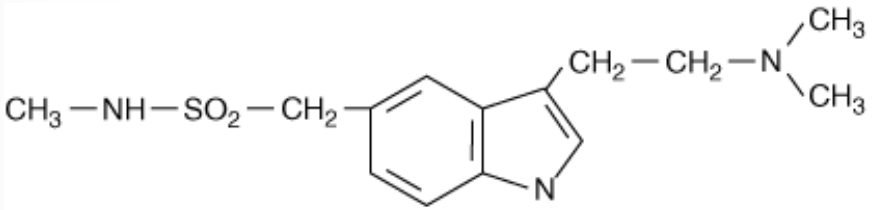
Module: Autacoids
Subject: Pharmacology
Lecture:



Sumatriptan

Autacoids-Serotonin, Ergot Alkaloids & Migraine-1 & 2

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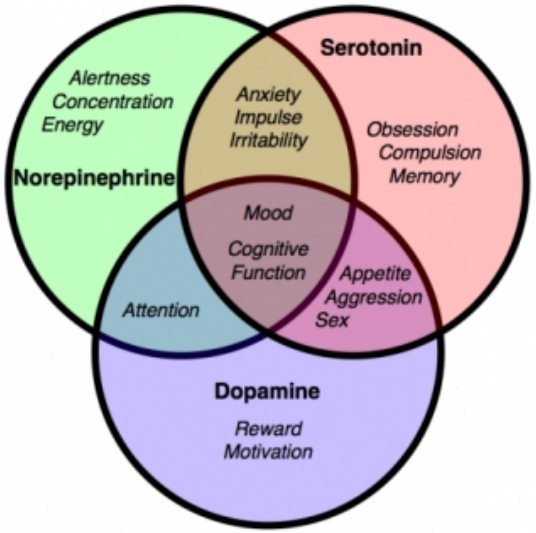
Serotonin(5-HT)-Introduction

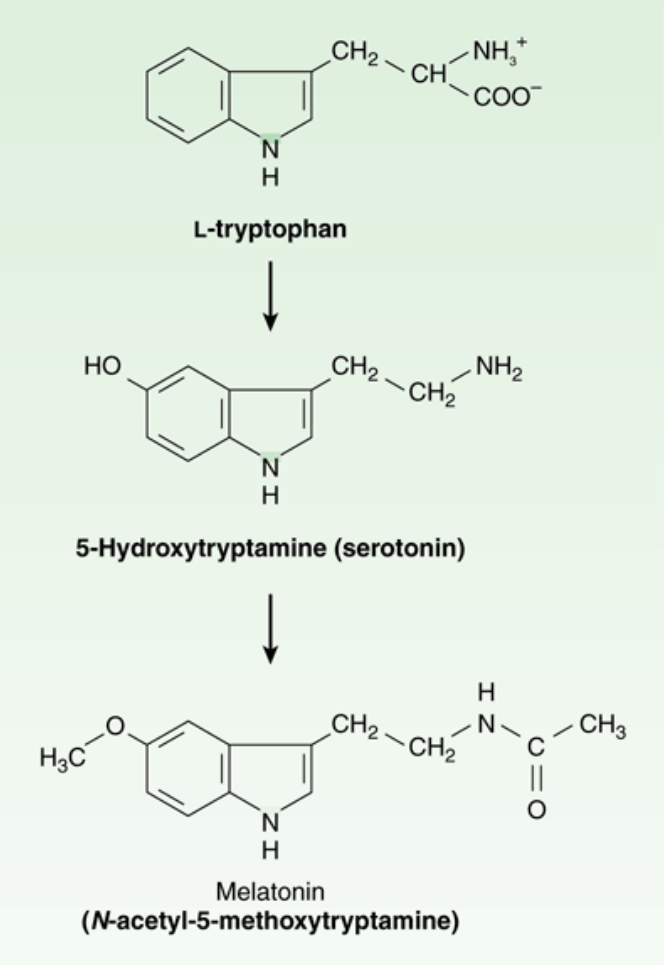


- Serotonin is
  - an important neurotransmitter
  - a local hormone in the gut
  - a component of the platelet clotting process, &
  - thought to play a role in migraine headache & several other clinical conditions, including carcinoid syndrome

Serotonin(5-HT)-Introduction

- Carcinoid syndrome is an unusual manifestation of carcinoid tumor, a neoplasm of enterochromaffin cells
- In patients whose tumor is not surgically resectable, a serotonin antagonist may constitute a useful treatment

Serotonin(5-HT)-Synthesis/Storage



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

- Like histamine, serotonin is widely distributed in nature, being found in plant & animal tissues/venoms/ stings
- Produced from tryptophan
- Stored in vesicles in the enterochromaffin cells of the gut & neurons of the CNS & enteric nervous system

Serotonin(5-HT)-Release/Metabolism

- After release, it is metabolized by monoamine oxidase
- Excess production in the body (e.g., in carcinoid syndrome) can be detected by measuring its major metabolite, 5-hydroxyindole acetic acid (5-HIAA), in the urine

