

# ***AUTACOID***

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# **INTRODUCTION**

**AUTACOIDS auto=self coids=healing/remedy**

**Local Hormones**

# **CLASSIFICATION**

- **Amine derived: Histamine (amino acid: Histidine), Serotonin (Tryptophan)**
- **Peptide derived: Angiotensin, Bradykinin**
- **Lipid derived: Prostaglandins, Leukotrienes, Interleukins, Platelet Activating Factor, etc.**

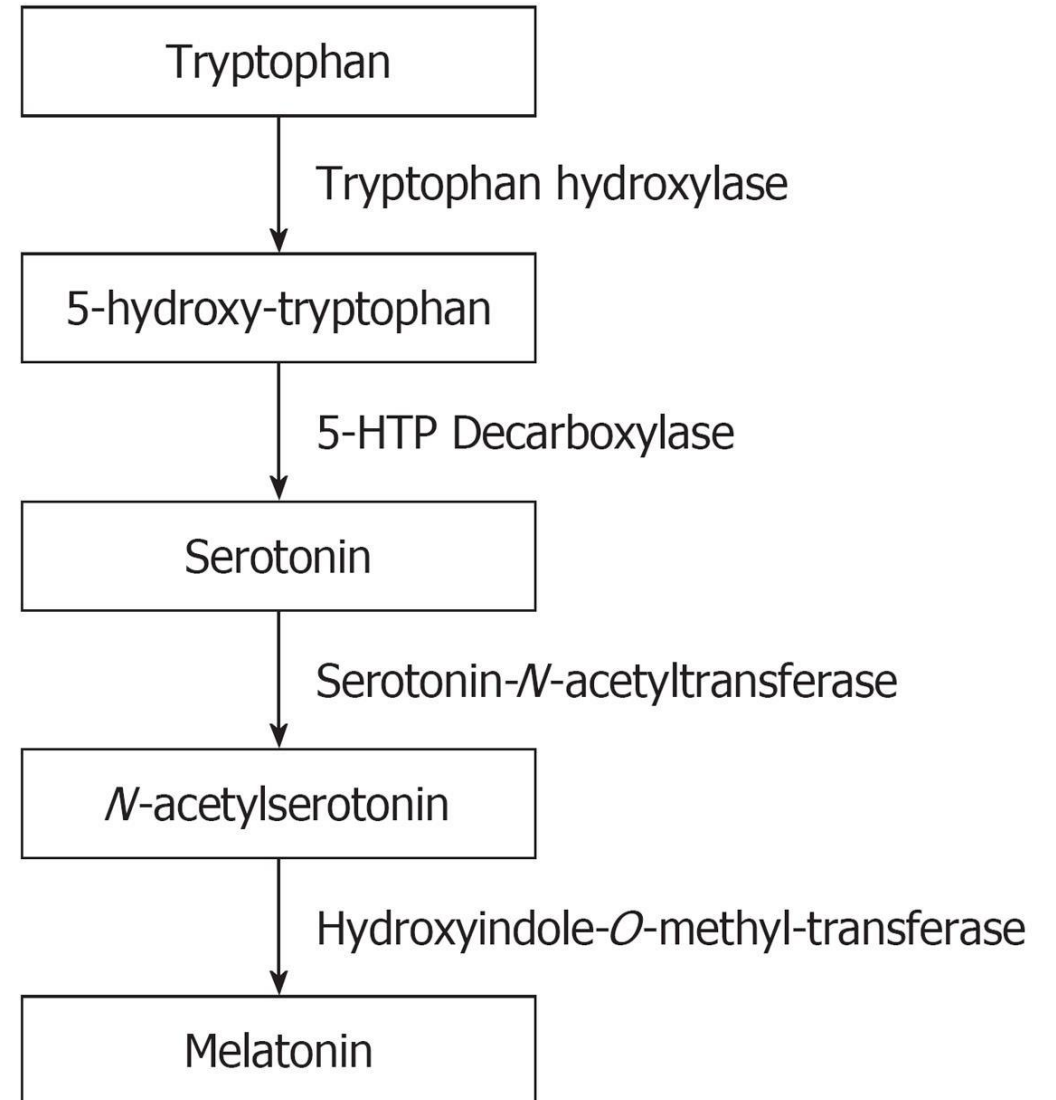
# **FUNCTIONS**

- **Physiological**
- **Pathophysiological (Reaction to injuries)**
- **Transmission and Modulation**

