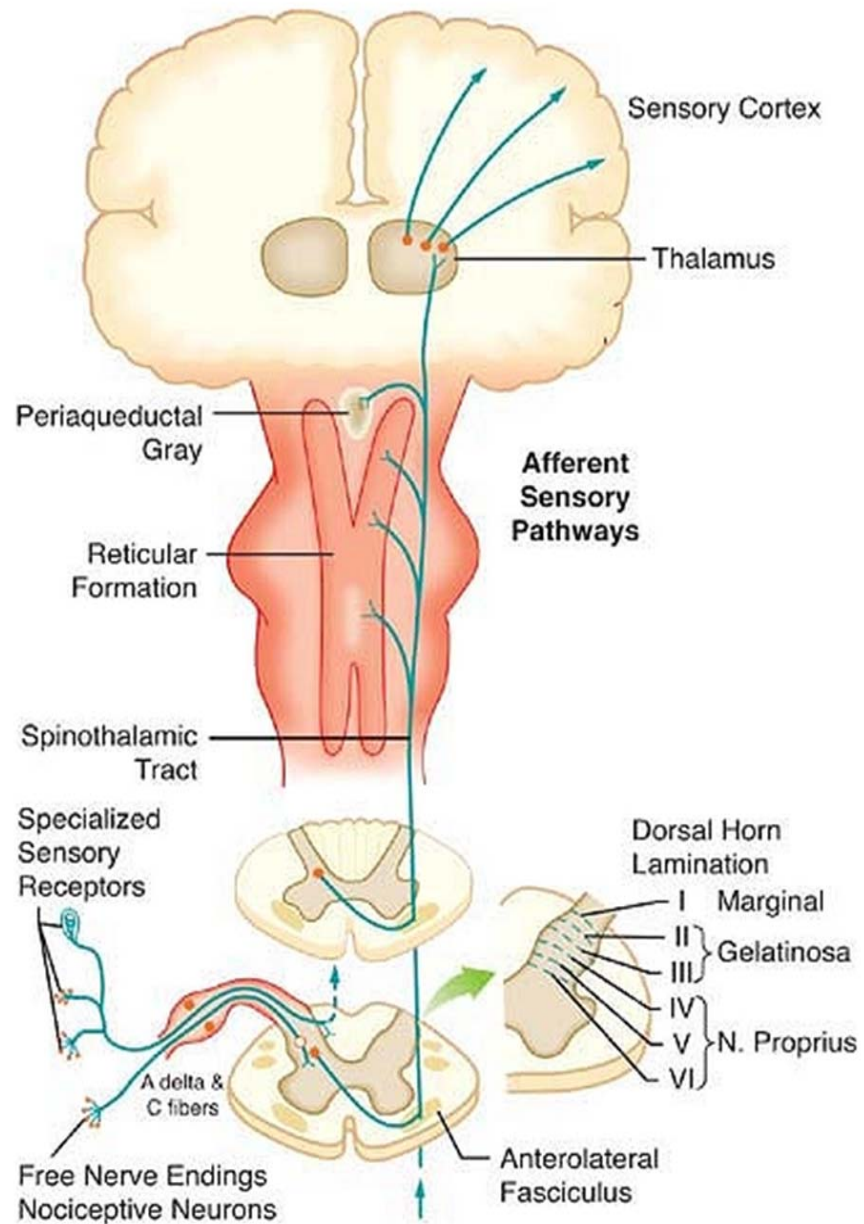


Mechanism of acute and chronic  
pain: Can acute pain relief prevent  
chronic pain?