Serotonin(5-HT)-Physiological Actions

- Serotonin plays a physiologic role as a neurotransmitter in both the CNS and the enteric nervous system and may have a role as a local hormone that modulates gastrointestinal activity
- Serotonin is also stored (but synthesized to only a minimal extent) in platelets
- In spite of the very large number of serotonin receptors(14 identified to date), most of the serotonin *agonists* in clinical use act at 5-HT $_{1D}$ receptors

Serotonin(5-HT)-Physiological Actions

- Brain serotonergic neurons are involved in numerous diffuse functions such as
  - Mood/sleep/appetite/temperature regulation/ perception of pain/regulation of blood pressure/vomiting
- Serotonin also appears to be involved in clinical conditions such as
  - Depression/anxiety/migraine

Serotonin Receptor Subtypes Currently Recognized

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT_{1A}	Raphe nuclei, hippocampus	G_i, ↓cAMP	8-OH-DPAT, repinotan	WAY100635
5-HT_{1B}	Substantia nigra, globus pallidus, basal ganglia	G_i, ↓cAMP	Sumatriptan, L694247	
5-HT_{1D}	Brain	G_i, ↓cAMP	Sumatriptan, Eletriptan	

Serotonin Receptor Subtypes Currently Recognized

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT_{1E}	Cortex, putamen	G_i, ↓cAMP		
5-HT_{1F}	Cortex, hippocampus	G_i, ↓cAMP	LY3344864	
5-HT_{1P}	Enteric nervous system	G_o, slow EPSP	5-Hydroxyindalpine	Renzapride

Serotonin(5-HT)-Receptors

- **5-HT_1 Receptors**
  - 5-HT_1 receptors are most important in the brain and mediate synaptic inhibition via increased potassium conductance
  - Peripheral 5-HT_1 receptors mediate both excitatory and inhibitory effects in various smooth muscle tissues
  - 5-HT_1 receptors are G_i-protein-coupled receptors

Serotonin Receptor Subtypes Currently Recognized

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
$5\text{-}HT_{2A}$	Platelets, smooth muscle, cerebral cortex	G_q, $\uparrow IP_3$	α-Methyl-5-HT, DOI	Ketanserin
$5\text{-}HT_{2B}$	Stomach fundus	G_q, $\uparrow IP_3$	α-Methyl-5-HT, DOI	RS127445
$5\text{-}HT_{2C}$	Choroid, hippocampus, substantia nigra	G_q, $\uparrow IP_3$	α-Methyl-5-HT, DOI, lorcaserin	Mesulergine

Serotonin(5-HT)-Receptors

- **5-HT_2 Receptors**
  - 5-HT_2 receptors are important in both brain and peripheral tissues
  - These receptors mediate synaptic excitation in the CNS and smooth muscle contraction (gut, bronchi, uterus, vessels) or relaxation (other vessels)

Serotonin(5-HT)-Receptors

- **5-HT_2 Receptors**
  - Several mechanisms are involved, including (in different tissues) increased IP_3, decreased potassium conductance, and decreased cAMP
  - This receptor class probably mediates some of the vasodilation/diarrhea/bronchoconstriction occuring as symptoms of carcinoid tumor, a neoplasm that releases serotonin and other substances

Serotonin Receptor Subtypes Currently Recognized

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT_3	Area postrema, sensory and enteric nerves	Receptor is a Na^+/K^+ ion channel	2-Methyl-5-HT, *m*-chlorophenylbiguanide	Dolasetron, Granisetron, Ondansetron, Palonosetron, Tropisetron
5-HT_4	CNS and myenteric neurons, smooth muscle	G_s, ↑cAMP	BIMU8, Renzapride, Metoclopramide	GR113808
$5\text{-HT}_{5A,B}$	Brain	↓cAMP		

Serotonin(5-HT)-Receptors

- **5-HT_3 Receptors**
  - 5-HT_3 receptors are found in the CNS, especially in the chemoreceptive area and vomiting center, and in peripheral sensory and enteric nerves
  - These receptors mediate excitation via a 5-HT-gated cation channel
  - Antagonists acting at this receptor have proved to be extremely useful antiemetic drugs

