



# AUTACOIDS AND COVID-19: OPTIMISTIC IMPLICATION OF GAME THEORY

**Samarjeet Tripathi**

(Writer, Social worker (founder SEWA) and Authored- Game Theory: a non technical appraisal of game theory with new dimension)

**Drx. Amarjeet Tripathi**

(Lecturer at R.K. College of Pharmacy and pursuing Master in Pharmacology)

## ABSTRACT

Autacoids are chemical substances that our body releases periodically that act as local hormones. They are released due to various stimuli and bring about various physiological changes in the body. Autacoids handle several biological actions including modulation of the activity of smooth muscles, glands, nerves, platelets and other tissues. Typically, autacoids are short-lived and rapidly degraded. Autacoid modulators interfere with the synthesis, inhibit the release or the receptors upon which they act. Autacoids are biological factors synthesized and released locally that play a role in vasoconstriction, vasodilation, and inflammation. These include serotonin, bradykinin, histamine, and eicosanoids. Vertebrates have evolved remarkable mechanisms for the repair and maintenance of their own tissues (i.e., host tissues) that simultaneously preclude the invasion and growth of non-host cells and viruses. The front line of host defense relies on the skin, mucosal surfaces, and cornea, where epithelial tissues provide not only the critical physical barrier to a constant exposure to pathogens, but also an interface with commensal microbes.] Inflammation is a major component of host defense, and a fundamental feature of this vital response is the recruitment of leukocytes to sites of injury. Polymorphonuclear leukocytes (PMN) and macrophages in particular are essential for preventing infection and the concomitant threat of life-threatening sepsis. Indeed, in humans, vulnerability to infection is an inevitable consequence of all known genetic or acquired defects in leukocyte function, including defects in adhesion, microbial killing, and phagocytosis; deficiencies in the generation of leukocytes in the bone marrow increase rates of infection and also other illnesses and raise mortality rates. In fact, any injury that compromises the external epithelial barrier triggers a robust inflammatory response.

**KEYWORDS:** Autacoids, Histamine, Antihistamine, TCR Philosophy, 5-HT(SEROTONIN), Game theory, GAEORY, Therapeutic uses, Covid-19.

### **OBJECTIVE:**

This research paper discusses **the Pharmacology of autacoids** and its basic tenets while briefly overviewing real life application. Recently, research on autacoids has given rise to the nascent field of "Autacoids Medicine ". as GAEORY (Game theory as a science) application taking universal space in the health sector as well. Game theory application is immensely important in the pharmacy sector as well.

### **INTRODUCTION:**

*Autacoids have diverse physiological and pharmacological activities. They usually have a brief lifetime and act near their sites of synthesis.* Autacoids are made up with two Greek words – Auto + Acos. Where **Auto** means self and **Acos** means cure (relief) so simply it means Self remedial power. So ultimately we can say that autacoid means automatic healing material. Autacoids are produced by various cells in the body. It is also known as **Local hormones** because Their responses are localised to affected sites. Vasodilator autacoids are released during period exercise.

They are **the endogenous biomolecules** (produced within the organisms) and act directly in **tissues** (groups of cells with similar shape and function) where they produce. It Participate in physiologic or pathologic responses to injury. It is endogenous organic molecules with potent pharmacologic effects, that are not part of traditional immune or autonomic groups. Histamine and serotonin (5-hydroxytryptamine) are two important amine autacoids. Other autacoids, which produce paracrine type effects, include polypeptides (angiotensin, bradykinin, and kallidin), lipid-derived substances (prostaglandins, leukotrienes, and platelet-activating factor), and nitric oxide. Autacoids are 'local hormones' in immediate proximity to their site of production.

**Numerous substances belong to this group. mainly classification of autacoids are as follow -**

- **Histamine** produces either vasoconstriction, with an accompanying increase in the permeability of the vascular wall, or vasodilation. In inflammatory processes, histamines produce arteriole vasorelaxation, venular vasoconstriction, and increased capillary permeability. Allergy symptoms such as hay fever illustrate the resulting effect.
- **Bradykinin** is produced by salivary glands and sweat glands.
- **5-Hydroxytryptophan (5-HTP)** is produced by blood platelets, the central nervous system, and some cells of the digestive tube wall.
- **Prostaglandins** are made by macrophages, fibroblasts, leukocytes, and vascular endothelium.
- **Leukotrienes** are released by leukocytes during the inflammatory response. They are vasoconstricting and also increase the permeability of the capillary wall.
- **Platelet activating factor (PAF)** is produced by macrophages as part of the inflammatory response. It causes vasodilation and increased capillary permeability.
- Autacoids derived from **membrane phospholipid**

## Why is autacoid known as a local hormone?

Autacoid has a lot of activity in the body like hormones. Hormones are produced from one place and working on another targeted place but autacoids are produced and working on the same local place.

