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A Review Study about Inflammation, Types and Treatment

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ABSTRACT

This article enlightens physiological components of pain and inflammation. The objective is to study pain, inflammation and their pathophysiology as well as mechanism of inflammation and different types of pathways which are used for inflammatory response mechanism and Intracellular and Extracellular signaling which are used to initiate and to stimulate different types of receptors and hormones. It is one of the common and one of the most difficult problems to diagnose and is generally found in common people. Pain is a complex experience which includes psychological and behavior components and results from trauma, diseases, surgical interventions. Different mediators like IL, PG, PAF, LT, cytokines are producing inflammation and leading to pain. Differrent type of medicines are used for treatment of inflammation like Salicylates, Propionic acids derivative, Pyrazolones derivatives, Aryl acetic acid, oxicam, Pyrrole-Pyrrole derivatives.

INTRODUCTION

Inflammation is a defensive response which causes the different physiological adaptations which limits the tissue damage and removes pathogenic insult & Pain is an expected result of many diseases, medical care, surgical interventions and trauma. Pain is a complex experience which includes affective, cognitive and behavioral features, all of which are the result of mental process, as such; it represents psychological conditions (1, 2).

The phenomenon of pain, therefore, involves pathophysiological and psychological components that are frequently difficult to interpret. Suffering is a term frequently used in conjunction with pain, implying the conscious endurance of pain or distress and referring to a wide range of intense and unpleasant subjective states that may be of physical or psychological origin. The most comprehensive and exhaustive definition of pain is provided by International Association for the study of Pain, namely "an unpleasant sensation and an emotional experience associated with a real or potential damage to tissue, or equivalent of such damage (3).

Inflammation: Inflammation is a defensive response which causes the different physiological adaptations which limits the tissue damage and removes pathogenic insult. This type of mechanism involves a complex series of events which includes dilation of arterioles, venules and capillaries with increased vascular permeability, exudation of fluids which includes plasma proteins and the migration of leukocyte into the inflammatory area. In the inflammation, there is immediate infiltration of a specific site or lesion with PMN followed by monocytes and lymphocytes (4,5).

The objective of inflammation is to destroy and eliminate the damaging agent. However, if doesn't occur or is protracted process then inflammation will isolate and contain the injury. In each aspect, the objective is to allow the repair and healing of injured tissue with the minimum damage of host's physiology. Inflammation occurs due to the stress responses and is an integral part of it (6,7,8). In the case of fight or flight reaction, acute psychosocial stress which can induce activation of the transcription nuclear factor k B and there is secretion of proinflammatory cytokines, presumably by adrenergic stimulation. Inflammation causes the destruction, dilution or the walls of injurious agent and at the same time precipitates number of events in a series that causes the healing and reconstitution of damaged tissues, either by regeneration of native parenchymal cells or by filling the defect with fibroblast tissue

(scarring) or by both processes. A critical functional of inflammation is the delivery of leukocytes to the site of injury which is achieved by increased blood flow, structural changes in the microvasculature to permit leukocyte emigration and their accumulation in the focus of injury.

Type of inflammation :- 1) Acute Inflammation

2) Chronic Inflammation

1) Acute inflammation: Acute inflammation is of short duration and its duration is from minutes to few days. The main characteristics are:

a) Exudation of fluids

b) Plasma protein (edema)

c) Emigration of leukocytes specially neutrophils

2) Chronic inflammation: Chronic inflammation is having longer duration than acute inflammation. It is associated histologically with the presence of lymphocytes, macrophages, proliferation of blood vessels, fibrosis, and tissue necrosis. It is the processes of active inflammation and tissue destruction occurs. It is followed by acute inflammation and it starts from the low grade, smoldering asymptomatic response. It may also arise due to the persistent infection by certain organisms such as tubercle bacilli or *Treponema pallidum*, prolonged exposure to highly toxic agents, either exogenous like silica or endogenous like plasma lipid component resulting into atherosclerosis, autoimmune like rheumatoid arthritis. Acute inflammation response is the initial response after the infection or trauma. It is non- specific in nature and is the first line of defense of body after the danger (9,10). In acute inflammation, there is increased level of copper, decreased level of zinc. There is occurrence of leukocytosis, thrombocytosis, negative nitrogen balance, increased BMR, increased lipogenesis and lipolysis. There is decrease in plasma protein level, increased C reactive protein level (11).