# **SEROTONIN OR 5-HYDROXYTRYPTAMINE (5-HT)**

- Molecular formula :  $C_{10}H_{12}ON_2$
- A monoamine neurotransmitter biochemically derived from tryptophan.
- Structurally it contains an indole ring, hydroxyl group and ethyl amine group attached to the ring.

# SEROTONIN SYNTHESIS



- ❑ Approximately 90% of the human body's total serotonin is located in the enterochromaffin cells in the alimentary canal (gut), used to regulate intestinal movements.
- ❑ The remainder is synthesized in serotonergic neurons of the CNS, where it has various functions including the regulation of mood, appetite, and sleep.
- ❑ Serotonin secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood. There, it is actively taken up by blood platelets, which store it. When the platelets bind to a clot, they release serotonin, where it serves as a vasoconstrictor and helps to regulate homeostasis and blood clotting.

# IMPORTANCE OF SEROTONIN

Serotonin is believed to play a central role in:

Modulation of vasoconstriction

Body temperature

Mood

Sleep

Sexual desire

appetite

Stimulation of vomiting reflex

Memory and Learning



# **SOURCES OF 5HT**

- Meat and Banana are the direct sources of serotonin.
- Main source: L-tryptophan, an amino acid, which is found in proteins. So proteins are the main sources of serotonin:
  - ☐ Meat, eggs, milk, fishes
  - ☐ Pulses
- Enough calcium, magnesium and oxygen are also needed for serotonin production.
- Vitamin B6 also promotes its production.

## **HIGH LEVEL OF SEROTONIN:**

- Obsessive-compulsive disorders e.g. compulsive hand-washing
- Pulmonary vasoconstriction causing an acute or chronic pulmonary hypertension
- Cardiac fibrosis

## **LOW LEVELS OF SEROTONIN:**

- Irritability, Irrational emotions, Sudden unexplained tears, Sleep disturbances, Depression, Suicidal tendencies
- When we have enough Serotonin we have: Emotional stability, Reduces aggression, Sleep cycle, Appetite control

# 5-HT RECEPTORS

➤ Receptors are divided into 7 types: 5-HT1 to 5-HT7

➤ 5-HT1 group consist of 5 receptor subtypes:

➤ 5-HT1A

➤ 5-HT1B

➤ 5-HT1D

➤ 5-HT1E

➤ 5-HT1F

# 5-HT<sub>1A</sub> RECEPTORS

Most extensively distributed of all 5-HT receptors.

In CNS, these receptors are present in high density in cerebral cortex, and raphe nucleus.

Involved in inhibition of discharge of neurons, regulation of production of behaviour and eating.

Play an important role in the emergence of anxiety.

Agonists: Buspirone, Ergotamine, Yohimbine and Antagonists are Alprenolol, Pindolol, Propranolol.

## 5-HT<sub>1B</sub> RECEPTORS

Present in CNS where they induce presynaptic inhibition and behavioural effects

Exhibit vascular effects as well, such as pulmonary vasoconstriction

Agonists: Ergotamine, Dihydroergotamine, Zolmitriptan

Antagonists: Yohimbine, Propranolol, Pindolol

➤ The Clinical significance of 5-HT<sub>1D</sub> receptor is still largely unknown

➤ The function of 5-HT<sub>1E</sub> receptor is unknown but it is hypothesized that they are involved in regulation of memory

➤ 5-HT<sub>1F</sub> receptor has a possible role in vascular contraction.  
Distribution in brain appears limited



# 5-HT<sub>2</sub> RECEPTORS

This class has 3 subtypes:

