IJPSR (2012), Vol. 3, Issue 12 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 August, 2012; received in revised form 12 October, 2012; accepted 29 November, 2012

PAIN AND INFLAMMATION: A REVIEW

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Keywords:
Pain, inflammation, definition, classification, mechanisms, physiological components

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ABSTRACT

This article enlightens physiological components of pain and inflammation. The objective is to study pain, inflammation and their pathophysiology. It is one of the common and one of the most difficult problems to diagnose and is generally fund in common people. Pain is a complex experience which includes psychological and behavior components and results from trauma, diseases, surgical interventions. Pain is an unpleasant sensation and an emotional experience associated with a real or potential damage to tissue, or equivalent of such damage. Inflammation is a process which arises due to tissue damage causing dilation of venules, increase in vascular permeability, and infiltration of histamine, cytokines and other inflammatory components. Inflammation occurs due to the stress responses and is an integral part of it. The paper is related with the pathological changes in pain, inflammation, components producing the changes. Different mediators like IL, PG, PAF, LT, cytokines are producing inflammation and leading to pain.

INTRODUCTION: 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].

Epidemiology: Fifty million Americans are partially or totally disabled because of pain (Joint Commission on Accreditation of Healthcare, 2000; Baumann, 2005. Seriously ill hospitalized patient have reported a 50% increase in incidence of pain; 15% had extremely or moderately severe pains occurring at least 50% of the time and 15% were dissatisfied with overall pain control [4]. The U.S centre for healthcare statics had carried out for 8 years of study, showed that there are 32.8% of U.S. civilian population was suffering from symptoms related to chronic pain [5].

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Recent studies carried by world health organization involving more than 25,000 patient in 14 different countries and there were 22% of primary care patients had suffered from pain which have present for most of the time for more than 6 months [6]. In some cases the percentage of individual of different kind of pains rises, to 50% and this is related with significant impairment of social functioning and quality of life; there are one third suffering from chronic pain in elderly people are not recognized by their caretakers. Statics from the

American migraine studies 2 revealed that in adolescent of 12-17myears of age, 7% girls and 5% of boys reported, at least 1 severe migraine headache in previous 12 months [7,8]. In different studies there was examination of chronic pain among children and adolescent in different genders. A study was made for the prevalence of chronic pain in the Dutch children up to 18 years of age and found out that overall prevalence was 30% of girls as compared to 20% of boys [8,9]. There is an increase in chronic pain with age and sex differences and becomes prevalent in 12-14 years of age [10].

Classification of pain: Pain can be classified into neuropathic, nociceptive, psychogenic, overall can be classified onto either acute or chronic pain [11,12]. 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 [12,13]. 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 [14,15,16]. 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 pin point and is also insidious and arises as a result of primary dysfunction in the nervous system [17,18].

It arises from excessive nociception, or nociception sensitization, alteration of physiological pathway [19]. Nociceptive pain arises due to damage of tissue. It can further be classified into two parts

Somatic pain 2: Visceral pain: Somatic pain is cutaneous in nature and occurs in deep tissues. It is localized in nature, constant, aching, gnawing, and throbbing.

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).

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. Post herpetic 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.

Psychogenic pain: Psychogenic pain arises due to anxiety or depression [11,12].

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 [20,21,22].

Acute nociceptive somatic pain can be of:

- Physiological: Physiological pain also called as first or fast pain and is a protective and is a useful event, helps the organism in order to locate the pain rapidly and also help in withdrawing from the stimulus so that further tissue damage is reduced. It is produced by stimulation of high threshold thermal/ mechanical nociceptors. It is sharp, short duration and localized

- Pathophysiological [23]: Pathophysiological pain also called as second or slow pain. It is responsible for delayed pain sensation, occurs after tissue injury. It encourages the tissue healing by eliciting behavior to protect the damaged area. It occurs after the surgery, inflammation, and trauma. It is dull, diffuse, long duration [24].