Inflammatory Phase:-

Inflammatory phase is the natural process of wound healing. After preliminary wound, the blood vessels within the wound bed contract and a clot is formed. Once haemostasis has been done, blood vessels then dilate to allow vital cells, antibodies, white blood cells, boom factors, enzymes and vitamins to reach the wounded vicinity. In this level the function, signs and symptoms of irritation may be seen, such as erythema, heat, oedema, ache and functional disturbance. Neutrophils help to free from contamination of wound through phagocytosis (12,13).

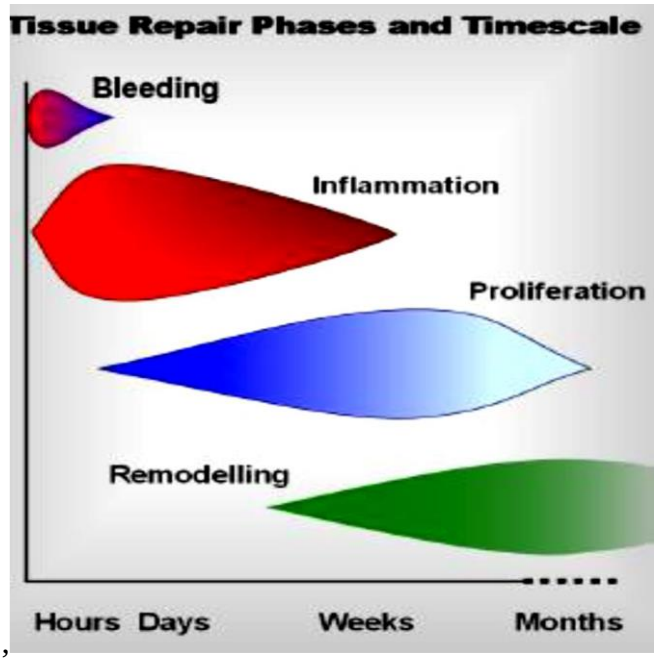

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Figure No. 1: Tissue Repair phases and time scale.

The Inflammatory Response Mechanism:-

The inflammatory response is the coordinate activation of signaling pathways that regulate inflammatory mediator levels in resident tissue cells and inflammatory cells recruited from the blood (8). Inflammation is a common pathogenesis of many chronic diseases, including cardiovascular and bowel diseases, diabetes, arthritis, and cancer (9). Although inflammatory response processes depend on the precise nature of the initial stimulus and its location in the body, they all share a common mechanism, which can be summarized as follows: a) cell surface pattern receptors recognize detrimental stimuli; b) inflammatory pathways are activated; c) inflammatory markers are released and d) inflammatory cells are recruited.

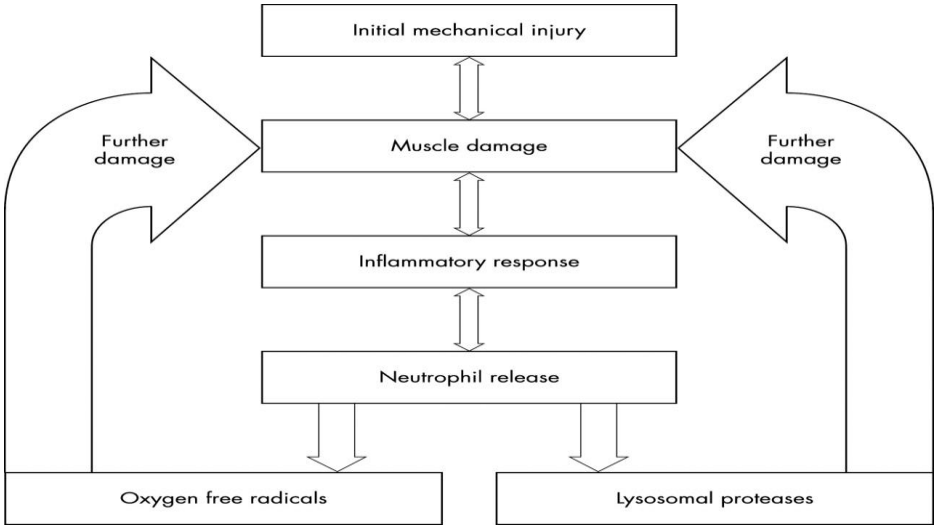

Figure No. 2: Inflammatory Response and Mechanism.