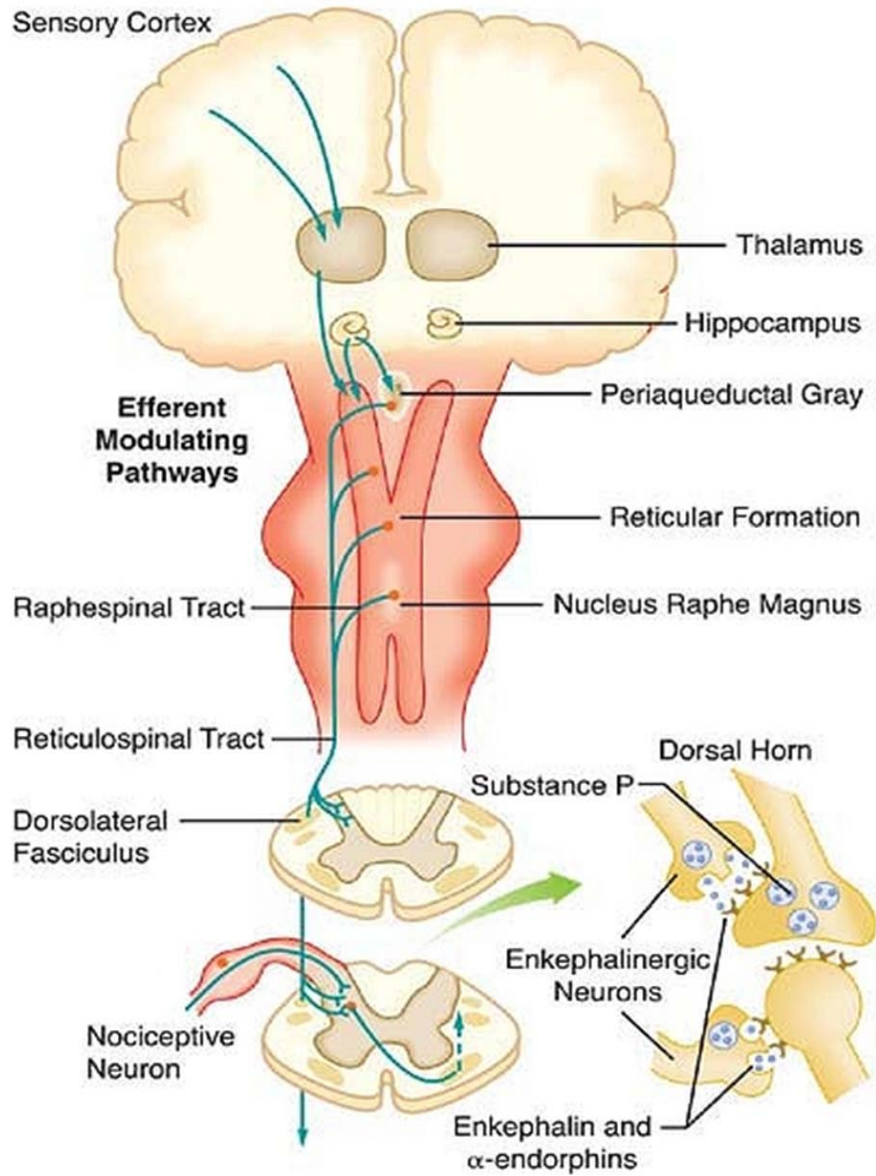
- Definition
- Anatomy
- Physiology
- Acute pain
- Chronic pain
- Mechanisms of pain
- Why treat Acute pain?
- Persistent postsurgical pain
- Potential for prevention of postsurgical chronic pain
- Role of APS
- Conclusion

# What is pain?

- IASP Definition- pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.



