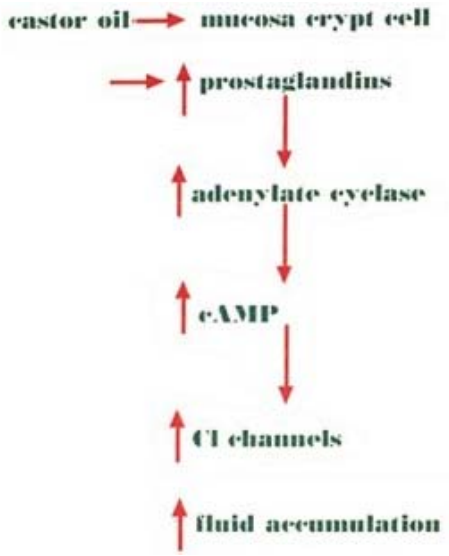
- ▪stuff in the GI tract is pushed by lubrication…this lubrication is largely due to the amount of water secreted by the GI tract cells
- ▪by increasing water secretion, you increase lubrication

-you can also change the chemistry of the lumen (e.g. **saline)**
- ▪by putting a membrane in a high-salt situation, water will come out
- ▪this is a CHEMICAL action, not a pharmacological one

-you can add **emollients**, which essentially act as lubricants on their own

-can also add **bulk forming** things to the diet (such as bran) which will absorb water and help move material through the GI tract

-the secretory agents (pharmacological agents) are the least preferable to use, which the bulk forming agents are the most favorable (scaled)



-an example of a secretory laxative is **castor oil**
-here, prostaglandins serve to INCREASE adenylate cyclase (opposite to the situation in the stomach)
- ▪this occurs because the prostaglandins are acting on a different receptor

-overall, this leads to <u>increased fluid flow and peristalsis</u>
-there are possibly other castor oil mechanisms such as the inhibition of water reabsorption in the lower intestine
-all of these activities are done through prostaglandin receptors

Emollients
e.g. **Mineral Oil** = lubricates lower bowel in condition of irritation
- ▪non-absorbable

Adverse Effects:
- ▪elicitation of foreign-body reaction with resultant rectal irritation
- ▪competes with fat soluble vitamins leading to malabsorption (same with fat-soluble drugs)
- ▪**lipid pneumonitis** (in the lungs, inflammation)

Bulk-Forming Agents
e.g. **Bran, methylcellulose, psyllium**

-work by forming large hydrophilic masses
-these masses increase bulk and water content, leading to a decrease in intestinal transit time
-increased water content and decreased transit time leads to a decrease in the viscosity of the luminal content, causing GREATER FLOW through the bowel
-this treatment is essentially <u>innocuous</u> (harmless)

Saline Laxatives-work on osmotic pressures
-e.g. **Magnesium hydroxide, sodium phosphate, sodium sulfate**

-another example is **magnesia milk**: a poorly absorbed ion
-all of these draw water into the intestine by osmotic processes

Disadvantages of Laxatives:

- ▪lead to habituation
- ▪damage to **myenteric plexus** (nerve ends in the gut)
- ▪colonic atony-*as a result of damage to nerves…muscles will stop contracting*
- ▪excessive loss of water and electrolytes
- ▪excessive loss of Ca
- ▪protein losing gastroenteropathy

-both antacids and laxatives can damage important physiological processes
-the easy availability of laxatives has led to ABUSE

Therapeutic Priorities: Laxatives

1. Dietary modification, increased fiber and fluids
2. Bulking Agents
3. Osmotic Laxatives
4. Stimulants (intermittent use)

ANTIDIARRHEAL DRUGS
-if chronic, you need to use antidiarrheal agents

-diarrhea is caused by increased fluid secretion paired with a reduction in absorptive capacity

-this can be treated by blocking the secretion

- ▪increase viscosity and contraction
- ▪increase absorption of water (opposite to laxatives)
- ▪reduce secretion of water, etc.

-it is important to remove the chemicals that are stimulating the diarrhea, if present

-**Opioids** act both centrally and locally to block the secretion of water and stimulate the retention of food

- ▪these act on intestinal neurons to increase absorption and decrease secretion
- ▪CNS effects→absorption

-because the gut is highly controlled by the brain, the CNS effects of opioids also have effects!

