Anti-migraine Drugs

What is a Migraine?
- A debilitating neurobiological headache disorder
- Affects 28 million people in the US
- 18% of women & 6% of men
- Decrease with age
- Two categories
  - 80% = common migraine
  - 20% = classic migraine (w/ aura)
- Status migrainosus

Causes of Migraine
- Increased excitability of CNS
- Meningeal blood vessel dilation
- Activation of perivascular sensory trigeminal nerves
- Pain impulses
- Vasoactive neuropeptides contain:
  - Substance P
  - Calcitonin gene-related peptide (CGRP)
  - Neurokinin A
- Combination of increased pain sensitivity, tissue and vessel swelling, and inflammation

Interaction in Brain
Nerve signals travel to the pain nuclei in the brain stem, where the sensation of pain is processed
- Pain of a migraine arises between the skull and the brain tissue
- 3 meningeal membranes
  - Dura mater
  - Arachnoid membrane
  - Pia mater
History of Treatment

- Herbal brews and folk practices
- 1200 BC: Egyptians – clay crocodile & magic herbs
- 10th century AD: Arabian physicians – garlic or hot iron to incision at temple
- Mid-1600’s AD: Dr. Thomas Willis – enemas, blood letting, leeches, and natural products
- 1870’s: cold bandage on head, quiet room, and sleep

**Ergots**

- 1868: use of ergot in the treatment of one-sided headache
- Ergot: potent neurotoxin & vasoconstrictor found in a fungus that grows on rye
- 1925: identified active chemical of ergot (ergotamine)
- 1940’s: ergotamine tartrate became the preferred treatment for acute migraine

**Ergotamine**

- Structurally similar to amines,
  - serotonin, norepinephrine, and
  - dopamine
- interact with multiple receptors
  - in these systems
- cause constriction of the blood
  - vessels
- wide-range of effects
- Problems: avoid if patient has coronary disease; safety margin is small; overdose

**5-hydroxytryptamine receptors**

- natural 5-HT neurotransmitter called serotonin
- serotonin is involved in migraine
- anti-migraine drugs mimic the action of serotonin

**1980’s... discovery of Receptors**

- 2 subtypes of serotonin receptors
  - 5-HT1B
  - 5-HT1D
• Located in brain blood vessels – responsible for constriction
• Calcitonin gene-related peptide (CGRP) blocked
• CGRP - dilation of blood vessels and inflammatory changes in membrane around brain

**Tritpans**
• serotonin identified as a key player in the generation of a migraine attack
• early 1980’s: attempts to synthesize a more selective serotonin agonist
• “migraine medicines of today”

**Sumatriptan**
• Acts on receptors at smooth muscle cells of brain vessels (also in peripheral blood vessels like coronary artery = side effects)
• The first selective serotonin agonist approved for the treatment of migraine
• Rapid relief
• Triptans are an advance over ergots
• Relieves pain of migraine and associated symptoms
• 3 dosage forms: oral, nasal, & parenteral

**Sumatriptan Side-effects**
• Side effects:
  • Change in taste
  • Discomfort in the jaw or mouth
  • Dizziness
  • Drowsiness
  • Lightheadedness
  • muscle aches
  • nausea or vomiting
  • Rare side effects:
  • Severe chest pain
  • Convulsions
  • Swelling of the eyelids
  • Shortness of breath and trouble breathing

**Zolmitriptan**
• Oral bioavailability improved to ~50% (sumatriptan 14%)
• half-life of 3 hours
• take orally at the onset of headache pain

Side effects:
• Dizziness
• Nausea
• Sleepiness
• Muscle weakness
• Chest pain
• may cause serious side effects in some people, especially those with a heart or blood vessel disease

**Naratriptan**
• Oral bioavailability improved to ~60%
• half-life of 5-6 hours
• take orally at the onset of headache pain
• not as effective as sumatriptan, but has fewer side effects
• Side effects:
  • Dizziness
  • Nausea
  • Sleepiness
  • Muscle weakness
  • Chest pain

**rizatriptan**
• Oral bioavailability ~40%
• half-life of 2.5 hours
• shows the fastest time of onset!
• Side effects:
  • Dizziness
  • Nausea
  • Tiredness
  • Hot flashes
  • Chest pain
  • Shortness of breath

**Nonspecific Drugs**
• NSAIDs
• Beta blockers
• Antidepressants
• Calcium channel blockers

**Conclusion**
• Migraine treatment
• Migraine prevention
• Migraine remains a highly individual disorder

**The End**