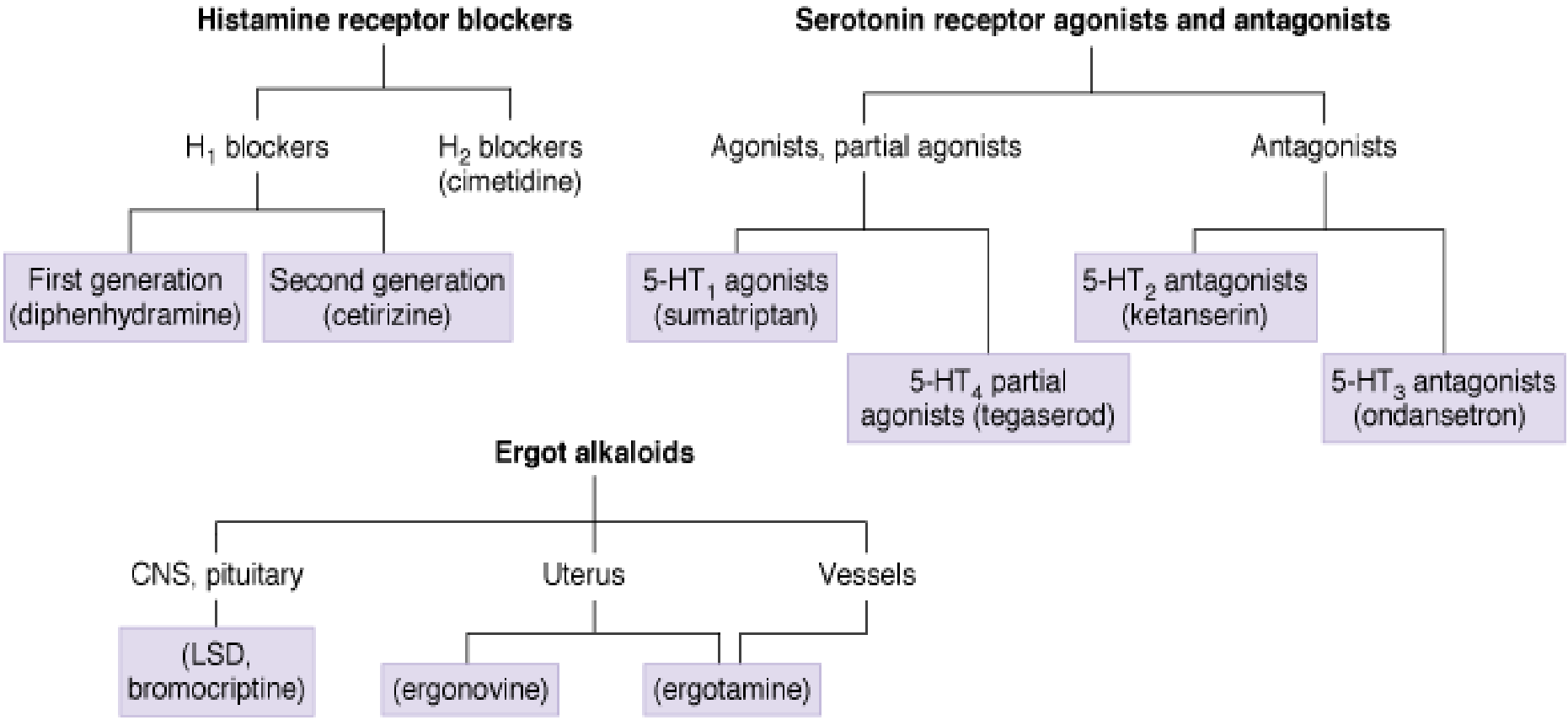
Serotonin(5-HT)-Receptors

- **5-HT_4 Receptors**
  - 5-HT_4 receptors are found in the gastrointestinal tract and play a very important role in intestinal motility

Serotonin Receptor Subtypes Currently Recognized

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-$HT_{6,7}$	Brain	G_s, ↑ cAMP		Clozapine (5-HT_7)