### Drugs affecting the Autacoids:

**Peptic ulcers:** Misoprostol is sometimes used to inhibit the secretion of gastric acid and to enhance mucosal resistance to injury in patients with gastric ulcer who are chronically taking non-steroidal anti-inflammatory agents. Proton-pump inhibitors, such as omeprazole, and H2 antihistamines also reduce the risk of gastric ulcer and are better tolerated than misoprostol, which induces intestinal disorders.

**Leukotrienes** are a family of eicosanoid inflammatory mediators produced in leukocytes by the oxidation of arachidonic acid (AA) and the essential fatty acid eicosapentaenoic acid (EPA) by the enzyme arachidonate 5-lipoxygenase. As their name implies, leukotrienes were first discovered in leukocytes, but have since been found in other immune cells.

Leukotrienes use lipid signaling to convey information to either the cell producing them (autocrine signaling) or neighboring cells (paracrine signaling) in order to regulate immune responses. Leukotriene production is usually accompanied by the production of histamine and prostaglandins, which also act as inflammatory mediators.

One of their roles (specifically, leukotriene D4) is to trigger contractions in the smooth muscles lining the bronchioles; their overproduction is a major cause of inflammation in asthma and allergic rhinitis. Leukotriene antagonists are used to treat these disorders by inhibiting the production or activity of leukotrienes.

### Classification of Autacoids : it can be classified in as below-

- 1.Amin derived:** Histamine (Histidine); Serotonin (Tryptophan): 5-HT
- 2.Peptide derived:** Angiotensin, Bradykinin
- 3.Lipid derived(Eicosanoid/Platelet activating factor):** Prostaglandins, Leukotrienes, Interleukins, Thromboxane
- 4.Others:** Gastrin, Cytokines

**Is autacoids good for our body :** Autacoids play a key role in allergy, inflammation, smooth muscle function, pain, and certain types of drug reactions (Anaphylaxis).

The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands.

### Why are they very important:

Because they regulate certain aspects of Gastrointestinal, uterine and renal function. They are ubiquitously distributed, that is, they are found in most tissues and Body fluids, and they regulate a variety of major physiological functions and participate in some well defined pathologic processes.

### How are Autacoids different from Hormones?

Although autacoids have been defined as auto-hormones, they differ from hormones in that they are made, play their role, and are destroyed at the same sites. Many tissues make, respond to, and metabolize autacoids.

### **The Covid-19 and overlooked Autacoids synthesis:**

*Coronavirus infection causes tissue damage, which triggers the endoplasmic reticulum stress response and subsequent eicosanoid and cytokine storms. Although proinflammatory eicosanoids, including prostaglandins, thromboxanes, and leukotrienes, are critical mediators of physiological processes, such as inflammation, fever, allergy, and pain, their roles in COVID-19 are poorly characterized. Arachidonic acid-derived epoxyeicosatrienoic acids could alleviate the systemic hyperinflammatory response in COVID-19 infection by modulating endoplasmic reticulum stress and stimulating the resolution of inflammation. Soluble epoxide hydrolase (sEH) inhibitors, which increase endogenous epoxyeicosatrienoic acid levels, exhibit potent anti-inflammatory activity and inhibit various pathologic processes in preclinical disease models, including pulmonary fibrosis, thrombosis, and acute respiratory distress syndrome. Therefore, targeting eicosanoids and sEH could be a novel therapeutic approach in combating COVID-19.*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leads to severe tissue damage, which releases cell debris. Both primary infection and the accumulation of cell debris initiate the endoplasmic reticulum (ER) stress response and up-regulate inflammatory enzymes, including microsomal prostaglandin E synthase-1 (mPGES-1) and prostaglandin-endoperoxide synthase 2 [cyclooxygenase 2 (COX-2)], which subsequently produce eicosanoids, including prostaglandins (PGs), leukotrienes (LTs), and thromboxanes (TXs). These proinflammatory lipid autacoids induce cytokine storms that mediate widespread inflammatory responses and organ damage in severe coronavirus disease 2019 (COVID-19) patients. By contrast, epoxyeicosatrienoic acids (EETs), which are stabilized by inhibition of their metabolizing enzyme, soluble epoxide hydrolase (sEH), are anti-inflammatory and proresolving mediators that promote the termination (resolution) of inflammation by suppressing the ER stress response, inflammatory enzyme induction, and proinflammatory cytokine production. EETs also shift arachidonic acid metabolism to favor the production of specialized proresolving mediators (SPMs), which initiate downstream anti-inflammatory and proresolving programs.

## **HISTAMINE And 5-HT & its antagonists**

If you have an allergy, chances are you've heard of histamine. It is an amine produced by your body that is used to maintain homeostasis (the body's natural balance of chemicals, temperature, metabolic rates, etc). It is also a neurotransmitter and plays a role in your immune system by acting as a white cell director. Histamine imbalances in your body cause a variety of effects. Histamine shortage (*Histapenia*) causes effects ranging from heavy body hair growth (see photo, below, right) and headaches to anaphylactic shock and paranoia. Histamine abundance (*Histadelia*) in the body also causes a variety of effects ranging from the mundane (such as phobias, symptoms of seasonal allergies - such as runny nose, inflammation, soreness, etc - and an increased metabolism) to the serious (like chronic depression).