➤ 5-HT<sub>2A</sub>

➤ 5-HT<sub>2B</sub>

➤ 5-HT<sub>2C</sub>

Receptors	Effects & Function	Agonist	Antagonist
5-HT <sub>2A</sub>	CNS: Anxiety, Imagination, Learning, Perception SM: Contraction Platelet: Aggregation	Yohimbine	Aripiprazole, Clozapine, Olanzapine, Trazodone
5-HT <sub>2B</sub>	CNS: Anxiety GIT: GI Motility	Norfenfluramine	Agomelatine
5-HT <sub>2C</sub>	CNS: Mood, Sleep, Anxiety	--	Clozapine, Olanzapine

# **5-HT<sub>3</sub> RECEPTORS:**

□ With the exception of the 5-HT<sub>3</sub> receptor, a ligand-gated ion channel, all other serotonin receptors are G protein-coupled receptors that activate an intracellular second messenger cascade to produce an excitatory or inhibitory response

□ The 5-HT<sub>3</sub> receptor antagonist suppress vomiting and nausea by inhibiting serotonin binding to the 5-HT<sub>3</sub> receptors

## **5-HT<sub>4</sub> RECEPTORS:**

- Found on CNS and Myenteric neurons.
- Prucalopride (brand name Resolor, developed by Johnson & Johnson) is drug acting as a selective, high affinity 5-HT<sub>4</sub> receptor agonist which targets the impaired motility associated with chronic constipation, thus normalising bowel movements

## **5-HT<sub>5</sub> RECEPTORS:**

- Pharmacological functions of these receptors are unknown. Based on their localization, it has been speculated that they may be involved in motor control, anxiety, learning, adaptive behaviour and brain development.

## **5-HT<sub>6</sub> RECEPTORS:**

➤ The exact clinical significance of these receptors remain still unclear. Selective antagonist of this type of serotonin receptor have an impact on behaviour and seem to improve the spatial memory of laboratory animal

## **5-HT<sub>7</sub> RECEPTORS:**

➤ Expressed abundantly in the vessels and are responsible for persistent vasodilation. 5-HT<sub>7</sub> receptors are also expressed in CNS and in smooth muscles (in GIT tract).

# **SEROTONIN SYNDROME**

❑ Extremely high levels of serotonin can cause a condition known as Serotonin Syndrome, with toxic and potentially fatal effects.

❑ Drugs used to treat SEROTONIN SYNDROME

➤ Non-specific blocking agents: Methysergide, Cyproheptadine

➤ Beta blockers: Propranolol, Pindolol

➤ Benzodiazepines: Lorazepam, Diazepam, Clonazepam

# MIGRAINE

- 5-HT<sub>1</sub> agonists (e.g. Sumatriptan) are first- line therapy for severe migraine and are effective on cluster headache.
- Many other different drugs are also used in migraine such as Propranolol, valproic acid. NSAIDs such as aspirin and ibuprofen are often helpful in controlling the pain of migraine.

# VOMITING

5-HT<sub>3</sub> receptors participate in the vomiting reflex.

Particularly important in vomiting caused by anti cancer drugs.

Ondansetron is the prototypical 5-HT<sub>3</sub> antagonist.

Important in the prevention of nausea and vomiting associated with surgery and cancer chemotherapy.



# DEPRESSION

A class of drugs, such as fluoxetine or sertraline, that inhibit the uptake of serotonin by neurons of the central nervous system are primarily used in the treatment of depression and obsessive compulsive disorder known as SSRIs

A few of them are: Citalopram (Cipram, Seropram), Fluoxetine (Prozac, Evorex), Paroxetine (Paxil, Seroxat, Aropax), Sertraline (Zoloft, Lustral, Serlain)

# LIPID DERIVED AUTACOIDS

# PROSTAGLANDINS

➤ Biologically active derivatives of 20 C-atoms polyunsaturated essential fatty acids that are major lipid derived autacoids.

➤ Derived from arachidonic acids.