Serotonin Receptor Agonists & Antagonists-Classification



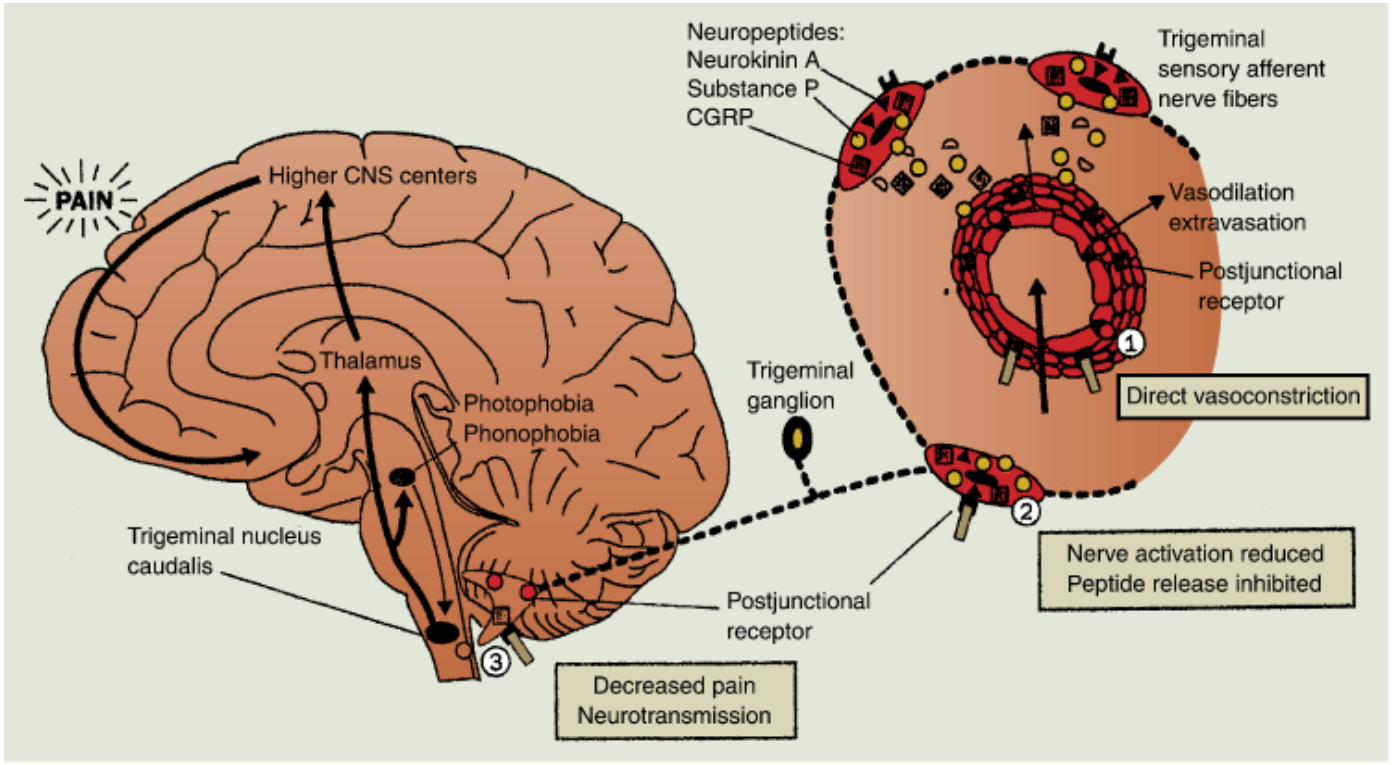
Serotonin(5-HT) Agonists-Clinical Uses

- **5-HT_{1D} Agonists**
  - Sumatriptan, a substituted indole compound, is the prototype
  - Naratriptan and other "-triptans" are similar to sumatriptan
  - They are the first-line treatment for acute and cluster headache attacks, an observation that strengthens the association of serotonin abnormalities with these headache syndromes

Serotonin(5-HT) Agonists-Clinical Uses

- **5-HT_{1D} Agonists**
  - Sumatriptan and the other triptans are selective agonists for 5-HT_{1D} and 5-HT_{1B} receptors
  - Similarity of the triptan structure to that of the 5-HT nucleus
  - These receptor types are found in cerebral and meningeal vessels and mediate vasoconstriction
  - They are also found on neurons and probably function as presynaptic inhibitory receptors