Pathophysiology of pain: Pain is an experience which is different from nociception. Nociception is the neural process which involves the transduction and transmission of noxious stimulation to the brain via pain pathway. Pain is a result of complex sequences between signaling systems, modulation from higher centers and perception of the individual [25].

Chronic pain is associated with aberration of the normal physiological pathway, produces hyperalgesia, allodynia, or spontaneous pain

Hyperalgesia is painful, which occurs due to increase response after the stimulation. It is a leftward shift to the stimulus response and is a function which relates the magnitude of perceived pain to stimulus intensity [26,27]. It is increased intensity of pain after the noxious stimulus.

Tissue injury related to hyperalgesia has two components:

Primary hyperalgesia is observed in the area of tissue injury and is as a result of primary afferent nociceptor sensation by inflammatory mediators. It occurs at the immediate area of tissue injury [26,27,28].

Secondary hyperalgesia is observed outside the immediate area of injury as a event of spinally mediated event. It is the spreading of sensitivity or pain to the nearby areas, to the injured tissues [29].

Allodynia is defined as the painful response after there is normal innocuous stimulus [30]. It is result which occurs due to change in functioning of the large diameter primary afferent neurons which normally concerned with the processing of innocuous stimuli [31,32].

Nociceptors are the receptors in the tissue and activated specifically after there is application of pain stimulus. Noxious means transduction of information by the help of receptors into an internal signal and is transmitted from the periphery to the central nervous system along axons. There are two types of nociceptors.

High Threshold Mechanoreceptors:

Polymodel Nociceptor: High-Threshold Mechano-receptors (HTM) are those which respond to mechanical deformation.

Polymodel Nociceptors (PMN) are those which respond to a variety of tissue damage inputs such as hydrogens (protons), 5 Hydroxtryptamine (5HT), cytokines, bradykinin, histamine, prostaglandins, leukotriene.

These inflammatory mediators bathe the nociceptors, activate and sensitizing them. Prostaglandins and bradykinin causes the sensitization of nociceptors when there is an application of low intensity stimuli. Histamine and 5HT causes pain when there is a direct application to the nerve endings. Hydrogen ions and 5HT act directly on ion channels of the cell membrane, but most of them bind to the membrane receptors and activate second messenger system via G proteins.

Nociceptors are having free nerve endings of a nerve fiber. There are two types of fibers: Aδ fibers and C fibers.

Aδ are finely myelinated nerve fibers. The diameter of fiber is 2-5 µm and its conduction velocity is 5-15 m sec^{-1}. The distribution of fibers is on the body surface, muscles and joints. The sensation of the pain is rapid, pricking type and is well localized. The position of synapse within dorsal horn of spinal cord is from laminate I and V [25].

Conduction continues takes place from the secondary afferent fibers via the more laterally placed Neospinothalamic tract which is monosynaptic and it ascends to the posterior thalamic nuclei (VPL and VPM) and from here there is occurrence of synapse with the tertiary afferents to somatosensory post central gyrus at the cortex [12,24].

C fibers are of unmyelinated fibre type. The diameter of fibre is less than 2 µm. The conduction velocity is 0.5-2 m sec^{-1}. It is distributed in most of the tissues. The sensation of pain is slow, diffuse, dull, aching. The position of synapse within dorsal horn of spinal cord is lamina II (*substantia gelatinosa*) (Steeds, 2009). C fibers comprise 70% of all the nociceptors. These can be further divided into two classes :

First class consists of a variety of neuropeptides, including substance p and calcitonin gene related peptides and express trkA receptors which has a high affinity receptor for Nerve Growth Factor (NGF) [33]. These neurons originates from the outermost region of the spinal dorsal horn (lamina I and outer lamina II) and gets terminated largely on spinal neurons which gets projected to the higher order of the pain centers of the brain.

Second class consist of a few neuropeptides but it causes the expression of the surface carbohydrate group which selectively binds to a plant lectin called as isolectin B4 (IB4) [34,35].