➤ Two major types of eicosanoids-

❑ Prostaglandins (PGs)

❑ Leukotrienes (LTs)

➤ The eicosanoids are important local hormones and they may act as circulating hormones as well.

➤ In the body PGs, TXs and LTs are all derived from eicosa (Referring to 20c atoms).

# PROSTAGLANDINS

**WHAT ARE PROSTAGLANDINS ?**

- **Group of hormone-like lipid compounds**
- **Derived enzymatically from fatty acids**
- **Perform important functions in the body**
- **Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring.**
- **They are produced in many places throughout the body and their target cells are present in the immediate vicinity of the site of their secretion.**
- **They are autocrine and paracrine lipid mediators that act upon platelets, endothelium, uterine and mast cells. They are synthesized in the cell from the essential fatty acids (EFAs).**

# **BIOSYNTHESIS AND ACTIONS OF PROSTAGLANDINS**





**Actions:**

- Bronchoconstriction
- Myometrial Contraction

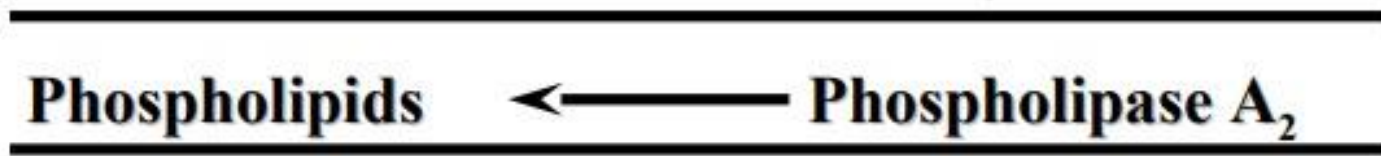
**Actions**

- Inhibits Platelet aggregation
- Vasodilator

**Actions**

- Vasodilator
- Hyperalgesic

**Inflammatory stimulus**



**Arachidonic acid**

**5-lipoxygenase**

**Cyclooxygenase (Cox)**

**15-lipoxygenase**

**Endoperoxides**

**Leucotrienes**

**Lipoxins**

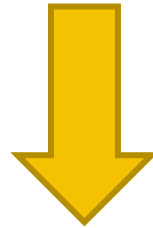
**PGs**

**TxA<sub>2</sub>**

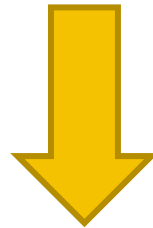
# PHARMACOLOGICAL ACTIONS

# 1) REGULATION OF BLOOD PRESSURE

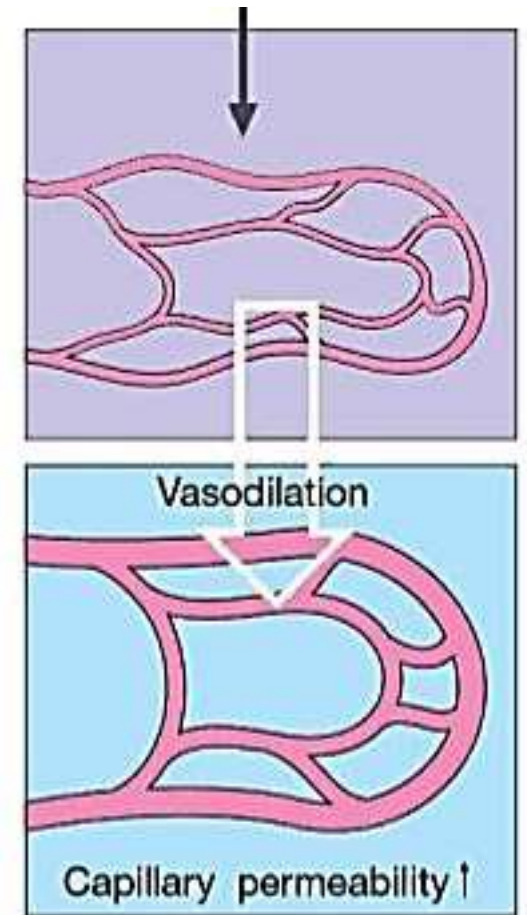
PGE<sub>2</sub> and PGI<sub>2</sub> are vasodilators in vascular beds



Increased blood flow and decreased peripheral resistance



Lower BP



## **2) INFLAMMATION**

PGE1 and PGE2 induce the symptoms of Inflammation (redness, swelling etc.) due to vasodilation.