Migraine-Biologic Basis/Pathophysiology

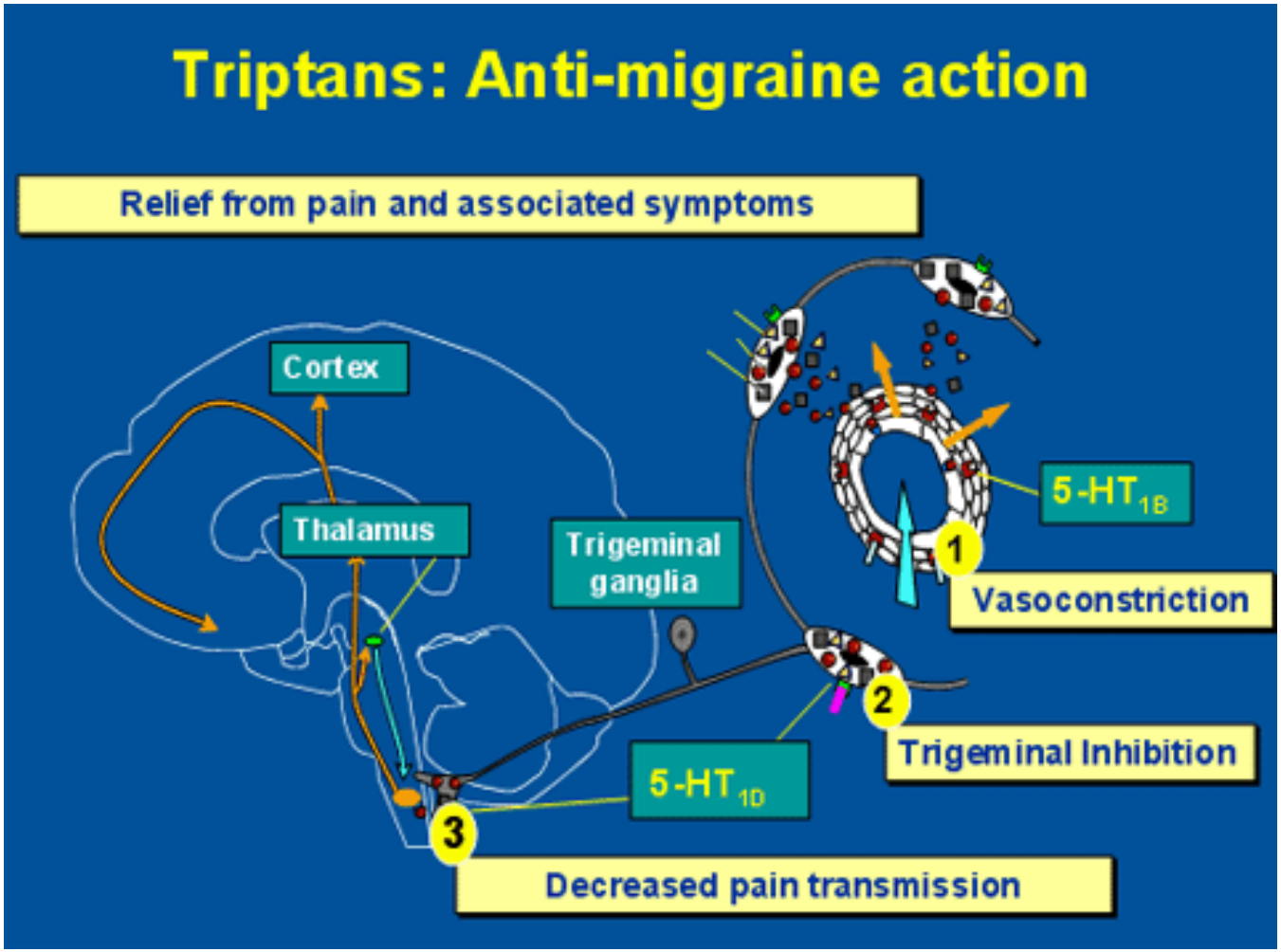


DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach,* 7th Edition: Http://www.accesspharmacy.com

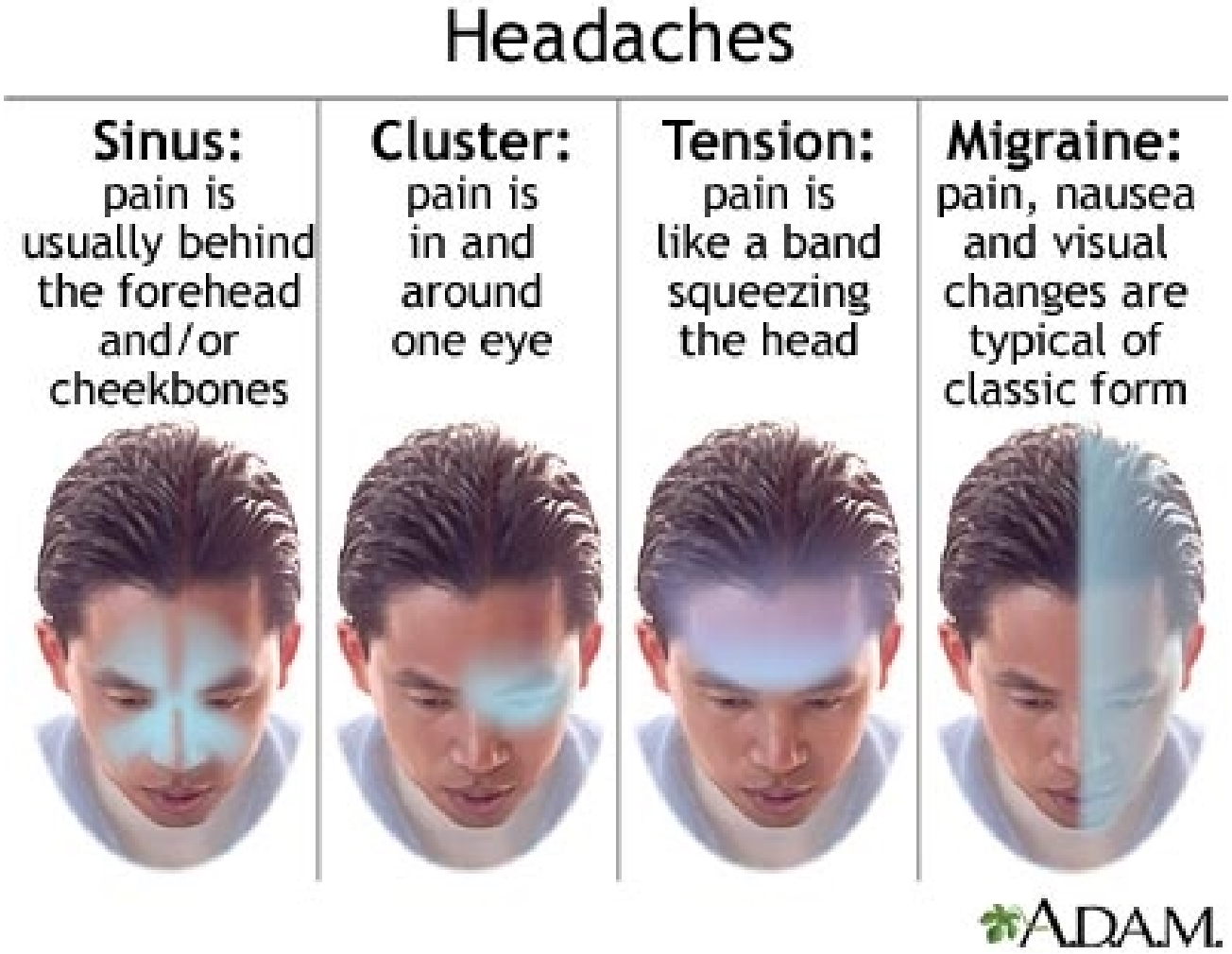
- Vasodilation of intracranial extracerebral blood vessels (possibly the result of an imbalance in the brainstem) results in the activation of the perivascular trigeminal nerves that release vasoactive neuropeptides to promote neurogenic inflammation
- Central pain transmission may activate other brainstem nuclei, resulting in associated symptoms (nausea, vomiting, photophobia, phonophobia)
- The antimigraine effects of the 5-$HT_{1B/ID}$ receptor agonists are highlighted at areas 1, 2, and 3

