blocked. Convergence of large and small diameter afferents at the level of the dorsal horn underlies this phenomenon.

## Allodynia

The stimuli that normally are not painful *e.g.*, movement and light touch become painful. The pain produced by touching sun burnt skin or movement of an arthritic joint[3].

## Hyperalgesia

Hyperalgesia is an exacerbated pain produced by a noxious stimulus *e.g.*, slapping, sun burnt skin or reaction to noxious stimuli in a subject, whose large fibres in the arm are blocked by compression.

NSAIDs are effective through cyclooxygenase inhibition. COX-2 enzyme inhibitors, Celecoxib and Rofecoxib have a better utility without GIT side effects of Aspirin and NSAIDs.

## Substance-P

An 11 amino acid peptide neurotransmitter synthesized by primary afferent nociceptors, substance-P is released in the dorsal horn and activates second order "pain" transmission neuron in the dorsal horn. It is released from the peripheral terminals of C-fibres and contributes to local, neurogenic inflammatory mechanisms, including vasodilatation, warmth, redness and swelling.

Capsaicin, an irritant is the pungent ingredient in the hot pepper. It stimulates C-fibres, because they express

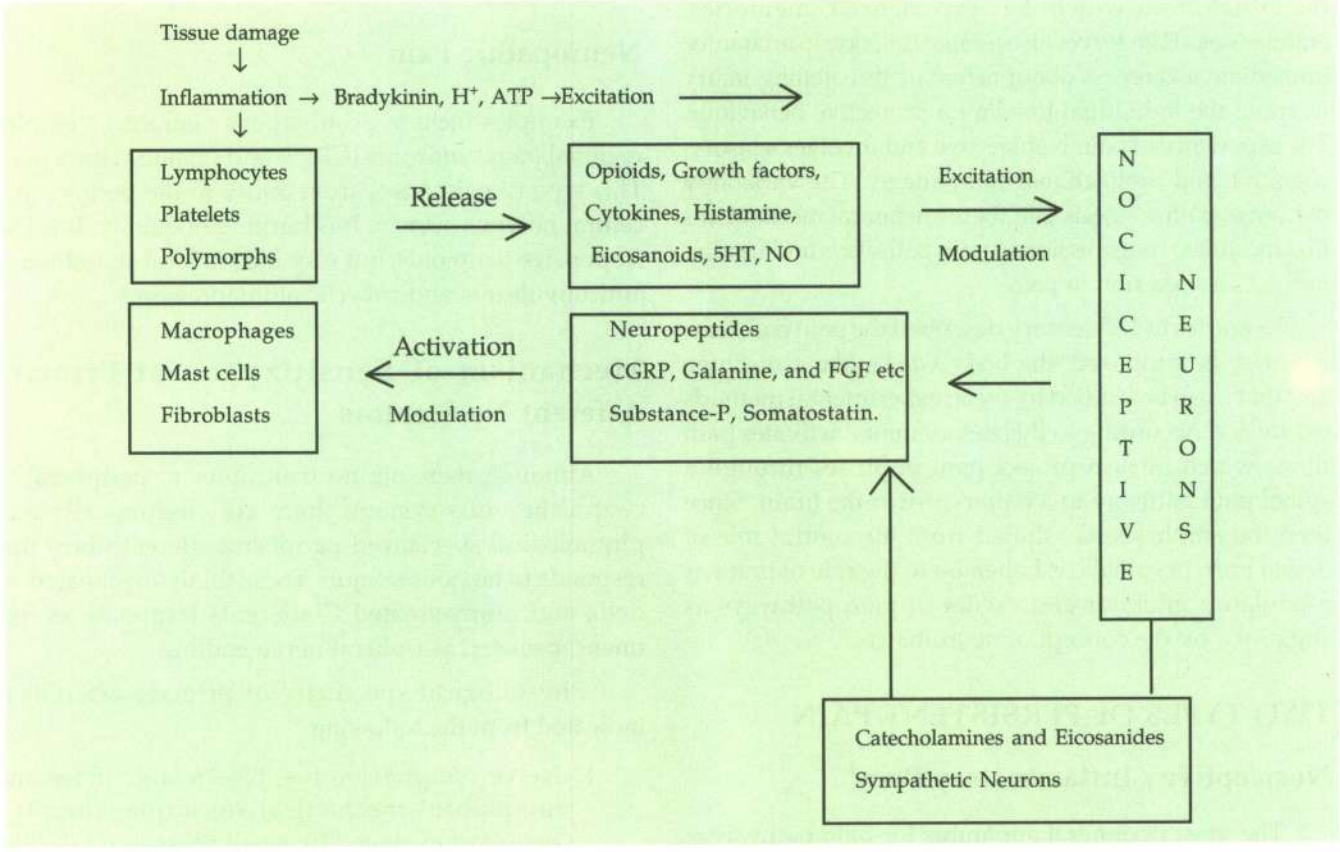


**Fig. 2.1 : Mediators produced by injury, inflammation at the terminal neurons**

## Primary Sensitization Mechanism

After a tissue injury, the threshold for firing of A-delta and C-nociceptive afferent are lowered to a non-noxious range. Mechanism involves synthesis of arachidonic acid from membrane lipids via steroid sensitive phospholipase A2 enzyme. Arachidonic acid is acted upon by cyclooxygenase enzyme to produce prostaglandins which act directly on the peripheral terminals of A-delta and C-fibers, while their electrical activity remains unchanged. Light touch can now activate a C-fibre and produce pain. Aspirin and the venilloid (VR1) / capsaicin receptor. VR1 receptor also responds to noxious heat and is gated by pH. The acidity of injured tissue may enhance pain via VR1. Topical Capsaicin creams have been introduced to control a variety of pains. Their efficacy remains to be established.

## Onward Transmission of Pain Impulse[4]

When the depolarization at the junction of the receptor and the axon to which it is attached reaches threshold level, an impulse is propagated along the surface of the axon. The nociceptive information is

system. Glial activation and its associated proinflammatory cytokine release are being implicated in exaggerated pain states, thus linked to acute peripheral inflammation, chronic nerve trauma and infection.[1]