**AFFERENT NOCICEPTIVE PATHWAY**

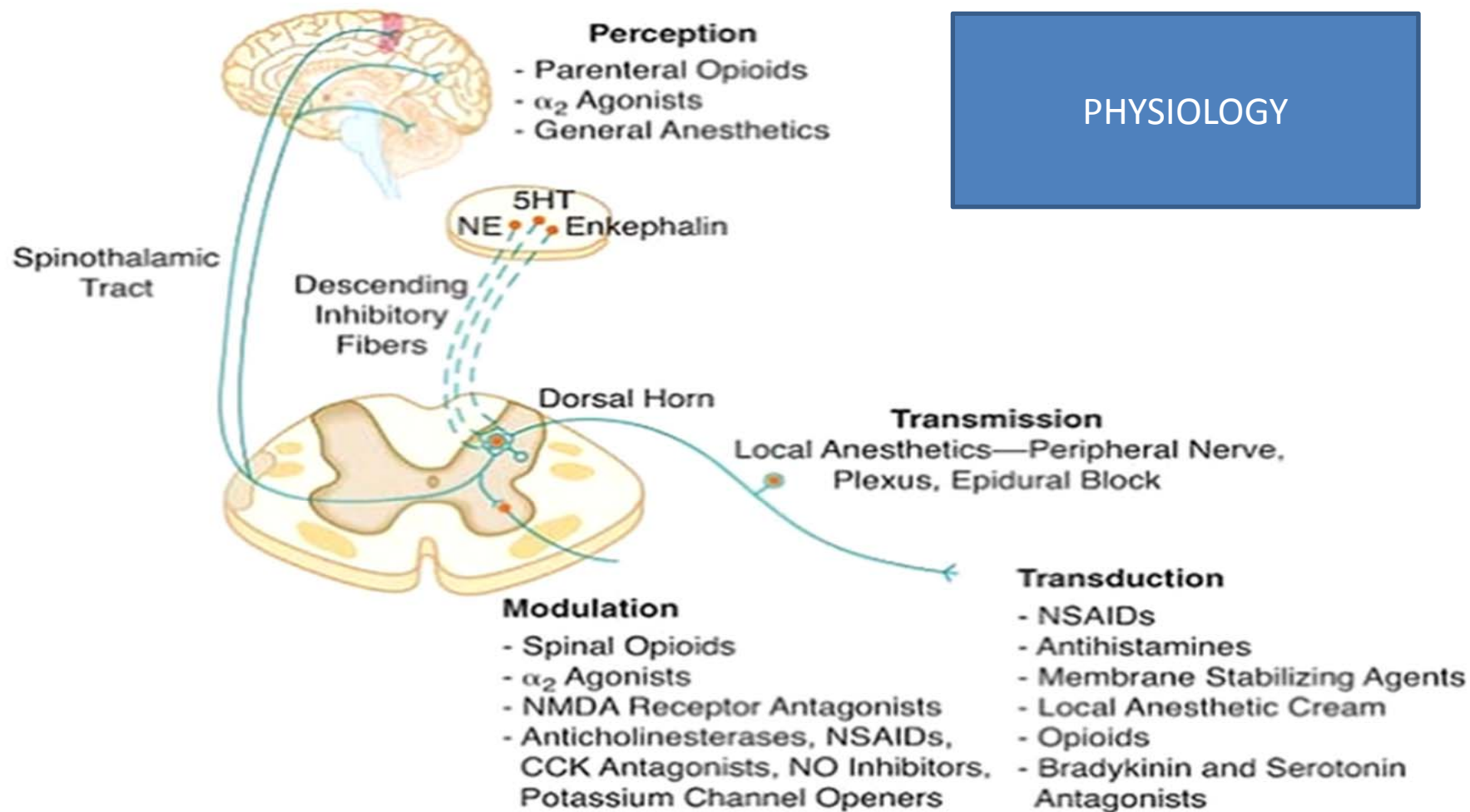


**EFFERENT NOCICEPTIVE PATHWAY**

# Nociceptors

- Peripheral sensory neurons which respond selectively to noxious stimuli.
- Discriminate between painful and nonpainful sensory input.

- Nociceptors belong either to the  $A\delta$  or the C type of sensory fibers.
- Types
  1. High-Threshold Mechanical Nociceptors (HTM)
  2. Myelinated Mechano-Thermal Nociceptors (MMTN)
  3. C-fiber Mechano-Heat Nociceptors (CMH)
  4. Pure Thermal Receptors
  5. C Polymodal Receptors (CPN).



**Figure 57-4.** The four elements of pain processing are transduction, transmission, modulation and perception. 5HT = 5-hydroxytryptamine (serotonin); CCK = cholecystikinin; NE = norepinephrine; NMDA = N-methyl-D-aspartate; NO = nitric oxide; NSAID = nonsteroidal anti-inflammatory drug.



# Acute Pain

- Pain with sharp and well-defined onset.
- Short duration.
- Etiology : Nociceptive  
Inflammatory
- Serves an adaptive (protective) function.
- Disappears with tissue healing.
- Usually responds well to analgesics and anti-inflammatory agents.

# Examples of Acute Pain

- Acute postoperative pain
- Post trauma
  - fractures
  - soft tissue injury
  - flail chest
  - stab injury
- Labour pain
- Post burn
- Pain associated with cancer, acute zoster, neurological diseases, haematological disorder

# Chronic pain

- Persists month beyond the usual course of acute disease or a reasonable time for an injury to heal usually taken to be 3 months.
- Etiology
  - Inflammatory
  - Neuropathic
  - Dysfunctional
- Usually does not serve any adaptive function.
- Can be difficult to treat.

# Examples of chronic pain

- Persistent postsurgical pain
- Neuropathic pain
  - nerve injury pain
  - nerve compression pain
  - complex regional pain syndrome

# Pain Mechanisms

- Altered perception of localization of the painful input underlies the phenomenon of “referred pain.”
- Plasticity is the inducible capacity of the nociceptive transmission systems that mediate pain for change.
- The incoming messages may be attenuated or enhanced. The latter state can result from central sensitization

- Cervero and Laird proposed that pain can be viewed in three phases.
- These phases are not exclusive at any given time, several of the underlying mechanisms may coexist in the same individual.