## **3) REPRODUCTION**

PGE2 AND PGF2 $\alpha$  causes contraction of Uterine smooth muscles in pregnant women.

## **4) PAIN AND FEVER**

It acts on thermoregulatory centre of hypothalamus to produce fever

Pyrogens (fever producing agents) promotes PG synthesis



Formation of PGE<sub>2</sub> in hypothalamus



Fever associated with Pain

## **5) REGULATION OF GASTRIC SECRETION**

➤ PG inhibits Gastric secretion

➤ PG stimulate pancreatic secretion and increase the motility of the intestine leads to diarrhea.

## **6) INFLUENCE ON IMMUNE SYSTEM**

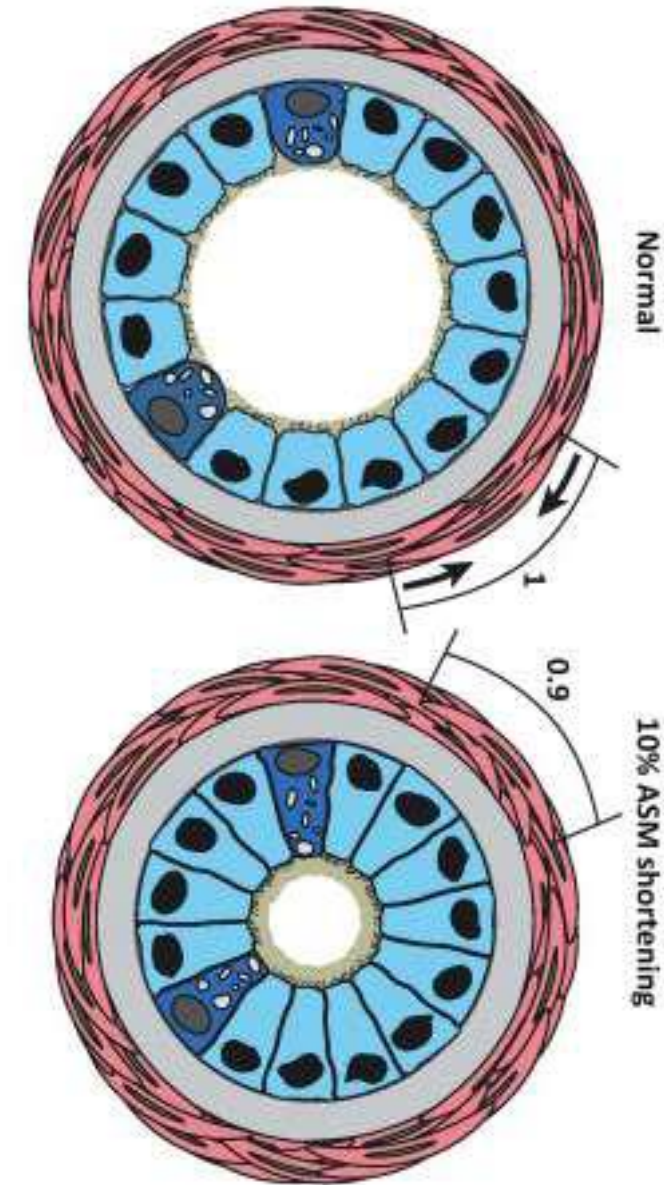
➤ PGE decreases immunological functions of B and T lymphocytes

## 7) EFFECT ON RESPIRATORY FUNCTION

- PGEs causes bronchial smooth muscle relaxation
- PGFs causes bronchial smooth muscle constriction
- PGE and PGF oppose the action of each other in the lungs

## 8) INFLUENCE ON RENAL FUNCTIONS

- PG increases Glomerular Filtration rate
- Promotes Urine Output





## **9) EFFECT ON PLATELET AGGREGATION**

➤ PGI<sub>2</sub> inhibits platelet aggregation

➤ Thromboxane and PGE<sub>2</sub> promotes platelet aggregation and blood clotting which might lead to thrombosis.