There are two main classes of Aδ nociceptors, both of which give response to intense chemical stimuli but they can be differentiated by their differential response to the intense heat or by tissue injury. Most of C fibers nociceptors are polymodel and responds to noxious thermal and chemical stimuli [36,37]. Others are mechanically insensitive but it gives response to noxious heat. C nociceptors also give response to noxious chemical stimuli e.g., acid, capsaicin. There are some natural nociceptors but is difficult to identify and are called silent or sleeping nociceptors and are responsive after the sensitization.

Spinal cord and gate control theory: The dorsal horn of the spinal cord is the site where the primary afferent fibers make a synapse with the order neurons. It is also the site where there is an occurrence of complex interaction between the excitatory and inhibitory interneurons and where descending inhibitory tracts from higher centers to exert their effect. The dorsal horn is divided to laminae and also called as rexed laminae. They are having numerous connections between the laminae. Laminae laminae also called substantia.

This extends from the trigerminal nucleus in the medulla to the filum at the caudal end of the of the spinal cord, The C fibers gets terminated into laminae II and Aδ fibers gets transmitted into laminae I and V. There is entrance of Aβ fibers from the cord medial to the dorsal horn and get passed without synapse to the dorsal horns. They give off the collateral branches to the dorsal horn which get terminated into several laminae (III-V). They also get synapsed directly with the terminals of unmyelinated C fibers in lamina II. These laminae II and V are very important and are the area of modulation and pain.

There are three types of second order neuron in the dorsal horn.

Nociceptive Specific (NS): It gives response to selectively high threshold noxious stimuli and is found in laminae II and III.

Wide Dynamic Range (WDR): It gives response to a range of sensory stimuli and is found in laminae V and VI.

Low threshold (LR): It gives response solely to innocuous stimuli. There is passage of information from periphery to the central areas and is controlled by various mechanisms which helps in the modulation of pain and are based on the spinal cord level:

- Inhibitory control by higher centers
- Activity in the Aβ collaterals
- Segmental (spinal) modulation by a variety of mechanisms including endogenous, opioids and other cannabinoids systems, inhibitory amino acids e.g., GABA, galanin, cholecystokinin and nitrous oxide

Here the first two mechanisms causes the ‘close the gate’ after the onwards transmission of C fiber activity. Melzack and Wall purposed the ‘gate control’ theory in 1965. They postulated that laminae II inhibitory interneurons can be activated directly or indirectly after the stimulation of non noxious large sensory afferent from the skin (Aβ fibers) leading to the suppression of transmission in small unmyelinated (C fibers) afferent and the pain is blocked. Hence after the rubbing in the painful area, pain gets blocked.

This represents the working mechanism in the transcutaneous electrical nerve stimulation in the pain control.

Brain: Thalamus is the processing area for somatosensory information. The axons in the lateral and medial spin thalamic tract and gets terminated in the medial and lateral nuclei afterwards the neurons project in the primary and secondary cortices. These areas play a different role in the perception of pain and also interect in different areas of brain e.g., Cerebellum and basal ganglia.

Descending tracts: They have a big role of modulation in the pain. Two important areas in the brain system for reducing the pain are Periaqueductal Grey (PAG) and Nucleus Raphe Magnus (NRM).

PAG: It is important in controlling the pain and surrounds the cerebral aqueduct. PAG receives inputs from the thalamus, hypothalamus, cortex and also collaterals from the spin thalamic tract. PAG neurons (antinociceptor) cause the excitation of cells in NRM and further projects down to the spinal cord so as to block the transmission by the dorsal horn cells.

NRM: Second descending systems of serotonin containing neurons exist. The cell bodies of these types of neurons are present in raphe nuclei of the medulla like that of noradrenaline containing neurons and axons get synapsed with lamina II and also get sometimes synapsed with lamina III. Activation of raphe nuclei results in a powerful analgesia. Perhaps, the serotonin release by this stimulation activates the inhibitory interneurons even more powerful than norepinephrine and blockage of pain transmission.