1) Pattern recognition receptor activation:-

Microbial structures known as pathogen-associated molecular patterns (PAMPs) can trigger the inflammatory response through activation of germline-encoded pattern-recognition receptors (PRRs) expressed in both immune and nonimmune cells (14,15).Some PRRs also recognize various endogenous signals activated during tissue or cell damage and are known as danger-associated molecular patterns (DAMPS) (15). DAMPs are host biomolecules that can initiate and perpetuate a non-infectious inflammatory response (16). Disrupted cells can also recruit innate inflammatory cells in the absence of pathogens by releasing DAMPs.

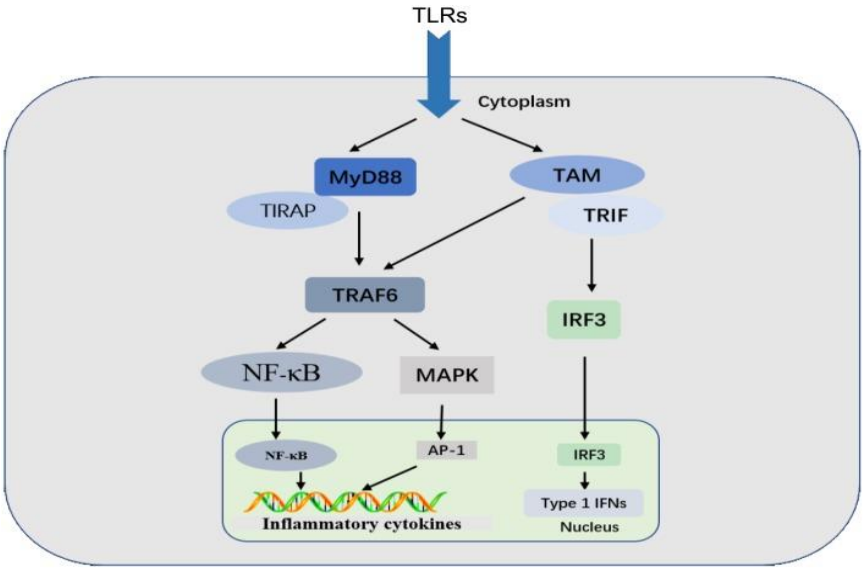

Fig No. 3 TLR signaling (MyD88-dependent and TRIF-dependent pathways are shown. Signaling through TLRs activates intracellular signaling cascades that lead to nuclear translocation of AP-1 and NF-κB or IRF3, which regulates the inflammatory response**).**

2) Activation of inflammatory pathways

Inflammatory pathways impact the pathogenesis of a number of chronic diseases and involve common inflammatory mediators and regulatory pathways. Inflammatory stimuli activate intracellular signaling pathways that then activate production of inflammatory mediators. Primary inflammatory stimuli, including microbial products and cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), mediate inflammation through interaction with the TLRs, IL-1 receptor (IL-1R), IL-6 receptor (IL-6R), and the TNF receptor (TNFR) (16). Receptor activation triggers important intracellular signaling pathways, including the mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways (17,18).

3) NF-κB pathway

The NF-κB transcription factor plays important roles in inflammatory, immune response, survival, and apoptosis processes(19,20). The NF-κB family includes five related transcription factors: P50, p52, RelA (p65), RelB, and c-Rel(21,22). NF-κB activity is induced by a range of stimuli, including pathogen-derived substances, intercellular inflammatory cytokines, and many enzymes(23,24). Under physiological conditions, IκB proteins present in the cytoplasm inhibit NF-κB. PRRs use similar signal transduction mechanisms to activate IκB kinase (IKK), which is composed of two kinase subunits, IKKα and IKKβ, and a regulatory subunit, such as IKKγ. IKK regulates NF-κB pathway activation through IκB phosphorylation(25). IκB phosphorylation results in its degradation by the proteasome and the subsequent release of NF-κB for nuclear translocation and gene transcription activation(26). This pathway regulates pro-inflammatory cytokine production and inflammatory cell recruitment, which contribute to the inflammatory response (Figure No. 4).