## Opiates, Opioids and Endorphins

PAG and dorsal horn have high opiate receptor concentration which bind morphine and naloxone and intrinsic endorphin peptides. The latter has been cloned providing future development of newer analgesics. The placebo activates the endorphins and reversed by naloxone. TENS, acupuncture also does the same. Hypnosis does not involve endorphin release. The morphine injection inhibits Laminae-I, V and blocks release of neurotransmitters *e.g.*, substance-P from small fibres.

## Mechanism Underlying Progression of Acute to Chronic Pain State

Acute and chronic pain states have been identified as two markedly different entities from all aspects of their pathophysiology to manifestations, diagnosis and management. While acute pain serves a definitive protective and reparative function, easy to identify and treat chronic pain has been recognized as a disease state which persists beyond the usual course of an acute disease or healing process or recurs for months or years. An understanding of mechanisms underlying the development of chronic pain is important for its management and prevention of progression of acute to chronic pain.

Elegant neurophysiological experiments on inflammatory and arthritic pain models have supported clinical studies reporting peripheral as well as central sensitization following persistent stimulation of primary nociceptors.[7] Liberation of allogenic substance (serotonin, histamine, bradykinin, prostaglandins) alter the micro environment around the nociceptors causing their further stimulation and increased capillary permeability adding more mediators and increased sensitivity of nociceptors, development of oedema, allodynia and hyperalgesia. Peripheral sensitization is followed by spinal sensitization. Studies have revealed increased excitability of dorsal horn neurons and their receptive field, elevated levels of Glutamate, $PGE_2$, NO along with Neuropeptides (substance-P, calcitonin gene related peptide), upgrading of receptors followed by expression of genes coding neurotransmitters, if stimulation continues. The increased excitability spreads to lateral and ventral horn neurons activating sympathetic nervous activity and skeletal muscle spasm. This in turn creates a vicious cycle maintaining abnormal spinal neuron activity which may spread to suprasegmental and higher brain regions evoking neuroendocrinal responses.[6]