## **10) EYE**

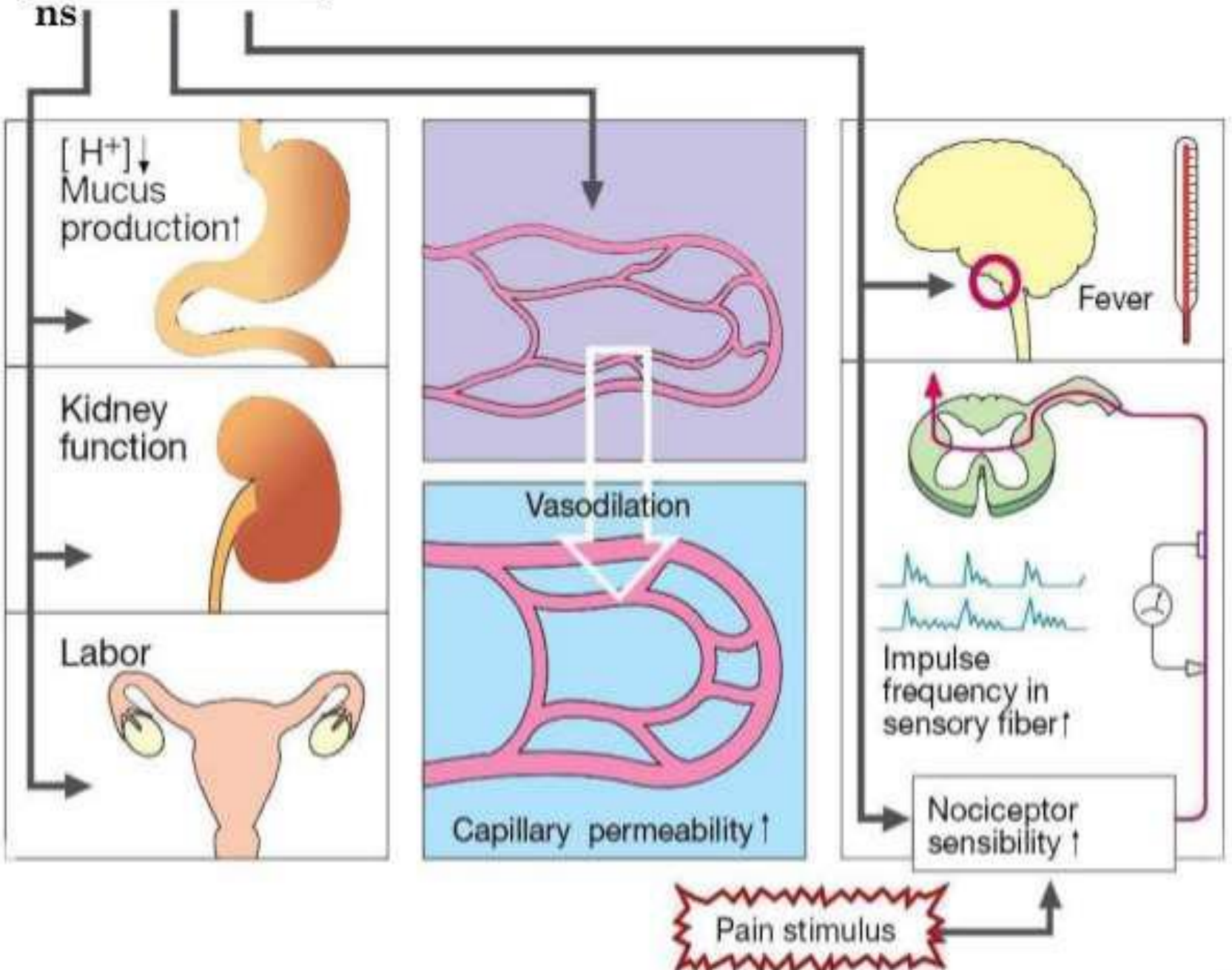
It decreases intraocular pressure

## **11) CNS**

regulate hormones

sensitize spinal neurons to pain

# Prostaglandins



# LEUKOTRIENES

Leukotrienes are so named because they were first obtained from leukocytes (leuko) and conjugated double bonds