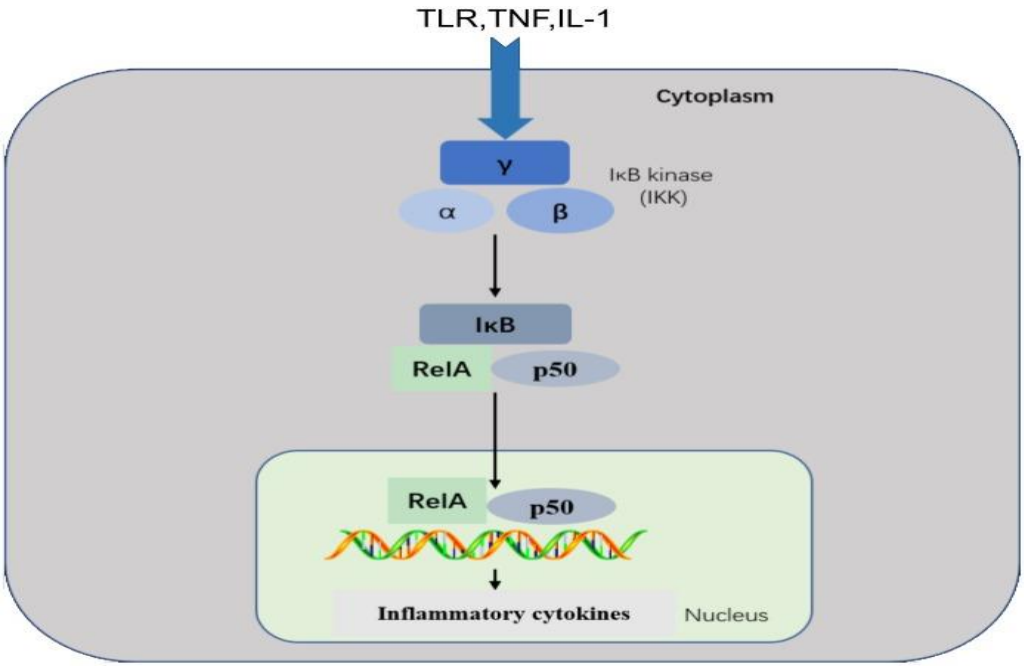

Figure No. 4: NF-κB pathway (This pathway is triggered by TLRs and inflammatory cytokines, such as TNF and IL-1, leading to activation of RelA/p50 complexes that regulate expression of inflammatory cytokines. NF-κB signaling requires IKK subunits which regulate pathway activation through IκB phosphorylation**).**

4) MAPK pathway

MAPKs are a family of serine/threonine protein kinases that direct cellular responses to a variety of stimuli, including osmotic stress, mitogens, heat shock, and inflammatory cytokines (such as IL-1, TNF-α, and IL-6), which regulate cell proliferation, differentiation, cell survival and apoptosis(27,28). The mammalian MAPKs include extracellular-signal-regulated kinase ERK1/2, p38 MAP Kinase, and c-Jun N-terminal kinases (JNK)(29). Each MAPK signaling pathway comprises at least three components: a MAPK, a MAPK kinase (MAPKK), and a MAPK kinase (MAPKKK). MAPKKKs phosphorylate and activate MAPKKs, which in turn phosphorylate and activate MAPKs(30,31). ERKs are generally activated by mitogens and differentiation signals, while inflammatory stimuli and stress activate JNK and p38(32). MKK1 and MKK2 activate ERK1/2, MKK4 and MKK7 activate JNK, and MKK3 and MKK6 activate p38. Activation of the MAPKs, including Erk1/2, JNK, leads to phosphorylation and activation of p38 transcription factors present in the cytoplasm or nucleus, which initiates the inflammatory response(32)(Fig. No 5).