Pain resulting from nerve injuries, phantom limb and post herpetic neuralgia has been explained through hypothesis proposed by Wall and colleagues[4], which essentially suggests loss or imbalance of sensory input into the somatosensory system leading to inhibition of inhibitory mechanisms within neuraxis.

Role of sympathetic nervous system in several pain states is well documented. However, the studies revealed a significant hyperalgesia with cholinergic blockers and the effect was seen even in the spinal animals. An inhibitory role of acetylcholine on nociceptors and a link between cholinergic discharge noradrenergic receptors on peripheral nociceptors is suggested.[8]

Studies conducted on acute and chronic pain patients to evaluate acupuncture analgesia revealed varying degrees of pain relief and also basal autonomic status of these patients. Do the autonomic changes contribute to pain states or are just accompanying responses is not clear. It, however, seems that evaluation of autonomic status of pain patients may help identifying acute pain, patients likely to progress to chronic pain state.[4] Chronic pain affects 10% of the pain patients for more than 100 days. Examples are cancer pain, low back ache, arthritis, migraine with a history of multiple episodes.

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●●●

3. **Antibodies to cytokines :** Antibodies to cytokines represent another mechanism to interfere potentially with the effects of specific cytokines.
4. **Protein binding of cytokines :** Both autoantibodies to cytokines and soluble receptors may comprise a large part of this binding activity. Uromodulin and $\alpha_2$-macroglobulin, also may bind cytokines in vivo with mixed biologic consequences.
5. **Regulation of receptor expression :** Cell surface receptors for TNF-α are up-regulated by IL-1, IL-2, IL-4, IL-6, IFN-γ or TNF-α itself. In constrast, TNF-α receptor expression is down – regulated by bacterial liposaccharides (LPS).
6. **Soluble cytokine receptors :** This group has recently received a great deal of attention. The generation of soluble cytokines receptors appears to be a mechanism for regulating cytokines activities in vitro, since their levels are often raised in certain disease states. They have been described for most of the major cytokines including TNF-α, (sTNFR I and II), IL-1 (sIL-1R I and II), IL-2 (sIL-2R), IL-4 (sIL-4R), IL-6 (sIL-6R) and IFN-γ (sIFN-γR). The soluble cytokine receptors bind a cytokine in solution and prevent it from interacting with the cellular receptors and exerting its biological activities.
7. **Cytokine receptors antagonists :** Both TNF-α and IL-1 may be of central pathophysiologic importance in human autoimmune and chronic inflammatory diseases. The identification of a specific receptor antagonist for IL-1, termed IL-1ra, represents the first description of a naturally occurring receptor antagonist of any cytokine or hormone-like molecule. Clinical trials with IL-1ra have commenced in sepsis syndrome, rheumatoid arthritis, and other human chronic inflammatory diseases.

## A Functional Grouping

Knowledge of the structure of the cytokines and their receptors has allowed the division of cytokines into families based on the homology of their pattern.

It is a description of the major cytokines with an emphasis on their biological activities. This knowledge is based on in vivo studies.

## Antiviral Cytokines

The antiviral cytokines are the type I IFNs and include many subtypes of IFN-α, IFN-β and IFN-ω The type I IFNs are all derived from the same ancestral gene and have structural homology in between 165–172 amino acids. The type I IFNs can be produced by any cell type in the body. The induced IFNs stimulate the production of a range of proteins which produce many antiviral effects. This prevents the replication of majority of viruses in the target cell.