Histamine is a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain. Histamine has no clinical applications, but agents that interfere with the action of histamine (antihistamines) have important therapeutic applications. Histamine has been shown to have a key physiological role in the control of gastric acid secretion and a pathophysiological role in a range of allergic disorders.

**The synthesis** of, and pharmacological studies on, selective agonists and antagonists has established the existence of four types (**Classification**) of histamine receptor and histamine

receptor antagonists have found very important therapeutic applications. Thus, **in the 1940s, H1-receptor antagonists ('the antihistamines')** yielded and still provide valuable treatment for allergic conditions such as hay fever and rhinitis. **In the late 1970s and 1980s, H2-receptor antagonists** (in the discovery of which the two authors were personally involved) revolutionised the treatment of peptic ulcer and other gastric acid-related diseases. **The H3-receptor antagonists, although available since 1987,** have been slower to find a therapeutic role. However, the discovery of non imidazole derivatives such as brain-penetrating H3 antagonists has provided drugs that are in early-phase clinical trials, possibly for application in obesity, and a variety of central nervous system disorders, such as memory, learning deficits and epilepsy. Finally, **the most recently (1999) discovered H4 receptor** promises the potential to provide drugs acting on the immunological system with possible applications in asthma and inflammation.

**PHARMACOLOGY OF HISTAMINE:** It is an important nitrogenous organic compound, it is mainly involved in the pathogenesis of allergic reaction. It is a central mediator released from the mast cell through allergic reaction. **Location:** Histamine occurs in practically all tissues, but it is unevenly distributed, with high amounts found in lung, skin, and the gastrointestinal tract. It is found at high concentration in mast cells or basophils. Histamine also occurs as a component of venoms and in secretions from insect stings. eg. **H1-** heart, brain and mast cell; **H2-** heart, brain, neutrophils parietal cells; **H3-** brains and PNS; **H4-** blood cells.

**Synthesis:** Histamine is an amine formed by the decarboxylation of the amino acid histidine by histidine decarboxylase-2 an enzyme that is expressed in cells throughout the body, including central nervous system (CNS) neurons, gastric mucosa parietal cells, mast cells, and basophils. In mast cells, histamine is stored in granules as an inactive complex composed of histamine and the polysulfated anion, heparin, along with an anionic protein. If histamine is not stored, it is rapidly inactivated by amine oxidase enzymes.

**Release of histamine:** The release of histamine may be the primary response to some stimuli, but most often, histamine is just one of several chemical mediators released. Stimuli causing the release of histamine from tissues include the destruction of cells as a result of cold, bacterial toxins, bee sting venoms, or trauma. Allergies and anaphylaxis can also trigger release of histamine. Histamine may be released directly by certain drugs; Morphine (opioid analgesics) and d-tubocurarine (skeletal muscle relaxant, competitive antagonist of the NMJ Nicotinic Receptors for ACh), displace histamine from the heparin-protein complex in mast cells

**Agents that inhibit the release of Histamine from the mast cells are:**

1. Cromolyn (sodium cromoglycate)
2. Theophylline/aminophylline
3.  $\beta$  agonists

**Mechanism of action:**

**Histamine released in response to various stimuli exerts its effects by binding to one or more of four types of histamine receptors H1, H2, H3, and H4 receptors. H1 and H2 receptors are widely expressed and are the targets of clinically useful drugs. H3 and H4 receptors are expressed in only a few cell types, and their roles in drug action are unclear. All types of histamine receptors have seven**

trans-membrane helical domains and transducer (from transducers ) extracellular signals by way of G protein mediated second messenger systems. Some of histamine's wide range of pharmacologic effects are mediated by both H1 and H2 receptors, whereas others are mediated by only one class. For example, the H1 receptors are important in producing smooth muscle contraction and increasing capillary permeability. Histamine promotes vasodilation (vasodilatation) by causing vascular endothelium to release nitric oxide. This chemical signal diffuses to the vascular smooth muscle, where it stimulates cyclic guanosine monophosphate production, causing vasodilation. Histamine H2 receptors mediate gastric acid secretion. The two most common histamine receptors exert their effects by different second-messenger pathways. The actions of H1 antihistamines occur through at least two mechanisms. Anti-allergic activities of H1 antihistamines, such as inhibition of the release of mediators from mast cells and basophils, involves stimulation of the intracellular activity of the polyphosphate-tidylylino-sitol pathway. Other actions of H1 antihistamines involve the down-regulation of nuclear transcription factors that regulate the production of pro-inflammatory cytokines and adhesion proteins. In contrast, stimulation of H2 receptors enhances the production of cyclic adenosine monophosphate (cAMP) by adenylyl cyclase. The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions. These include contraction of smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings.