Serotonin(5-HT) Agonists-Clinical Uses

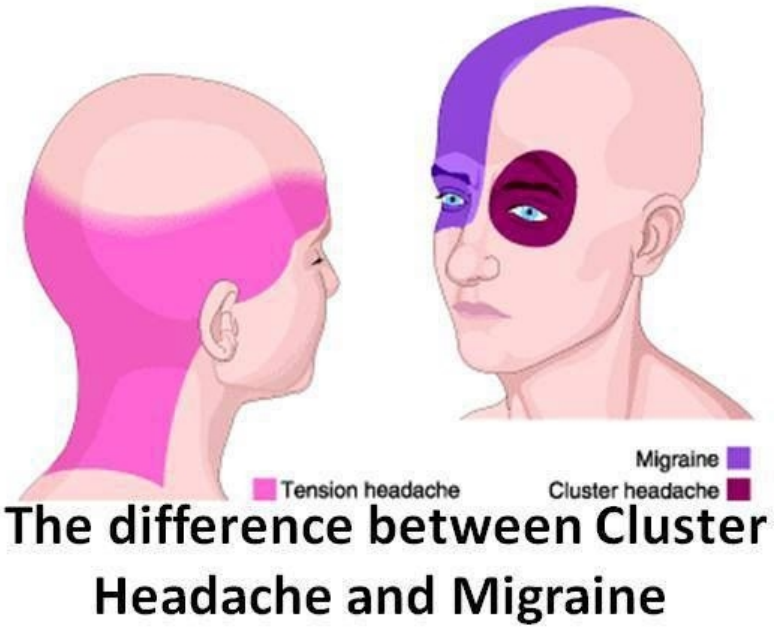
- **5-HT$_{1D}$ Agonists**

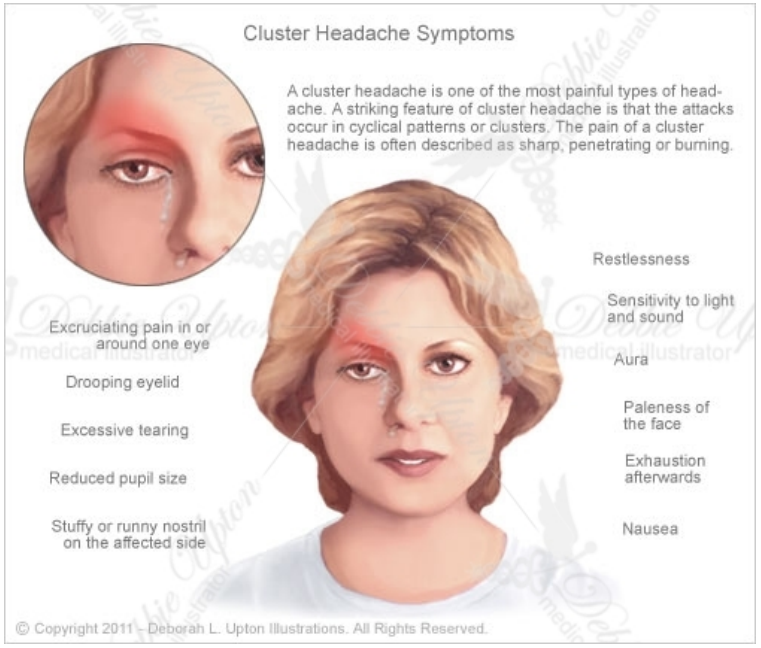


Characteristics of Migraine, Cluster, & Tension-type Headaches



Characteristics of Migraine, Cluster, & Tension-type Headaches





- Tension-type Headache
  - Originates from myofascial factors
  - Female-to-male ratio of 5:4
  - Psychophysiologic/Physical Therapy
  - Acetaminophen/NSAIDs(aspirin/ibuprofen/naproxen/ketoprofen/indomethacin/ketorolac)

- Cluster Headache
  - Hypothalamic dysfunction/resulting alterations in circadian rhythms
  - Men more likely to have
  - Abortive Therapy: 100% O_2/Ergotamine/DHE/Triptans
  - Prophylactic Therapy: Verapamil/Li^+/Ergotamine/ Methysergide/Corticosteroids/Lidocaine/Capsaicin, etc.

Serotonin(5-HT) Agonists-Clinical Uses

- **5-HT_{1D} Agonists**
  - The efficacies of all the triptan 5-HT_1 agonists in migraine are equal to each other and equivalent to or greater than those of other acute drug treatments, e.g., parenteral, oral, and rectal ergot alkaloids
  - The pharmacokinetics of the triptans differ significantly

Pharmacokinetics of Triptans

Drug	Routes	Time to Onset (h)	Single Dose (mg)	Maximum Dose per Day (mg)	Half-Life (h)
Almotriptan	Oral	2.6	6.25–12.5	25	3.3
Eletriptan	Oral	2	20–40	80	4
Frovatriptan	Oral	3	2.5	7.5	27