**The other functions :** Inhibition of replication of cells, modulation of expression of MHC class I molecules and upregulation of macrophage, cytotoxic T-cell and natural killer T-cell activity.

## Pro-Inflammatory Cytokines[6]

Although the pleiotropic activities of pro-inflammatory cytokines may directly result in disease symptoms, such as elevated temperature, muscle loss and weight loss, all these activities are in fact important in the host defence against infection.

The pro-inflammatory cytokines, sometimes referred to as primary cytokines include two members of the interleukin family, (IL-1α and IL-Iβ), TNF-α and IL-6. These cytokines are multifunctional and have effects on numerous cell types. The most important source is the macrophage.

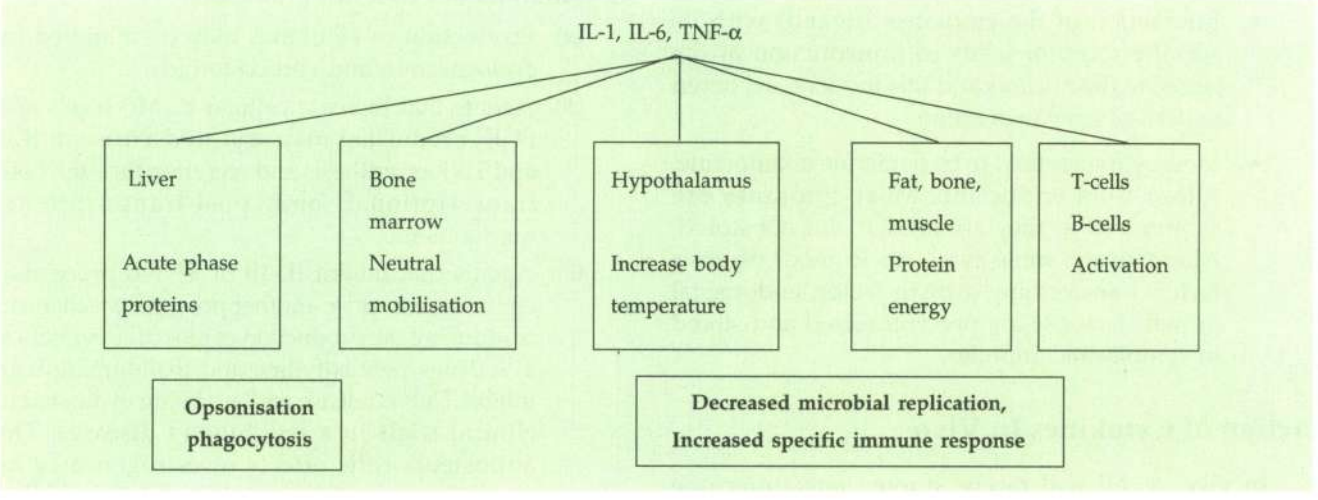


**Fig. 4.2 : Pro-inflammatory cytokines in host defence**

Essentially all the effects mediated by these cytokines have some antimicrobial activity. The metabolic activities of the cytokines provide fuel in the form of amino acids, fatty acids and glucose. This enables the specific immune system to mount an effective immune response against the stimulating microbe.

Opiate receptors belong to the superfamily of G protein coupled receptors constituting 80% of all known receptors *e.g.*, muscarinic, adenylate cyclase, adrenergic, GABA and somatostatin receptors. Direct inhibitory actions of opioids are mediated by receptors coupled to pertussis toxin – sensitive to $G_1/G_0$ proteins and direct excitatory effects via a cholera toxin – sensitive $G_5$ like protein. The opioid receptor activated G protein effector system can be divided into – short-term effectors ($K^+$ and $Ca^{++}$) and long-term effectors involving cAMP and phosphatidylinositol. Both μ and δ receptors activate inwardly rectifying $K^+$ channels and all opiate receptor types can inhibit opening of voltage dependent $Ca^{++}$ channels.[2] The $K^+$ channel effects results in hyper polarization of neuronal membranes, decreasing synaptic transmission while $Ca^{++}$ reduction can decrease neurotransmitter release (Table 5.1).