-opioids are also capable of changing the patterns of motility to increase resistance to flow

- ▪e.g. through an increase in contraction of the **circular muscles**, things remain in the lumen

-opioids such as **morphine** and **codeine** cross the blood-brain barrier (BBB) and have CNS action and local action

- ▪these increase segmental contraction
- ▪reduce propulsive contraction

-there are other opioids such as **loperamide** and **diphenoxylate** that have ONLY intestinal action

- ▪these DO NOT cross the BBB
  - = no CNS effects, low abuse potential

-opioids should be used cautiously and should NOT be employed in treatment of diarrhea induced by enteric infections

- ▪if it is a bacteria, the first thing you want to use is a proper anti-bacterial agent!

Thursday, March 22, 2007.
Dr. Bowie - Lecture #19

Intro to the Cardiovascular System

Cardiovascular drugs fall into 2 categories:

1. drugs that control heart rate
2. drugs that control blood pressure

There are three main disease states:

1. Hypertension

Hypertension, commonly referred to as "high blood pressure", is a medical condition where the blood pressure is chronically elevated. Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure.

2. Myocardial Ischemia

Myocardial ischaemia is the pathological loss of or reduction in blood flow (ischemia) to a part of the muscular tissue of the heart (myocardium).

3. Heart failure

Heart failure is a condition that can result from any structural or functional cardiac disorder that impairs the ability of the heart to fill with or pump a sufficient amount of blood throughout the body.

- Most people start off with hypertension. If the blood pressure is elevated for an extended period of time, blockage of heart vessels might occur and that leads to myocardial ischemia or stroke.
- With high blood pressure, heart failure occurs. In heart failure, the heart muscle becomes enlarged with poor pumping of the blood which decreases physiological functions and leads to death.

The Circulatory System

The circulatory system (cardiovascular system) is an organ system that moves substances to and from cells; it can also help stabilize body temperature and pH (homeostasis). There are three types of circulatory systems:

1) no circulatory system
2) open circulatory system
3) closed circulatory system

Circulatory systems are absent in some animals. An example is flatworms. Their body cavity has no lining or fluid. They have a muscular pharynx leading to a digestive system. Digested materials can be diffused to all the cells of the flat worm due to an extensively branched digestive system and being flattened dorso-ventrally. Oxygen can diffuse from water into the cells of the flatworm.

- Consequently, every cell is able to obtain nutrients, water and oxygen without the need of a transport system.

- An open circulatory system is an arrangement of internal transport present in some invertebrates, like simple molluscs and anthropods, in which circulatory fluid in a cavity called the hemocoel

bathes the organs directly; there is no distinction between blood and interstitial fluid - called hemolymph..

- Closed circulatory system Mammals and human beings.

The main components of the circulatory system are the heart, the blood, and the blood vessels.

- Blood is composed mainly of fluids (92%). The fluid volume determines the blood pressure.
- The heart consists of 4 chambers. The 2 upper chambers are the small ones and they are the right and left atrium.
- The function of the right side of the heart is to collect deoxygenated blood, in the right atrium, from the body and pump it, via the right ventricle, into the lungs (pulmonary circulation) so that carbon dioxide can be dropped off and oxygen picked up (gas exchange).
- The left side collects oxygenated blood from the lungs into the left atrium. From the left atrium the blood moves to the left ventricle which pumps it out to the body.
- On both sides, the lower ventricles are thicker and stronger than the upper atria.
- The muscle wall surrounding the left ventricle is thicker than the wall surrounding the right ventricle due to the higher force needed to pump the blood through the systemic circulation.

- **Cardiac cycle** is the term referring to all or any of the events related to the flow of blood that occurs from the beginning of one heartbeat to the beginning of the next. The frequency of the cardiac cycle is the heart rate.

- Every single 'beat' of the heart involves three major stages: atrial systole, ventricular systole and complete cardiac diastole.

- The term diastole is synonymous with relaxation of a muscle. Throughout the cardiac cycle, the blood pressure increases and decreases.
- Systole is the contraction of the chambers of the heart, driving blood out of the chambers. The chamber most often discussed is the left ventricle. However, all four chambers of the heart undergo systole and diastole in a timed fashion so that blood is propelled forward through the cardiovascular system.
    - Systole (or contraction of the heart) is initiated by the electrical cells of the sinoatrial node, which is the heart's natural pacemaker.
    - These cells are activated spontaneously by depolarization of their membranes beyond a certain threshold for excitation.
    - At this point, voltage-gated calcium channels on the cell membrane open and allow calcium ions to pass through into the interior of the muscle cell.