**Role of mediators:** Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include histamine, serotonin, leukotrienes, and the eosinophil chemotactic factor of anaphylaxis. In some cases, these cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract. Under other conditions, these mediators may cause a full-blown anaphylactic response. It is thought that the difference between these two situations results from differences in the sites from which mediators are released and in their rates of release. For example, if the release of histamine is slow enough to permit its inactivation before it enters the bloodstream, a local allergic reaction results. However, if histamine release is too fast for inactivation to be efficient, a full-blown.

#### RECEPTORS OF HISTAMINE AND THEIR LOCATION:

The biological impact of histamine follow their interaction with four types histamine receptors, **H1R, H2R, H3R, and H4R**, all of which belong to the G protein coupled receptor family (8, 16–20)

Histamine receptors are proteins situated in various parts of the body that bind with histamine to produce a specific effect on the organism. There are four known receptors, designated H1 - H4. The receptor that the histamine reacts with is dependant upon where the histamine is released in the body.

- **H1:** These are one of the most important receptors for modulating your internal clock, and are a main target for many clinical drugs. When histamine reacts with these receptors in your brain (see image, right), it alters your neurochemistry to make you more awake and alert. This is why antihistamines cause drowsiness, as they oppose the reaction of histamine with the H1 receptors. In


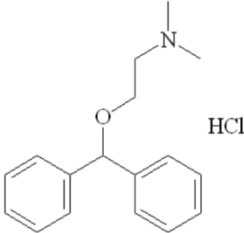

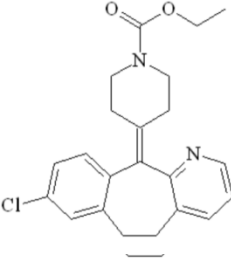

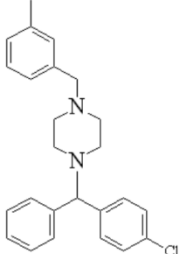

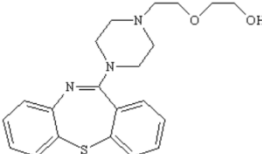
other areas of your body, stimulation of these receptors causes hives (skin rashes), broncho-constriction, motion sickness, separation of the cell-lining of blood vessels, and smooth muscle relaxation (and consequently vasodilation - the widening of blood vessels leading to redness of the skin). Excess activation of these receptors triggers the symptoms of hayfever and other seasonal allergies.

- **H2:** These are found on parietal cells located in the stomach lining, and are mainly responsible for regulating the levels of gastric acid. Histamine action at these receptors stimulates the release of gastric acid, excess of which can result in gastroenteritis. These receptors are also found on heart, uterus and vascular smooth muscle cells. Histamine reacting with the receptor at these places encourages smooth muscle relaxation. H2 receptors can finally be found on *neutrophils* (the most common type of white blood cell). Histamine can also inhibit antibody and cytokine production by reacting with these receptors.
- **H3:** These are present throughout the nervous system, though most notably in the central nervous system. They regulate histamine in the body, by inhibiting the further synthesis of histamine. The more of these receptors that are triggered by histamine, the less histamine is produced in the body.
- **H4:** Discovered in 2001, these receptors regulate the levels of white blood cell release from bone marrow. They have also been shown to direct mast cells. They are located in the thymus, small intestine, spleen, the colon, bone marrow and basophils.

In the body, histamine is synthesised by the enzyme catalysed decarboxylation of the amino acid histidine. It is then either stored, used in activating a receptor, or is broken down. Histamine is stored in several places around the body, mainly in special cells called *mast cells* (photo, right). These are found in abundance around areas particularly prone to injury, such as blood vessels and extremities. Histamine is also stored in a special type of white blood cell found in the bloodstream called *basophils*. Histamine from these sources is used mainly as part of your body's immune system, where the histamine release is stimulated by Immunoglobulin E, a type of mammalian antibody. The antibody is triggered by a number of causes, usually an invading bacterium or virus, but it could also be a pollen cell or an allergic reaction to something the body has come into contact with. In any case, whatever triggers the release of the antibody results in the stored histamine being released into the body. This flood of histamine has a different effect depending upon which of the four known receptors it comes into contact with.