At periductal grey area, opiate receptor stimulation results in impulses that alter the degree of inhibition of neuronal pods, reducing the transmission of nociceptive information from periphery. At spinal level action is at nerve synapses either presynaptically (as neuromodulators) or postsynaptically as neurotransmitters.[3]

to very high affinity site $\mu_1$ as well as to the high affinity site (*k, d* or *a*) depending upon the ligand used. Naloxazone and naloxonazine were reported to abolish the binding of each ligand to $\mu_1$ site. Furthermore in vivo studies, naloxazone was found to be selectively blocking morphine induced anti-nociception but did not block morphine induced respiratory depression or the induction of morphine dependence.[3]

**$\delta_1$ and $\delta_2$ :** This subdivision of δ receptor subtypes was proposed on the basis of in vivo pharmacological studies (Table 5.2). In rodents in vivo, the supraspinal antinociceptive activity of DPDPE can be selectively antagonized by BNTX2 or DALCE, whereas deltorpine I and $D_3$LET activity can be reversed by 5′-NTII.[5]

Best evidence to support subdivision of δ-receptors comes from inhibition of adenylcyclase activity and from δ receptor-mediated elevation of intracellular $Ca^{++}$ in the Ndb-47 cell line where BNTX selectively antagonized DPDPE and naltriben selectively antagonized deltrophin II.

The pharmacological properties of the cloned DOR-1 receptor are between those predicted for either the $\delta_1$ or $\delta_2$ subtypes. DPDPE and deltrophin II are both potent displacers of [3h]- diprenorphine binding to mouse and human receptors which is not consistent with $\delta_1$ or $\delta_2$

**Table 5.2 : Delta Receptor Subtypes[5]**

| Receptors subtypes | Antagonists | |
|---|---|---|
| | competitive | Non equilibrium |
| $\delta_1$ | DPDPE/DADLE | BNTX DALCE |
| $\delta_2$ | Deltorpine T1/DSLET | Naltriben 5′-NTII |
| DOR 1 | DPDPE | Naltriben |

## Newer Advances in Opiate Receptors

Recently it has been reported that heroin and morphine-6-glucuronidase but not morphine, still produce anti-nociception in mice in which MOR-1 gene in opioid receptors was disrupted in exon-1. However, MOR-1 gene disruption in exon-2 all three agonists were not effective antinociceptives. It was concluded that antinociceptive actions of heroin and morphine-6-glucuronide could be through a receptor produced through gene product[4] MOR $1_A$, $1_B$, $1_C$, $1_D$, $1_E$, $1_F$.

## Receptor Subtypes – $\mu_1$ and $\mu_2$ Subtypes

This subdivision was proposed by Pasternak et al. to explain their observation in radioligand binding studies that (3P) labelled $\mu_1$ and δ and κ ligands displayed biphasic binding characteristics[4]. Each radioligand binds

classifications the [3h]-diprenorphine binds to the recombinant receptor's displacement by naltriben suggests it to be $\delta_2$ subtype.[5]

**δcx and δncx :** This subdivision was based on the hypothesis that one type of δ-receptor (δcx) was complexed with μ-receptors or perhaps κ receptors, whereas δncx was not found to be associated with an opioid receptor complex.[6] There are in existence subtypes of δncx, *i.e.*, δ (ncx-1) and δ (ncx-2), the δ (ncx-1) receptor may be synonymous with $\delta_1$-receptor while δ cx synonyms with $\delta_2$ receptor.

**κ-receptors :** The first κ-receptors characterization came from work using [3H] ethylketocylazocine (EKC) in guinea pig brain. This pointed to the existence of a non-homogenous population of high affinity binding sites, thus leading to $\kappa_1$- and $\kappa_2$- sites sensitive for DADLE.