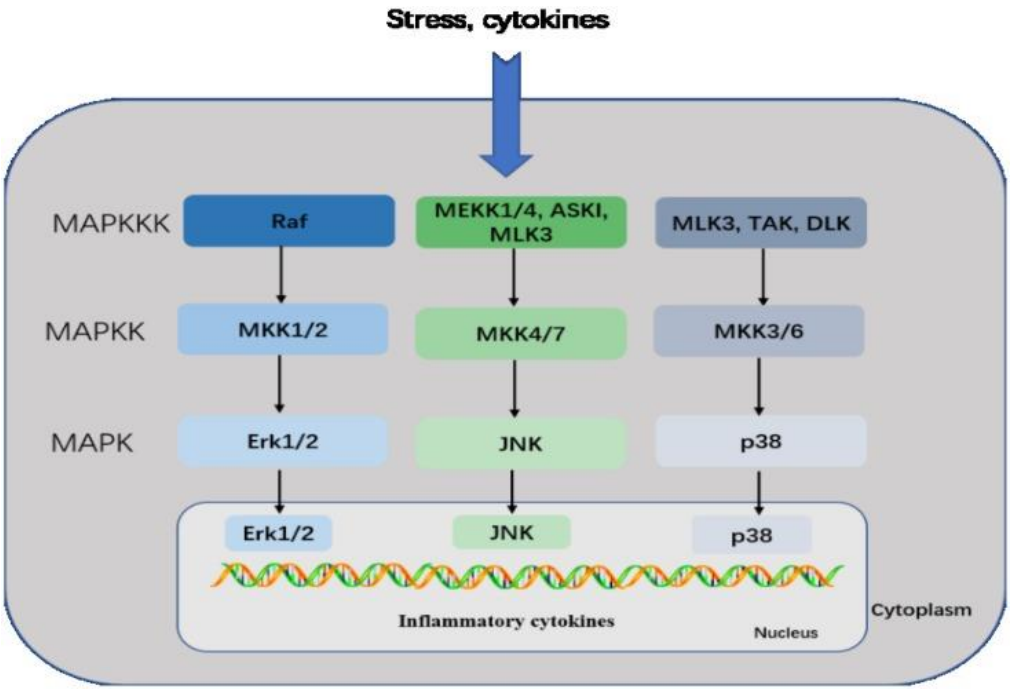

Figure No. 05: MAPK pathway (This pathway mediates intracellular signaling initiated by extracellular stimuli, such as stress and cytokines. MAPKKKs phosphorylate and activate MAPKKs, which in turn phosphorylate and activate MAPKs. The mammalian MAPK family includes Erk1/2, JNK, and p38. In the Erk1/2 pathway, Erk1/2 is activated by MKK1/2, which is activated by Raf. In the JNK pathway, JNK is activated by MKK4/7, which is activated by MEKK1/4, ASK1, and MLK3. In the p38 pathway, p38 is activated by MKK3/6, which is activated by MLK3, TAK, and DLK. Activated MAPKs phosphorylate various proteins, including transcription factors, resulting in regulation of inflammatory responses**)**.

Classification of pain:- Pain can be classified into neuropathic, nociceptive, psychogenic, overall can be classified onto either acute or chronic pain(33,34). Nociception is the process and it involves the series of information peripherally from the nociceptors in the tissue to the central structural present in the brain (34,35,36). The pathway of pain as follows:

Nociceptors → primary afferent fibers →dorsal horn of spinal cord → secondary afferent fibers →tertiary afferent fibers.

Chronic pain is related with different type of conditions like arthritis, back injury, migraine headache, herpes zoster, cancer, diabetic neuropathy, temporomandibular joint syndrome. It not only results from physical insult but is a combination of psychological, emotional, physical, social abnormalities. Chronic pain is defined as somatosensory processing in the peripheral or Central Nervous System (CNS) which is above the normal time which is

expected after the stimulation. It is very vague, difficult to pinpoint and is also insidious and arises as a result of primary dysfunction in the nervous system (37,38).

1) Somatic pain: Somatic pain is cutaneous in nature and occurs in deep tissues. It is localized in nature, constant, aching, gnawing, and throbbing.

2) Visceral pain: Visceral pain is innervated to the organs and this type of pain is surface transferred to the body. It is vague in distribution, quality. It is deep, produce ache, dragging. It causes sweating, changes in heart rate and sometimes Blood Pressure (BP).

3) Neuropathic pain: Neuropathic pain arises due to injury of nerve pathway. The injury can be central, mixed, or peripheral producing. Central pain when the tissue injury is central. Postherpetic neuralgia when the site of injury is mixed. Neuroma, nerve compression, neuralgic is produced when the tissue injury is peripheral. There is an occurrence of burning, tingling, numbness, pressing in case of neuropathic pain.

4) Psychogenic pain: Psychogenic pain arises due to anxiety or depression.

5) Acute pain: Acute pain occurs in the soft tissue damage, infection and in inflammation and is less than 1 month but in some cases it extends up to 6 months. The duration of pain is shorter in case of pain associated with dysmenorrhoea, common headache, migraine, sore throat, mild trauma last from few hours to few days and are acute pain are general practice (37,38,39).