Brain stem neurons may control nociception transmission by:

- Direct action on dorsal horn cells
- Inhibition of excitatory dorsal horn neurons
- Excitation of inhibitory neurons

Sensitization of pain and mediators of pain:

Peripheral activation: When there is stimulation of C fibers there is release of peptides which are proinflammatory and cause plasma extravasations, reinforcing the accumulation of mediators. These chemicals sensitize the high threshold nociceptors and hence after a small intensity stimuli they get activated, hence occurrence of peripheral sensitization at the site of injury or primary analgesia. These inflammatory mediators gets interacted and results in complex process events which not only changes the function of sensory afferent fibers in short term but can alter the gene transcription produces changes in biochemistry of sensory neurons [12,38]. Some of the mediators act directly on the ion channels in the membrane (protons and 5HT) and most of the mediators bind to the membrane receptors and act via regulatory intermediates (G proteins and secondary messengers such as c AMP) which activates the specific types of kinases. After this there is occurrence of phosphylation of cellular proteins which further causes the change in membrane ion channels or enzymes [28].

Central sensitization: After the nerve injury changes occur in the dorsal horn of the spinal cord. There is occurrence of activation by noxious stimuli to the repetitive C fibers produces a prolonged dorsal horn response and the phenomenon is called 'wind-up'. In the dorsal horn there is a reduction in the local inhibition of the neurotransmitters GABA, glycine and excitoxic death of inhibitory neurons, incoming neurons produce ectopic activity and output to spinothalamic tract neurons is increased. This process involves neurochemical changes via NMDA, neurokinins, NO and hence there is lowering of pain [25].

There are four principle receptors which are involved in the nociception, in which three are of ionotropic type and the fourth is of metabotropic type. Isotropic receptors are NMDA, AMPA, NK-1 and these are linked to ion channel and results in cell depolarization. The metabotropic results in production of secondary cellular messengers. Glutamate and aspartate act on the AMPA (α amino-3-hydroxy-5- methylisoxazole) and produces a fast post synaptic potential.

The potential is stimulated by substance P via neurokinin-1(NK-1) receptor and enough depolarization is generated so as to remove Mg^{2+} plug from NMDA (N methyl D aspartate) receptor ion channel so that the NMDA receptor is primed or activated and in the cell and there is intrusion of Ca^{2+} in the cell.

Stimulation of metabotropic receptors causes the activation of Phospholipase C (PLC) resulting in secondary intracellular messengers Inositol triphosphate (IP3) and Diacyl Glycerol (DAG). IP3 results in release of Ca^{2+} from Endoplasmic Reticulum (ER) resulting in increased expression of proto-oncogenes c-fos and c-jun. The release of Diacyl Glycerol (DAG) causes stimulation and the translocation of Protein Kinase C (PKC) occurs which further causes Ca^{2+} influx in the NMDA receptor and sustained depolarization. PKC also interacts with Ca^{2+} which stimulates for the expression of c-fos and c-jun. These types of proto-oncogenes plays a role in the regulation of mRNA which encodes for dynorphin and encephalin peptides in the spinal cord can influence long term changes in cellular function such as enhanced excitability and expanded receptive fields. There are various types of excitatory amino acids are aspartate and glutamate.