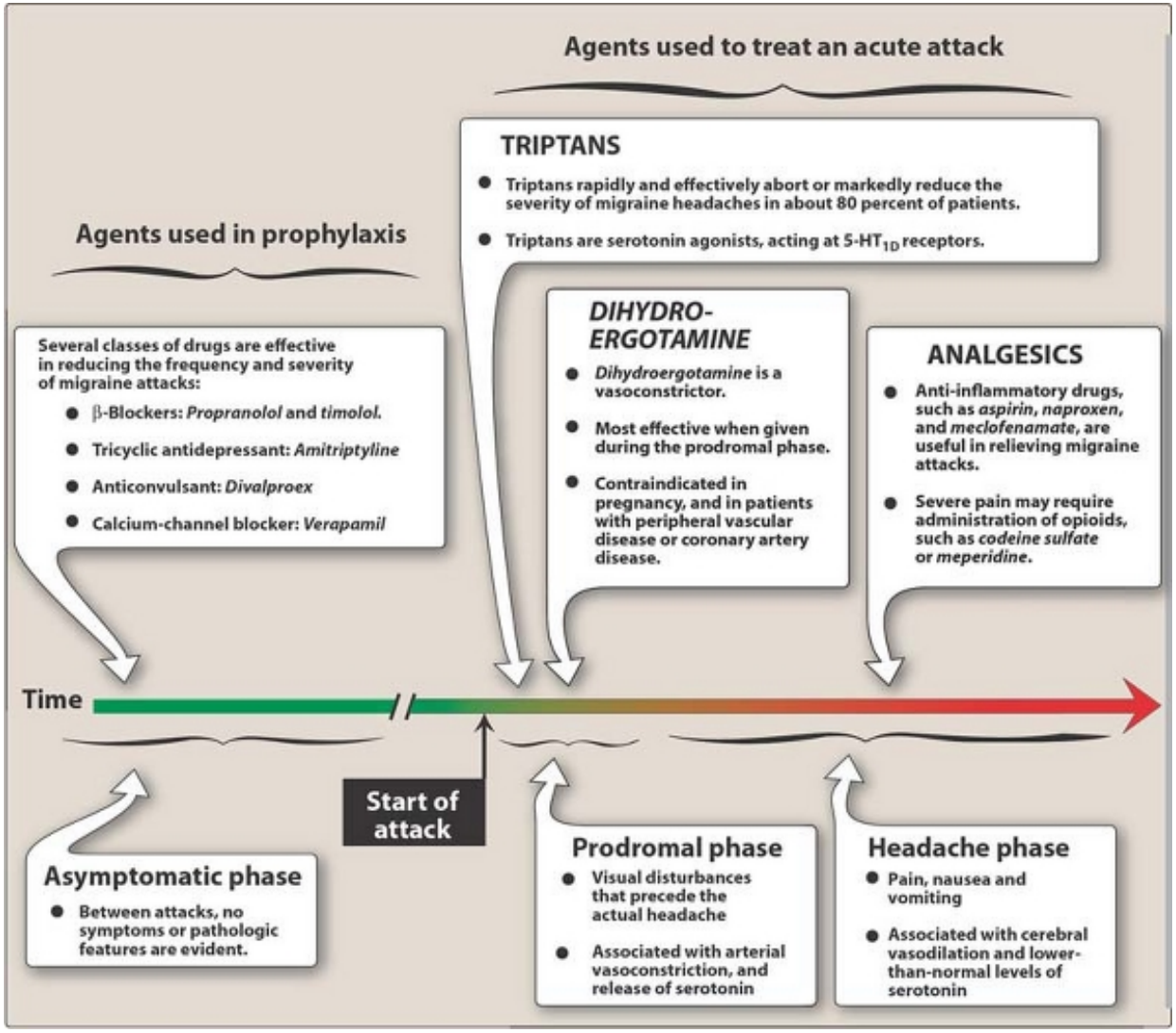
Pharmacokinetics of Triptans

Drug	Routes	Time to Onset (h)	Single Dose (mg)	Maximum Dose per Day (mg)	Half-Life (h)
Naratriptan	Oral	2	1–2.5	5	5.5
Rizatriptan	Oral	1–2.5	5–10	30	2
Sumatriptan	Oral, nasal, subcutaneous, rectal	1.5 (0.2 for subcutaneous)	25–100 (PO), 20 nasal, 6 subcutaneous, 25 rectal	200	2
Zolmitriptan	Oral, nasal	1.5–3	2.5–5	10	2.8

Serotonin(5-HT) Agonists-Adverse Effects

- **5-HT_{1D} Agonists**
  - Most adverse effects are mild and include altered sensations (tingling, warmth, etc), dizziness, muscle weakness, neck pain, and for parenteral sumatriptan, injection site reactions
  - Chest discomfort occurs in 1–5% of patients, and chest pain has been reported, probably because of the ability of these drugs to cause coronary vasospasm
  - They are therefore contraindicated in patients with coronary artery disease and in patients with angina

Drugs useful in the Treatment & Prophylaxis of Migraine Headaches



Serotonin(5-HT) Agonists-Clinical Uses

- **5-HT_4 Partial Agonist**
  - **Cisapride,** a 5-HT_4 agonist, was used in the treatment of gastro-esophageal reflux and motility disorders
  - Because of toxicity, it is now available only for compassionate use in the USA

Serotonin(5-HT) Agonists-Clinical Uses

- **5-HT_4 Partial Agonist**
  - Tegaserod is a newer drug that acts as an agonist in the colon
  - It was approved and briefly marketed for use in chronic constipation, but because of cardiovascular toxicity, its use is now restricted

Serotonin(5-HT) Agonists-Clinical Uses

- **Selective Serotonin Reuptake Inhibitors (SSRI)**
  - A number of important antidepressant drugs act to increase activity at central serotonergic synapses by inhibiting the serotonin reuptake transporter, SERT
    - Fluoxetine
    - Fluvoxamine
    - Sertraline, etc.