# **TYPES OF LEUKOTRIENES**

## ➤ **Cysteinyl leukotrienes: LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub> and LTF<sub>4</sub>**

### ➤ **LTB<sub>4</sub>**

- primary function is to recruit neutrophils to areas of tissue damage, though it also helps promote the production of inflammatory cytokines by various immune cells.

### ➤ **LTG<sub>4</sub>**

- A metabolite of LTE<sub>4</sub> in which the cysteinyl moiety oxidized to an alpha-keto-acid (i.e. the cysteine has been replaced by a pyruvate)

# **FUNCTIONS OF LEUKOTRIENES**

- Act principally on a subfamily of G protein coupled receptors
- May also act upon peroxisome proliferator-activated receptors
- Involved in asthmatic and allergic reactions and act to sustain inflammatory reactions; several leukotriene receptor antagonists
- Very important agents in the inflammatory response
- LTB<sub>4</sub> have a chemotactic effect on migrating neutrophils, and as such help to bring the necessary cells to the tissue



**USED IN PROPHYLAXIS**

- **Chronic asthma**
- **Allergic Rhinitis**
- **Chronic Urticaria**
- **COPD**
- **Atopic Dermatitis**
- **Migraine Prophylaxis**
- **Sino nasal polyposis**

# CHRONIC ASTHMA

➤ **Asthma is a common inflammatory illness**

➤ **Characterized by airway inflammation and hyperresponsiveness to stimuli that produce bronchoconstriction**

➤ **These stimuli include cold air, exercise, a wide variety of allergens and emotional stress—**

➤ **Extrinsic asthma: It is mostly episodic, less prone to status asthmaticus**

➤ **Intrinsic asthma: It tends to be perennial, status asthmaticus is more common**

# LEUKOTRIENES IN ASTHMA

**Leukotrienes assist in the pathophysiology of asthma, causing or potentiating the following symptoms:**

**➤ airflow obstruction**

**➤ increased secretion of mucus**

**➤ mucosal accumulation**

**➤ bronchoconstriction**

**➤ infiltration of inflammatory cells in the airway wall**

# **LEUKOTRIENE RECEPTOR ANTAGONIST**

## Mechanism of Action:

➤ **Attenuates bronchoconstriction and inflammation**

➤ **Leukotriene Receptor Antagonists**

➤ Zafirlukast (Accolate)

➤ Montelukast (Singulair)

➤ **Leukotriene Synthesis Inhibitor**

➤ Zileuton (Zyflo)





A word cloud centered around the words "thank" and "you". The words are arranged in a roughly circular pattern, with "thank" and "you" being the largest and most prominent. Other words include "dank", "gracias", "obrigado", "teşekkür ederim", "tack så mycket", "takk", "gràcies", "tänan", "dank u", "teşekkür edire", "mahalo", "dankie", "molte grazie", "baie", "merci", "dziękuję", "ngiyabonga", "tusind tak", "dakujem vám", "謝謝", "ありがとう", "شكرا", "suksema", and "danke". The colors of the words vary, including shades of blue, orange, yellow, and red.

suksema  
danke  
tusind tak  
謝謝  
dakujem vám  
ngiyabonga  
dziękuję  
merci  
thank  
baie  
dankie  
धन्यवाद  
molte grazie  
gracias  
obrigada  
takk  
you  
obrigado  
gràcies  
tänan  
dank u  
teşekkür ederim  
شكرا  
mahalo  
teşekkür edire  
tack så mycket