## Anti-histamines

In the strictest sense, anti-histamines are H1 histamine receptor antagonists. This means they block histamine from reacting with the H1-receptors, countering the effects of Histadelia that would normally result from H1 receptor stimulation. Thus, anti-histamines are often prescribed to relieve the symptoms of hayfever, rashes, and allergies . **Examples of these type of anti-histamines are:**

Name	Tradenames / Uses	Structure	3D JMol
<p><b>Diphenhydramine</b></p> 	<p><i>Benadryl, Dimedrol, Nytol</i> Used to treat colds and flu, and as a sleeping pill.</p>		
<p><b>Loratadine</b></p> 	<p><i>Claritin, Claritin-D, Claritine, Clarityn, Clarityne, Fristamin, Lomilan, Symphoral, Roletra, Rinolan, AllergyX, Alavert or Clarinase</i> Used to treat allergies.</p>		
<p><b>Meclizine</b></p> 	<p><i>Bonine, Antivert</i> Used to prevent motion sickness, vertigo and nausea.</p>		
<p><b>Quetiapine</b></p> 	<p><i>Seroquel, Ketipinor</i> Used to treat psychosis, schizophrenia, and acute manic episodes associated with bipolar disorder.</p>		

It is now possible to get other histamine receptor antagonists. For example, a number of H2 blockers are available which are used to reduce stomach acid, or in the treatment of stomach ulcers. These include: Cimetidine (*Tagamet*), Famotidine (*Pepcidine, Pepcid*), and Ranitidine (*Zinetac, Zantac*). H3 blockers are used to make people more awake, by allowing more histamine to be produced, therefore triggering more H1 receptors.

How does antihistamines work?

As

the word Anti suggests ,they are used to counteract the reaction caused by *Histamine* in the body. *But what is Histamine you ask ? , well*



*Histamine is a chemical produced and stored within the body. It is a part of our immune response and is released during an allergic reaction. so Allergic response include sneezing, itching, watery eyes etc. thus whenever an allergen enter's your body ,Mast cell (a type of White Blood Cell)releases Histamine.*

## ***Side effects of antihistamines***

*Antihistamines can cause troubling side effects. Drowsiness is the number one problem. Luckily the newer, second generation types tend to cause less drowsiness. **so let's have look on classification of antihistamine :***

*Antihistamines are divided into two major subtypes. The first subtype is called H-1 receptor antagonists or H-1 blockers. This subtype of antihistamines is used to treat allergy symptoms. The second subtype is called H-2 receptor antagonists or H-2 blockers. They are used to treat gastrointestinal conditions, including gastroesophageal reflux disease [GERD] (also called acid reflux), peptic ulcers, gastritis, motion sickness, nausea and vomiting. The naming structure (H-1 and H-2) tells doctors and scientists the cell type the location of the histamine receptor that the antihistamine medication blocks.*

*The H-1 blocker subtype is further broken down into two groups — first-generation antihistamines and second-generation antihistamines.*

**5-HT or SEROTONIN, also known as 5 hydroxytryptamine, is an endogenous neurotransmitter made from tryptophan and is largely found in the gastrointestinal tract.**

IT is involved in the pathophysiology of depression, anxiety, hypertension etc. All the physiological and pathophysiological effects of 5-HT are due to its interaction with various distinct membrane receptors. Thus basic studies on the 5-HT interaction with the receptor and behavioural changes following administration of monoclonal antibodies might help us in understanding the interaction at the receptor level and its involvement in the modulation of the behaviour. In addition, studies on the metabolism of drugs which modulates the concentration and availability of 5-HT in the brain is also quite useful as the variability in the effect of drugs could be partly explained on this basis also. Studies on herbal drugs have shown that some of these drugs/active components exert their effect by modulating the 5-HT levels in the brain or periphery. Interestingly changes in the central serotonergic system have been reflected in the platelets of the patients of social phobia and in epi-lepsy patients in comparison to the controls. In the diabetic patients and in the toxemia associated with pregnancy, levels of 5-HT were elevated in the platelets.

*The pharmacology of 5-HT in **the gastrointestinal tract** has been the centre of intense interest and research for several decades since Vialli and Erspamer showed that the gut is an important source of 5-HT. Originally, Erspamer and Asero called this substance enteramine and only in 1952 was enteramine found to be identical to the vasoconstrictor substance known as serotonin. (next research would be based on Gastrointestinal tract, where we will discuss it in detail.)*

*Thus,*

5-hydroxytryptamine (5-HT) has become one of the most investigated and complex biogenic amines. The main receptors and their subtypes, e.g., 5-HT<sub>1</sub> (5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>1E</sub> and 5-HT<sub>1F</sub>), 5-HT<sub>2</sub> (5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub>), 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>5</sub> (5-HT<sub>5A</sub>, 5-HT<sub>5B</sub>), 5-HT<sub>6</sub> and 5-HT<sub>7</sub> have been identified. Specific drugs which are capable of either selectively stimulating or inhibiting these receptor subtypes are being designed. This has generated therapeutic potentials of 5-HT receptor modulators in a variety of disease conditions. Conditions where 5-HT receptor modulators have established their use with distinct efficacy and advantages include migraine, anxiety, psychosis, obesity and cancer therapy-induced vomiting by cytotoxic drugs and radiation. Discovery of 5-HT, its biosynthesis, metabolism, physiological role and the potential of 5-HT receptor modulators in various nervous, cardiovascular and gastrointestinal tract disorders, bone growth and micturition.