Serotonin(5-HT)-Adverse Effects

- **Hyperpyrexic Syndromes**
  - Serotonin and drugs with 5-HT agonist effects are sometimes associated with drug reactions with high fever, skeletal muscle effects, and cardiovascular abnormalities that can be life-threatening

Characteristics of Serotonin Syndrome & Other Hyperthermic Syndromes

Syndrome	Precipitating Drugs	Clinical Presentation	Therapy
Serotonin syndrome	SSRIs, second-generation antidepressants, MAOIs, linezolid, tramadol, meperidine, fentanyl, ondansetron, sumatriptan, MDMA, LSD, St. John's wort, ginseng	Hypertension, hyperreflexia, tremor, clonus, hyperthermia, hyperactive bowel sounds, diarrhea, mydriasis, agitation, coma; onset within hours	**Sedation (benzodiazepines), paralysis, intubation, and ventilation;** consider 5-HT_2 block with cyproheptadine or chlorpromazine

Characteristics of Serotonin Syndrome & Other Hyperthermic Syndromes

Syndrome	Precipitating Drugs	Clinical Presentation	Therapy
Neuroleptic malignant syndrome	D_2-blocking antipsychotics	Acute severe parkinsonism; hypertension, hyperthermia, normal or reduced bowel sounds, onset over 1–3 days	**Dantrolene** **Bromocryptine** **Diphenhydramine** (parenteral), cooling if temperature is very high, sedation with benzodiazepines

Characteristics of Serotonin Syndrome & Other Hyperthermic Syndromes

Syndrome	Precipitating Drugs	Clinical Presentation	Therapy
Malignant hyperthermia	Volatile anesthetics, succinylcholine	Hyperthermia, muscle rigidity, hypertension, tachycardia; onset within minutes	**Dantrolene**, cooling

Serotonin(5-HT)Antagonists

- **Classification and Prototypes**
  - Ketanserin, phenoxybenzamine, and cyproheptadine are effective 5-HT_2 blockers
  - Ondansetron, granisetron, dolasetron, palonosetron, tropisetron and alosetron are 5-HT_3 blockers
  - The ergot alkaloids are partial agonists (and therefore have some antagonist effects) at 5-HT and other receptors

Serotonin(5-HT)Antagonists

- **Mechanisms and Effects**
  - Ketanserin and cyproheptadine are competitive pharmacologic 5-HT_2 antagonists
  - Phenoxybenzamine is an irreversible blocker at this receptor
  - Ketanserin, cyproheptadine, and phenoxybenzamine are poorly selective agents
  - In addition to inhibition of serotonin effects, they also have α-blocking effects (ketanserin, phenoxybenzamine) or H_1-blocking effects (cyproheptadine)

Serotonin(5-HT)Antagonists

- **Mechanisms and Effects**
  - Ondansetron, granisetron, palonosetron, tropisetron and dolasetron are selective 5-HT_3 receptor blockers and have important antiemetic actions in the area postrema of the medulla and also on peripheral sensory and enteric nerves
  - Although it acts at the same receptor, alosetron appears to lack these antiemetic effects

Serotonin(5-HT)Antagonists

- **Clinical Uses**
  - Ketanserin has been studied as an antihypertensive drug
  - Ketanserin, cyproheptadine, and phenoxybenzamine may be of value(separately or in combination) in the treatment of carcinoid tumor, a neoplasm that secretes large amounts of serotonin (and peptides) and causes diarrhea, bronchoconstriction, and flushing

Serotonin(5-HT)Antagonists

- **Clinical Uses**
  - Ondansetron and its congeners are extremely useful in the control of vomiting associated with cancer chemotherapy and postoperative vomiting
  - Alosetron is used in the treatment of women with irritable bowel syndrome associated with diarrhea

Ergot Alkaloids

- Produced by *Claviceps purpurea*
- Amine Alkaloids:
  - 6-methylergoline/Lysergic acid/LSD/Ergonovine(Ergometrine)
- Peptide Alkaloids:
  - Ergotamine/α-Ergocryptine/Bromocryptine
- Clinical Uses:
  - Migraine: Ergotamine tartrate ± caffeine, DHE
  - Hyperprolactinemia: Bromocryptine/Cabergoline/Pergolide
  - Postpartum Hemorrhage: Ergonovine(Oxytocin is preferred)
  - Diagnosis of Vasospastic Angina: Ergonovine/Methylergonovine
  - Senile Cerebral InsufficiencyAlzheimer's Dementia: Dihydroergotoxine

THANK YOU..!

"I have a migraine, so I called you in for one of your mind-numbing conversations."