Neuropeptides are of three types:

- Nociceptive-Enhances the release of aspartate, tachykinins, substance P, Calcitonin Gene Related Peptide (CGRP), CCK (Cholecytokinin), Neurokinin (NK-2, NK-3), Vasoactive Intestinal Peptide (VIP)
- Anti nociceptive-Galanin, somatostatin
- Other inhibitory neuropeptides-α agonist(nor adrenaline), GABA, adenosine, opoids (endorphins, enkephalins, dynorphin A) [12,39]

GABA and glycine are involved in the tonic inhibition of the nociceptive response [40]. Substance P work by inhibition of NO and there is blockage of hyperalgesia induced by NMDA receptors [41]. Neurokinin-2 (NK-2) antagonists are potent for acute nociception [(42)]. Calcitonin Gene Related Peptide (CGRP) is released from nociceptive afferents and decreases depolarization of the dorsal horn cells [43]. There is no useful receptorantagonist until now, but the antibodies to CGRP are analgesic [44]. Cholecystokinin (CCK) acts indirectly than the action. It antagonizes the μ opoid agonist at the receptor, but don't produce the hyperalgesiawhen applied alone [45]. Somatostatin or stable peptides analoges is analgesic in humanbeing models [46]. Two ways have been discovered for understanding the pain:

- Molecular/cellular transduction mechanism
- Neuronal plasticity

Molecular/cellular transduction mechanism: There are some specific molecules which are involved in pain transduction processes. There are some vanilloid receptors which can detect the noxious heat [47,48]. VR1protein is a heat transducer since it changes thermal energy into electrical signals (action potential) is transmitted to CNS and cause for the detection of hot painful stimulus. WithoutVR1receptor, there is no effective detection of noxious heat specifically in setting of inflammation [49,50].

Neuronal plasticity: Plasticity refers to changes produced in the established nervous system. Changes in neuronal structures, connections between neurons, changes in quality and properties of neurotransmitters, receptors, and ion channels lead to increased functional activity of neurons in pain pathway. Injury, inflammation and other disease can sometimes lead to neuronal plasticity and there is increased pain due to increased excitatory or decreased inhibitory mechanisms.

Inflammation: Inflammation is a defensive response which causes the different physiological adaptions which limits the tissue damage and removes pathogeneic 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 [51,52].

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 [53,54,55,56]. 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 no 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.

Leukocyte ingests the offending agents, kill bacteria and other microbes and degrade other necrotic tissue and foreign antigens. Leukocytes also prolong inflammation and induce tissue damage by releasing enzymes, chemical mediators and toxic oxygen radicals. Although inflammation is a protective response, uncontrolled inflammation may be potentially harmful and may underlie the pathogenesis of many acute and chronic diseases [57,58].

Inflammation is the first step in the development of various disorders like atherosclerosis and diabetes mellitus and is currently having interest in worldwide. This response in nature defining the body response in a surgical incision would be same as that of the episode in tissue hypoxia [59]. Inflammation originates with a cellular injury and there is release of chemical messengers from the damaged tissues. There are no of chemicals that are released, which includes chemotactic factors which causes the announcement of the injury to the body and hence activate the WBCs and the immune system.

Also there is release of cytokines which locally dilates the vascular tissue resulting into the distension and increased blood flow into the area of tissue damage and finally this distension and increased blood pressure within the lumen of the blood vessels results in leaking of plasma and the cells from blood vessels into the damaged or infected tissues, defined as exudate, development of the cardinal signs of inflammation like redness, warmth and swelling [59]. Inflammation can be divided into two parts.

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

- Exudation of fluids
- Plasma protein (edema)
- Emigration of leukocytes specially neutrophils

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 ***(60,61)***. 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 lipogensis and lipolysis. There is decrease in plasma protein level, increased C reactive protein level [62].

Pathophysiology and mediators of inflammation: The process of inflammation is associated with many types of mediators like prostaglandins, leukotrienes, histamine, bradykinin, Platelet-Activating Factor (PAF) and the proinflammatory cytokines including interleukin-1 (IL-1), 1L8, Tumor Necrosis Factor (TNF) [63,64,65,66]. The humoral factors (chemical mediators) play an important part in initiating and further maintenance of the inflammatory response [67,68]. Their function include vasodilation, increased vascular permeability, chemotaxis, leukocyte adhesion and activation, direct toxicity to the invading organism (or to the cells) and to the extracellular matrix, fibroblast proliferation, collagen deposition and angiogensis.