### **Biosynthesis and Metabolism Pathway and Distribution**

Serotonin is biosynthesized from tryptophan amino acid. Tryptophan is converted to 5 hydroxy tryptophan by tryptophan hydroxylase which by action of dopa decarboxylase is converted into serotonin. This synthesized serotonin is mainly stored in chromaffin and enteric neurons (90%). This biosynthesis does not occur in CNS and Platelet but they take up 5-HT from circulation. 5-HT is metabolized by monoamine oxidase enzyme (MAO) to 5 Hydroxyindole acetaldehyde, which through aldehyde dehydrogenase is converted into 5-Hydroxyindole Acetic Acid (5-HIAA). This 5-HIAA serve as marker for Malignant carcinoid syndrome in which higher concentration of 5-HT in body lead to 20 fold higher excretion of 5-HIAA. 5-HT is converted into N-acetyl 5-HT through enzyme 5-HT N-acetylase which is with help of hydroxy indole c-methyl transferase converted into melatonin. Melatonin is an important hormone that maintains sleep cycle and also acts as antioxidant.

### **Physiological Role of Serotonin**

Serotonin (5-hydroxytryptamine) is principally found stored in three main cell types - (a) serotonergic neurons in the CNS and in the intestinal myenteric plexus, (b) enterochromaffin cells in the mucosa of the gastrointestinal tract and (c) in blood platelets.

### **What is the distribution of 5-Hydroxytryptamine (5-HT or Serotonin) XX and what does it do?**

#### *Distribution of Serotonin (5-HT) : GIT, Platelets & Brain*

(i) Enterochromaffin cells in the GI tract: approximately 90% of the 5 HT is found in these cells in the GIT. Carcinoid syndrome is related to tumors of this enterochromaffin tissue. increase GIT Motility & Gastric Secretion. (ii)

Platelets - 5-HT found in platelets contributes to Platelet Aggregation. 5-HT released from the Platelets also contributes to vasoconstriction and increase in BP. (iii)

Brain - 5-HT is one the major neurotransmitters in the brain. It plays a role in the regulation of sleep, temperature regulation, depression, and anxiety.

# Therapeutic Uses of Drugs Acting on Serotonin Receptors

## Central Nervous System

**Depression** :The hypothesis in affective disorders focuses on an involvement of neurotransmitters noradrenaline (norepinephrine), 5-HT and dopamine. It has been found that some depressed patients appear to have reduced cerebral concentration of 5-HIAA (5-Hydroxy indole acetic acid) (the metabolite of 5-HT), whereas others appear to have reduced level of methyl hydroxyphenyl glycerol (MHPG), a metabolite of noradrenaline.

**Psychosis**: The idea that 5-HT dysfunction could be involved in schizophrenia was based on the fact that LSD (Lysergic acid diethylamide) produces schizophrenia-like symptoms. Many effective anti-psychotic drugs in addition to blocking dopamine receptors, also act as 5-HT receptors antagonists. Clozapine, an atypical antipsychotic drug has more effect on limbic system and 5-HT<sub>2</sub> receptors, which may explain its reduce risk of extrapyramidal symptoms

**Migraine**: 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors are found mainly as presynaptic inhibitory receptors in basal ganglia. 5-HT<sub>1D</sub> receptor subtype which is expressed in cerebral blood vessels is believed to be involved in migraine. Sumatriptan, 5-HT<sub>1D</sub> receptor agonist is used to treat acute migraine. It constricts large arteries and inhibits trigeminal nerve transmission. Sumatriptan causes pain at site of injection and also causes hypertension, so contraindicated to patients with IHD (Ischemic Heart Disease) while zolmitriptan is fast acting and doesn't cause chest pain.

**Pain**:5-HT stimulates nociceptive (pain mediating) sensory nerve ending, an effect mediated by 5-HT<sub>3</sub> receptors. Thus 5-HT<sub>3</sub> receptors could play a role in nociception at spinal level

**Anxiety**: Buspirone is a partial agonist at 5-HT<sub>1A</sub> receptors used to treat various anxiety disorders

**Parkinsonism**: the three cardinal symptoms of parkinsonism, i.e., rigidity, tremor and bradykinesia, tremor may be mediated by 5-HT<sub>2</sub> receptors. This was revealed by the success of ritanserin, a potent and selective 5-HT<sub>2</sub> receptor antagonist, in reducing the tremor of parkinson's patients

**Treatment of drug abuse**: 5HT<sub>3</sub> receptor antagonism has also been shown to reduce the alcohol intake in animals and in human .However, more preclinical and clinical studies are required, to arrive at any meaningful conclusion about the usefulness of 5-HT<sub>3</sub> receptor blockers in treatment of drug abuse

**Temperature regulation**:Changes in temperature were determined following injection of noradrenaline, adrenaline, isoprenaline, dopamine and 5-hydroxytryptamine (5-HT) into the cerebral ventricles of the conscious mouse. 5-HT (10-160 µg) caused a fall in body temperature.5-HT could be the effective target to control body temperature

**Antiemetic Action**:The central neural regulation of vomiting is vested in two separate units in medulla. These are vomiting centers and chemoreceptor trigger zone(CTZ).Impulses from CTZ pass to vomiting centre and integrate the visceral and somatic functions involved in vomiting .The main neurotransmitters considered to be involved in the control of vomiting are acetylcholine, dopamine, histamine and 5-HT.Receptors for these neurotransmitters have been demonstrated in relevant areas.