    - The action potential spreads via the passage of sodium ions through the gap junctions that connect the sarcoplasm of adjacent myocardial cells.

    - Blood filling up in the atrium starts to accumulate in the ventricles. In the ventricles, the pressure starts to build up because the volume is increasing. The ventricles then contract. Because arterial blood pressure is higher than ventricular blood pressure the chamber closes temporarily. As a result, the blood pressure in the ventricle picks up, and gets above the blood pressure in the atria. Then, the valves between the atria and the ventricles close and the pressure keeps building up until the ventricle contracts. As a result, the valves between the ventricle and the artery open and the blood is pumped out.

- The efficiency of the heart's function depends on the pressure that builds up and the elasticity of the heart's tissue that is involved. A disease occurs when any of these components is not functioning well.

- Anything that changes the arterial blood pressure can affect the ability of the heart to funtion. When blood pressure drops, the speed at which cells receive blood fluid (oxygen and nutrient) decreases.

- Sensory nerves sense the blood pressure in the aorta and send it to the brain stem. Depending on blood pressure changes, the brain sends an impulse to the heart to speed up and increase the force of contraction or slow down and reduce the force of contraction.

- If arterial blood pressure increases, more parasympathetic impulses and fewer sympathetic impulses are sent to the heart (increase inhibition and reduce excitation).
- This results in an increase of the heart rate and a reduction in its force of contraction. That leads to a decrease in the cardiac output and eventually restoration of the blood pressure (by decreasing it).
- Drugs interfere with various steps of this pathway. In heart failure, they increase the cardiac output. In hypertension, they decrease blood pressure.

The autonomic nervous system consists of the sympathetic nervous system (SNS) and the parasympathetic nervous systems (PNS).

- In PNS, stimulation of muscarinic receptors act on muscarinic receptors, activate G-protein and decrease cAMP.

Parasympathetic Nervous System

- Dilates blood vessels leading to the GI tract, increasing blood flow. This is important following the consumption of food, due to the greater metabolic demands placed on the body by the gut.
- The parasympathetic nervous system can also constrict the bronchiolar diameter when the need for oxygen has diminished.

- During accommodation, the parasympathetic nervous system causes constriction of the pupil and lens.

- The parasympathetic nervous system stimulates salivary gland secretion, and accelerates peristalsis; so, in keeping with the rest and digest functions, appropriate PNS activity mediates digestion of food and indirectly, the absorption of nutrients.

In SNS, norepinephrine and noradrenaline activate β1 receptors on the heart which increase cAMP.

Sympathetic Nervous System:

- Diverts blood flow away from the gastro-intestinal (GI) tract and skin via vasoconstriction.

- Blood flow to skeletal muscles, the lung is not only maintained, but enhanced (by as much as 1200%, in the case of skeletal muscles).

- Dilates bronchioles of the lung, which allows for greater alveolar oxygen exchange.

- Increases heart rate and the contractility of cardiac cells (myocytes), thereby providing a mechanism for the enhanced blood flow to skeletal muscles.

- Dilates pupils and relaxes the lens, allowing more light to enter the eye.

- At the effector organs, sympathetic ganglionic neurons release noradrenaline (norepinephrine) to act on adrenergic receptors.

- In the parasympathetic system, ganglionic neurons use acetylcholine as a neurotransmitter, to stimulate muscarinic receptors