Different types of mediators are [57,58] vasoactive amines such as histamine and serotonin that mediate vasodilation and increased vascular permeability [69]. Plasma proteases such as complements mediating vascular permeability, chemotaxis, leukocyte adhesion and activation and opsonization and phagocytosis: kinins cause the increase in the vascular permeability and the clotting systems generate thrombin and factor Xa which increase vascular permeability, leukocyte adhesion and fibroblast proliferation [70].

Arachidonic acid metabolites like Prostaglandins (PG), leukotrienes and lipoxins are the mediators which increase the vascular permeability, chemotaxis and leukocyte adhesion [71]. Cytokines like TNF-α, IL1, IL2, and IL-4, IL-6 and interferons and chemokines such as IL-8 and MCP-1 that have multifunctional properties influencing all aspects of inflammatory processes. The presence of the foreign material or the host tissue which has been damaged signals the stimulus and then there is triggering of inflammatory response by the activation of the complement, coagulation and kinin cascades.

Multiple mediators such as 5a, thrombin and bradykinin causes change in permeability, attraction of leukocytes and the alteration of vasomotor tone at the site of injury. These mediators also causes the activation of macrophages population leading to the production and the release of early proinflammatory mediators such as TNF-α and IL-1β as well as a group of chemoattractant cytokines known as chemokines. After the initial response most critical process is the leukocyte- endothelial cell interaction. These proinflammatory mediators causes the activation of leukocyte and endothelial cell population which further leads to the production of chemokines as well as increase in adhesion molecules on the endothelial surface.

The initial endothelial response is rapid and consists of the exocytosis of P-selectin from the Weibel-Palade bodies within the endothelial cell and an increase in vascular permeability. This response requires gene expression and results in the appearance of E-selectin, Intracellular Adhesion Molecule-1(ICAM-1) and other adhesion molecules on the endothelial surface. Chemokines provide directional signals and specificity for leukocyte recruitment.

Leukocytes move down the concentration gradient of chemokines. Chemokines predicts which cells are to be recruited at specific times. There are more than 40 different types of chemokines are known in atleast four families according to their chemical structure and the type of their leukocyte [72].

In case of sympathetic system epinephrine (adrenaline) is secreted from adrenal medulla and norepinephrine (noradrenaline) also released from adrenal medulla and modulates the release of cytokines and inflammation through α and β receptors on immune cells [73,74]. In case of nerves somatic and autonomic are associated with inflammatory cells especially true of mast cells which resemble in different aspects [75,76]. Stimulation of sensory nerves containing C fibers with an electrical current, mechanically by heat or by noxious chemicals such as formalin or mustard oil or even loss ligation of the sciatic nerve [76,77] and resulting in antidromic transmission and ensures inflammatory response which is demonstrated in the eye, dental pulp, joints, lungs [76,78,79,80].

There is occurrence of extravasation from the post capillary venules and resulting increased flow of blood due to arterioles dilation which in end produces wheal and flare respectively. Chemotaxis and polymorphonuclear leukocytes and adherence to the vascular wall may also occur [80,81,82]. When there is presence of substance P into the skin then it induces vasodilation and increased in vascular permeability due to its chemoattractants properties and leads to facilitation of traffic to the site of inflammation and in the end producing the wheal and flare or urticaria. CGRP is less potent in causing the wheal reaction but it can potentiate the effects of substance P and leads to the vasodilation and hyperthermia in skin.

Mediators of inflammation:

Bradykinin: It is the most important mediator and most potent endogenous alogenic 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 [28]. They act at the Bradykinin 2(B2) receptor to both activate and sensitize nociceptors . B2 receptors are present on sensory neurons and are to a G protein to induce phospholipase C activation which leads to the

production of secondary messengers which cause the release of calcium from intracellular stores and phosphorylation of cellular proteins including membrane ion channels. B2 antagonist significantly reduces pain and htperalgesia [83].