**Gastrointestinal tract**:5-HT<sub>1A</sub>, 5-HT<sub>1c</sub>, 5-HT<sub>2</sub>, 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors have been identified in the gut, in either the enteric nervous system or on smooth muscles

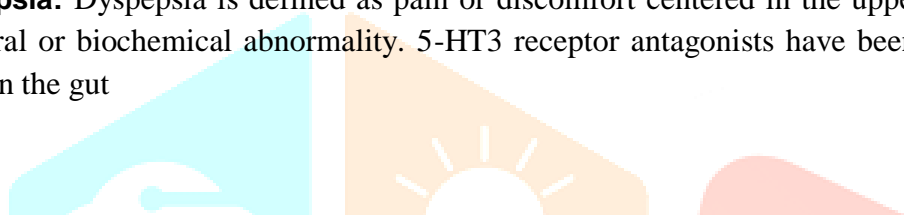
**Irritable bowel syndrome (IBS):** 5-HT<sub>4</sub> agonists increase intestinal motility and could be used in the treatment of gastroesophageal reflux, intestinal paresis (constipation), irritable bowel syndrome. The first drug of this group is tegaserod. A frequent adverse effect of tegaserod is diarrhea and a rare more severe effect is ischemic colitis.

**Malignant carcinoid syndrome:** Carcinoid syndrome is a rare disorder associated with malignant tumor enterochromaffin cells, usually arising in the small intestine and metastasizing to the liver. These tumors secrete a variety of hormones. 5-HT is the important one.

**Non-cardiac chest pain:** Sometimes referred to as chest pain of undetermined etiology (CPUE), it is an ill defined entity requiring urgent elimination of other differential diagnosis. 5-HT<sub>3</sub> receptor antagonists can reduce the visceral pain reflex in the gut, they would theoretically be of benefit in the management of such cases.

**Gastro-oesophageal reflux disease:** The symptoms of pain and anxiety, seen in gastroesophageal reflux disease (GERD) are due to a pathological acid reflux into the oesophagus which may result from a combination of decreased lower esophageal sphincter tone and impaired acid clearance.

**Dyspepsia:** Dyspepsia is defined as pain or discomfort centered in the upper abdomen in the absence of any structural or biochemical abnormality. 5-HT<sub>3</sub> receptor antagonists have been reported to reduce visceral pain reflex in the gut



**Cardiovascular system:** Ketanserin, a 5-HT<sub>2</sub> receptor antagonist with high affinity for peripheral 5-HT<sub>2</sub> sites, reduces blood pressure by causing vasodilation and reducing total peripheral resistance. The reflex tachycardia seen with other vasodilators is not seen with ketanserin. This 5-HT<sub>2</sub> receptor blockade may be very useful in protecting the microcirculatory bed against the detrimental effects of serotonin, which is massively released by aggregation of platelets, particularly when the vascular bed is pre damaged by atherosclerosis, diabetes mellitus and old age. Ketanserin has also been reported to be more effective in the elderly

**Ophthalmology:** 5-HT receptor modulators may have some potential in the treatment of ocular conditions such as glaucoma

**Diabetes:** 5-HT was found to produce dose dependant increase in serum glucose level. 5-HT may cause hyperglycemia

**Obesity:** Sibutramine is an inhibitor of 5-HT/Noradrenaline reuptake at the hypothalamic sites that regulate food intake. Sibutramine reduces food intake and causes dose dependent weight loss, the weight loss being associated with decrease in obesity related risk factors.

**Bone growth:** 5-HTT inhibition had significant detrimental effects on bone mineral accrual. Selective serotonin-reuptake inhibitors (SSRIs) antagonize the serotonin (5-hydroxytryptamine) transporter (5-HTT), and are frequently prescribed to children and adolescents to treat depression.

**Micturition:** The 5-HT receptor modulating drugs have now established their therapeutic role in various disease conditions like emesis, anxiety and migraine, in various other neurological conditions, as well as peripheral disorders.

**A serotonin receptor agonist is an agonist of one or more serotonin receptors. They activate serotonin receptors in a manner similar to that of serotonin (5-hydroxytryptamine; 5-HT), a neurotransmitter and hormone and the endogenous ligand of the serotonin receptors.** An agonist is a drug that **activates certain receptors in the brain.** Full agonist opioids activate the opioid receptors in the brain fully resulting in the full opioid effect. Examples of full agonists are heroin, oxycodone, methadone, hydrocodone, morphine, opium and others.