Mediators of inflammation:-

1) Bradykinin: Itis the most important mediator and most potent endogenous allogenic substance known. Bradykinin and their related kallidin are formed in the blood and tissues respectively and break down by kinases into active and inactive metabolites(40).

2) Histamine: Association of histamine with H1 receptors produces numerous effects associated with the symptoms of anaphylaxis and other allergic symptoms(41,42). Histamine lead to the production of allergic inflammatory responses by enhancing the secretion of proinflammatory cytokines such as interleukin 1α, interleukin 1β, interleukin 6 or interleukin 8 in different types of cells and tissues. Endothelial cells express functional histamine receptor HI and H2(43,44).

3) Nitric oxide and mast cells: Nitric oxide is generated due to the inflammation(45,46) Nitric oxide is a proinflammatory at the low concentration by inducing vasodilation and the recruitment of neutrophils but at the high concentration there is downregulation of adhesion molecules(47). Nitric acid is formed from Largenine by nitric oxide synthetase. There are two isoenzymes:

- c-NOS
- i-NOS

c-NOS is calcium dependent and i-NOS is calcium independent and is induced by inflammation in macrophages and microglia.

4) Neuropeptide: Neuropeptide Y is a cotransmittor of sympathetic nervous innervations and it causes the potentiation of actions of NE. NPY promotes smooth muscle proliferation in the vasculature which results in vascular hypertrophy. It causes the increase in leukocytes adhesion and together with CA, platelet aggregation and macrophage activation(48). The neuropeptide CRF is located within the PSGN as well as in sensory nerves. Substance P is a sensory neuropeptide which is present in autonomic nerves and ganglia.

5) Cytokines: Cytokines are different group of proteins and is called as hormone of the immune system. Interaction between the proinflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α) results in synergists activities in cytokine production and cytokine activities (32). There is other family of cytokine called as antiinflammatory cytokines (IL-1Ra, IL-4, IL-10, and TGFβ1) which antagonist the action of proinflammatory cytokines. There are two components for cytokine balance. First is the IL-1 which increases the synthesis and secretion of IL-1Ra upregulation which is purposed to attenuate the delirious effect of IL-1by blocking the IL-1(49,50) The second is balance between different kinds of cytokine system like TGF1β which inhibit IL-1 and TNF-α activity 114,115. Astrocytes and microglial secreates cytokines in the brain, neuron can also produce cytokines but under certain conditions(51).

6) Macrophages: Macrophages are involved in the inflammation. Macrophages cause the release of cytokines at a faster rate when they are activated 76,118. Macrophage can also get activated by increase in cholesterol caused by stress with the SNS agonist 118. Presence of cholesterol results in upregulation of β adrenergic receptors ultimately results in amplification

of catechols and hence macrophage activation. Oxidized LDL caused by stress, binds to the scavenger receptor results in macrophage activation(52).

Treatment of inflammation(53)**:-**

For the treatment of inflammation Non Steroidal AntiInflammatory Drugs (NSAIDs) are

Commonly used. Most commonly used drugs are:-

• Salicylates: Aspirin.

• Propionic acid derivatives: Ibuprofen, Ibuprofen + Paracetamol Combination.

Flurbiprofen, Ketoprofen, Naproxen, Fenamates and Mefenamic acid.

• Pyrazolones: Phenylbutazone and Oxyphenbutazone.

• Indole derivative: Ibuprofen.

• Arylacetic acid derivatives: Diclofenac sodium, Diclofenac potassium, Diclofenac+

Paracetamol Combination, Combination preparation of diclofenac and Serration peptidase.

• Oxicam derivatives: Piroxicam, Tenoxicamand Meloxicam.

• Pyrrole Derivatives: Ketorolac.

• Para-amino phenol derivative: Paracetamol.

• Others: Celecoxib, Rofecoxib, Valdecoxiband Nimesulide, Combination preparation of Nimesulide, Nabumeton.

CONCLUSION

From this article, we came to know about inflammation, [pain, mechanism of inflammation, types of inflammation as well as study about there are different types of mediators which cause nociception (pain) and inflammation like capsaicin, nitric oxide, histamine, cytokines, and prostaglandins. Apart from the mediators the article also gives light on the mechanism involved in the pain and inflammation. It also helps in understanding of neural pathway and mechanism of pain and inflammation, as well as treatment of inflammation which kind of

drug are available for treatment of inflammation and reduce pain which occur during the inflammation.

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