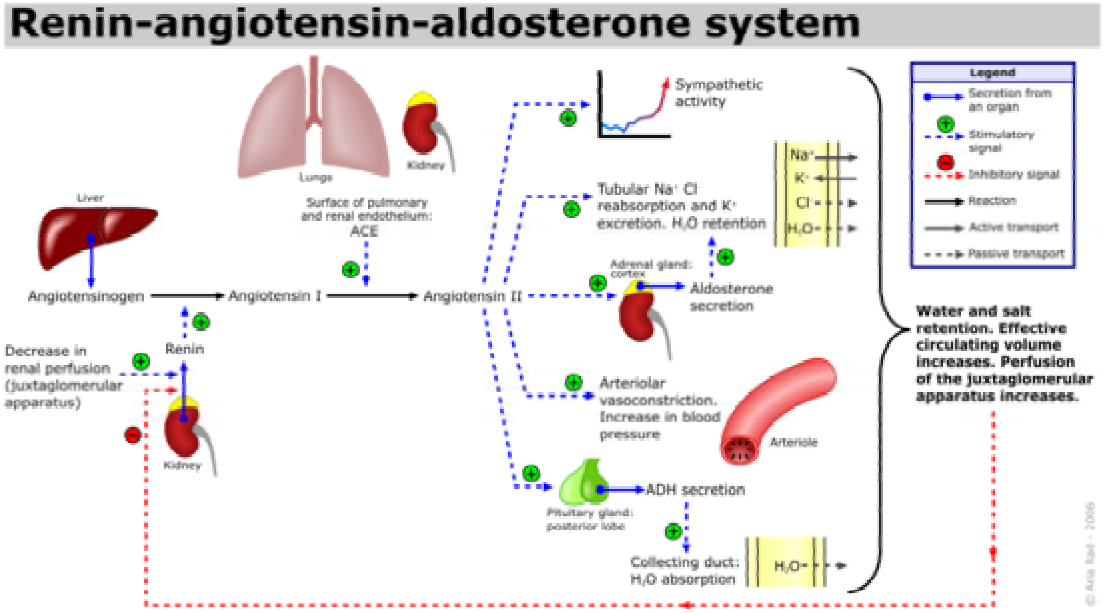
The following table reviews the actions of these neurotransmitters as a function of their receptors.

	Sympathetic (adrenergic, with exceptions)	**Parasympathetic (muscarinic)**
circulatory system		
cardiac output	increases	M2: decreases
SA node: heart rate (chronotropic)	β1, β2: increases	M2: decreases
cardiac muscle: contractility (inotropic)	β1, β2: increases	M2: decreases (atria only)
conduction at AV node	β1: increases	M2: decreases

- Cyclic AMP regulates potassium channels. If potassium channels open, they hyperpolarize the cell and make it less excitable.
- In the PNS, when cAMP goes down, potassium channels open up and decrease the cells' excitability.
- In the SNS, when cAMP goes up, potassium channels close and in contrast increase cells' excitability.

- The SNS and PNS affect the frequency and the force of contraction of the chambers and hence regulate blood pressure and heart rate.
- The SNS also regulates the **renin-angiotensin-aldosterone system** (RAAS). The RAAS is a hormone system that helps regulate long-term blood pressure and extracellular volume in the body. The system can be activated when there is a loss of blood volume or a drop in blood pressure.

Most of the drugs used to regulate the cardiovascular system affect the SNS. They regulate blood pressure by targeting the arterioles and the heart. Also the RAAS is targeted to regulate the blood volume.



- An increase in arterial blood pressure stimulates the SNS which send a message to the kidney to release renin and aldosterone release which regulates salt levels. Moreover, the angiotensin system has a vasopressor effect that decreases blood pressure.

Angiotensin II has a variety of effects on the body:

- Throughout the body, it is a potent vasoconstrictor.
- In the kidneys, it constricts glomerular arterioles, having a greater effect on efferent arterioles than afferent.
    - As with most other capillary beds in the body, the constriction of afferent arterioles increases the arterioler resistance, raising systemic arterial blood pressure and decreasing the blood flow. However, the kidneys must continue to filter enough blood despite this drop in blood flow, necessitating mechanisms to keep glomerular blood pressure up.
    - To do this, Angiotensin II constricts efferent arterioles, which forces blood to buildup in the glomerulus, increasing glomerular pressure. The glomerular filtration rate (GFR) is thus maintained, and blood filtration can continue despite lowered overall kidney blood flow.
- In the adrenal cortex, it acts to cause the release of aldosterone.
    - Aldosterone acts on the tubules (i.e. the distal convoluted tubules and the cortical collecting ducts) in the kidneys, causing them to reabsorb more sodium and water from the urine. Potassium is secreted into the tubule in exchange for the sodium, which is reabsorbed.
    - Aldosterone also acts on the central nervous system to increase a person's appetite for salt, and to make them feel thirsty.
    - Release of Anti Diuretic Hormone (ADH) → also called vasopressin, from the pituitary gland.

These effects directly act to increase the amount of fluid in the blood, making up for a loss in volume, and to increase blood pressure.