#### **EXAMPLES OF SEROTONIN AGONISTS -**

Buspirone. 5-HT(subscript 1A)- anxiety, depression

*Cisapride [withdrawn] A good prokinetic agent. 5-HT(4)- Gastroesophageal reflux disease; To Treat Gastrointestinal hypomotility.*

sumatriptan. 5-HT(1B/1D)- migraine headaches

Clozapine. 5-HT(2)- Schizophrenia.

Cyproheptadine. 5-HT(2)- Carcinoid syndrome; pruritus; urticaria.

Methysergide. 5-HT(2)- carcinoid syndrome; migraine headache.

Ondansetron. 5-HT(3)- Nausea and vomiting.

#### **CONCLUSION**

**Autacoids (principally histamine, beta adrenergic catecholamines, and prostaglandins E and A) have only recently been recognized as substantive moderators of a number of immune functions.** Control responses to epithelial and epidermal injury appear to rely on redundant circuits that tightly control the precarious, but essential, activation of the inflammatory processes. Anti-inflammatory lipid autacoids, have emerged as central regulators of leukocyte function and the active resolution of inflammation. Release of autacoids and activity of the autonomic nervous system may influence (or be directly responsible for) some of the physiological changes that occur in conjunction with this hyperthermia. Like this many applications have significantly increased the importance of autacoids concept analysis and research pragmatism. **Autacoids could have a crucial role of arachidonic cascade in covid-19 infection.** The World Health Organization has described the 2019 Coronavirus disease caused by an influenza-like virus called SARS-CoV-2 as a pandemic. Millions of people worldwide are already infected by this virus, and severe infection causes hyper inflammation, thus disrupting lung function, exacerbating breath difficulties, and death. Various inflammatory mediators bio-synthesized through the arachidonic acid (autacoids) pathway play roles in developing cytokine storms, injuring virus-infected cells. Since pro-inflammatory eicosanoids, including prostaglandins, and leukotrienes, are key brokers for physiological processes such as inflammation, fever, allergy, and pain, their function in COVID-19 is not well defined, but clinical implications of autacoids are beginning to be appreciated. Pharmacologic antagonists of the autacoids can have predictable but hitherto unanticipated effects on human systems. Yet, research due as **GAEORY** (game theory as a subject) is pragmatically very vital to core concepts i.e. autacoids application.

## TCR WAY OF BRAINSTORMING- LET'S DISCUSS

1. Write a note on autacoids and classification.
2. What is Antihistamine with examples and its classification.
3. Examine the drugs that can be used in various forms of allergic disorders. differentiate between first- and second-generation antihistamines.
4. Do it - few examples of H-1 first- and second-generation antihistamines and H-2 blockers.
5. What are the side effects of antihistamines?
6. Relation of Autacoids with Covid-19.
7. Is pandemic a prisoner dilemma? how autacoids potentially change the face of the health sector.
8. What is game theory? Who propounded the concept of GAEORY. How game theory concepts apply in the health sector chain?
9. Do you know the scope of autacoids and its implication in economics?

## REFERENCES

1. Kumar D, Tripathi HC, Mishra SK, Tandon SK, Ravi prakash, Mishra SC. **Role** of central serotonergic system in immunomodulation in rats. *Indian J Pharmacol* 1996
2. Sur TK, Bhattacharya D. The effect of Panax ginseng and diazepam on brain and hypothalamic 5-hydroxytryptamine during stress. *Indian J Pharmacol* 1997
3. Savithri S, Kuruvilla A. Effect of methylene blue on en-dothelium – dependent relaxation by acetylcholine in non-key aortic strips. *Indian J Pharmacol* 1997
4. Hore SK, Dumka VK, Tripathi, HC, Tandan SK, Kumar D. *Modulatory role* of central purinergic neurotransmitters on Brewer's yeast induced inflammation in rats. *Indian J Pharmacol* 1997
5. Tripathi Samarjeet. **Game Theory - A Non-technical Appraisal of Game Theory With New Dimension**, Notion Press. 2021
6. Sullivan T.J., The role of eosinophils in inflammatory reactions, *Prog Hematol.* 1979
7. Weissmann G, Smolen J.E., Korchak H.M., Release of inflammatory mediators from stimulated neutrophils.
8. Avella J, Binder H.J., Madsen J.E., Askenase P.W., Effect of histamine H2-receptor antagonists on delayed hypersensitivity. *Lancet.* 1978
9. Keppel Hesselink JM. The terms 'autacoid', 'hormone' and 'chalone' and how they have shifted with time. *Auton Autacoid Pharmacol.* 2015
10. Erspamer V, Asero B. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. *Nature* 1952
11. Rocklin R.E, Greineder D.K, Melmon K.L.; induced suppressor factor (HSF): further studies on the nature of the stimulus and the cell which produces it; *Cell Immunol.* 1979