Arachidonic acid metabolites or prostanoids includes PG, LT, hydroxy acids and are made of COX and LOX enzymes in inflammatory conditions [28]. PGE1 and prostacyclin stimulate nociceptor directly. Prostanoid act on specific receptors coupled with second message and hence generation of cAMP [84,85].

Histamine: Association of histamine with H1 receptors produces numerous effects associated with the symptoms of anaphylaxis and other allergic symptoms [86,87]. Histamine lead to the production of allergic inflammatory responses by enhancing the secretion of proinflammatory cytokines such as interlukin 1α, interlukin 1β, interlukin 6 or interlukin 8 in different types of cells and tissues [87,88,89,90,91]. Endothelial cells express functional histamine receptor HI and H2. Infusion of histamine leads to the expression of adhesion molecules like ICAM-1, VCAM-1(vascular cellular adhesion molecule) and P-selectin [92,93,94]. Histamine possesses the property of classical leukocytes chemoattractant, mobilization of intracellular of Ca^{2+}, up-regulation of adhesion molecular expression [95,96,97,98]. It is released from mast cell degranulation induced by several other mediators such as substance P, interleukin-1, NGF (Nerve growth factor) .

Nitric oxide and mast cells: Nitric oxide is generated due to the inflammation [99,100]. Nitric oxide is a proinflammatory at the low concentration by inducing vasodilation and the recruitment of neutrophils but at the high concentration there is down regulation of adhesion molecules [100,101]. Nitric acid is formed from L-argenine by nitric oxide systhetase. 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.

The first event that takes place in IgE mediated inflammatory disease in asthma is activation of mast cells by antigens. Mast cells release the histamine in association with the other mediators and causes dilation, increase in permeability in tissues, increase temperature, edema, and infiltration of WBC. Mast cells also release mediators like TNF-α which promotes later phase of inflammation by recruiting other type of cell types [102].

Neuropeptide: Neuropeptide Y is a cotransmittor of sympatheic 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 [103]. The neuropeptide CRF is located within the PSGN as well as in sensory nerves [(104)]. Substance P is a sensory neuropeptide which is present in autonomic nerves and ganglia [105].

These are the mediators in inflammation. Substance P is also involved in neurogenic inflammation, non-neuronal inflammation. Leukocytes, lymphocytes, macrophages, mast cells are having receptors of substance P and can be stimulated so as to produce cytokines by substance P [106,107,108,109]. SP is synthesized in macrophages, eosinophiles. Macrophage is also stimulated by SP results in production of inflammatory mediators like PGE2, TXA2 and superoxide ions [110,111].

SP causes the downregulation of synthesis of Transforming Growth Factor (TGF) which has anti-inflammatory properties [109]. Macrophages are having receptors for CRF and with association of SP, CRF induces the production of the proinflammatory cytokines, IL-1,IL-6 and TNF-α [112,113].

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 [(114,115)]. There is other family of cytokine called as anti-inflammatory 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 [115,116]. 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 [117].

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 [118,119].

Macrophages exposed to either or both produce cytokines, reactive oxygen intermediates, chemotactic molecules, inflammatory mediators (PGE2, NO) thrombogenic factors and various proteases all of which produces inflammatory reactions [120, 121]. Different cytokines and inflammatory mediators such as interferon-γ and TNF-α, interleukin-1, bacteria derived Lipopolysaccharide (LPS) resulting in Nitrogen Oxide (NO) production and these mediators binds to specific macrophages receptors resulting in a biochemical signaling cascade causes the activation of nuclear transcriptional factors including Nuclear Factor Kappa B (NF-KB), Interferon Regulatory Factor-1(IRF-1) and Gamma interferon Activating Sequence (GAS) [122,123].

CONCLUSION: From this article we came to know that 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.

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How to cite this article:
Singh BM, Negi G, Bhole P and Jaiprakash M: Pain and Inflammation: A Review. *Int J Pharm Sci Res*. 3(12); 1000-1012.