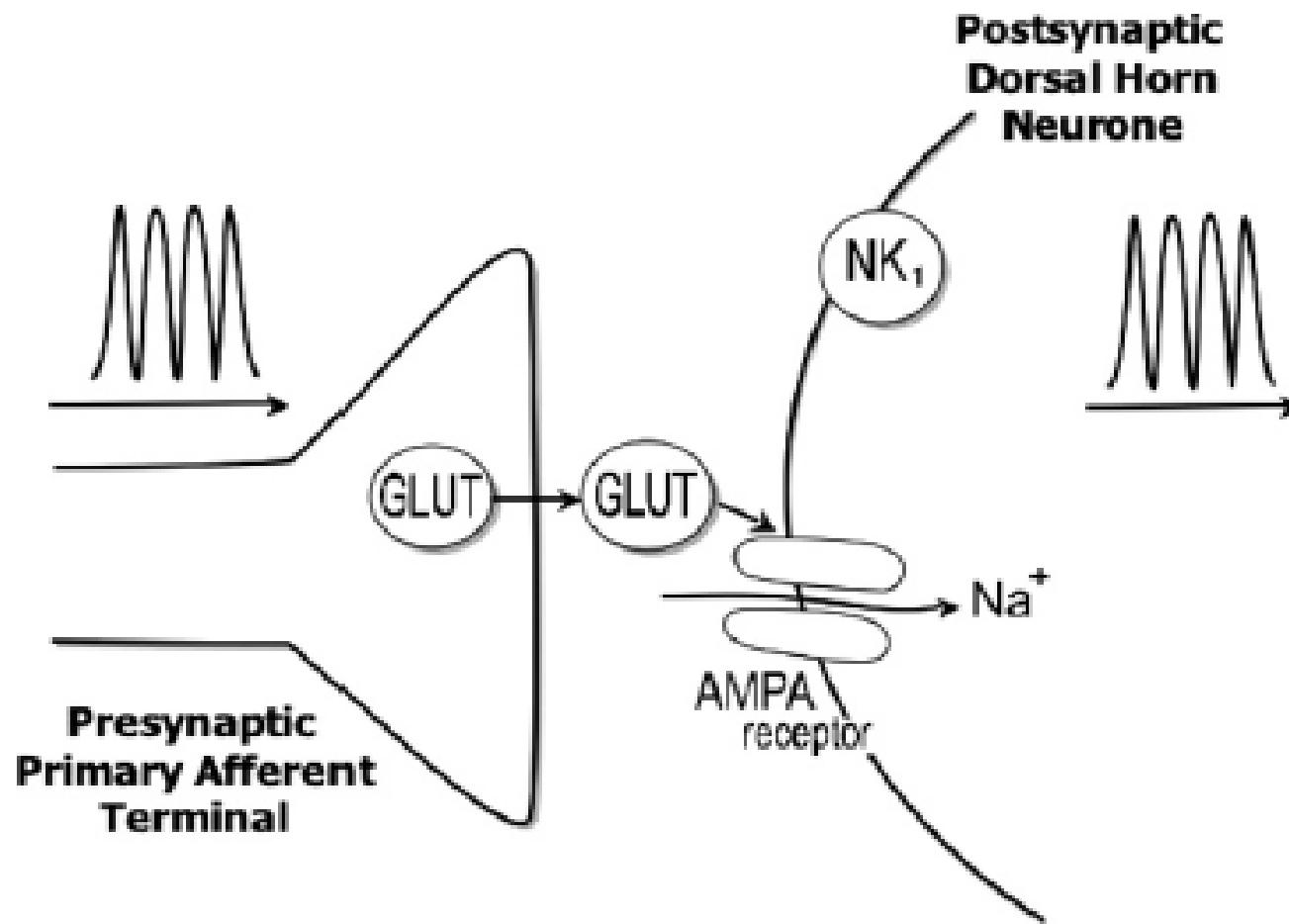
# Phases of Pain

- 1. Transient noxious stimulus, corresponding to **acute painful sensation**.
- 2. The consequences of a prolonged noxious stimulation comprise the substrate of the **chronic nociceptive pain states**.
- 3. The consequences of damage or injury to the neural tissue itself, this correlates with the various **neuropathic pain states**.

# Phase 1: Brief, Transient Acute Pain

- Information is propagated predominantly by the A $\delta$  fibers.
- The underlying synaptic events are mediated predominantly by glutamate acting at the AMPA/kainate receptors
- Only to a minimal degree by neurokinins (substance P) acting at NK1 receptors.



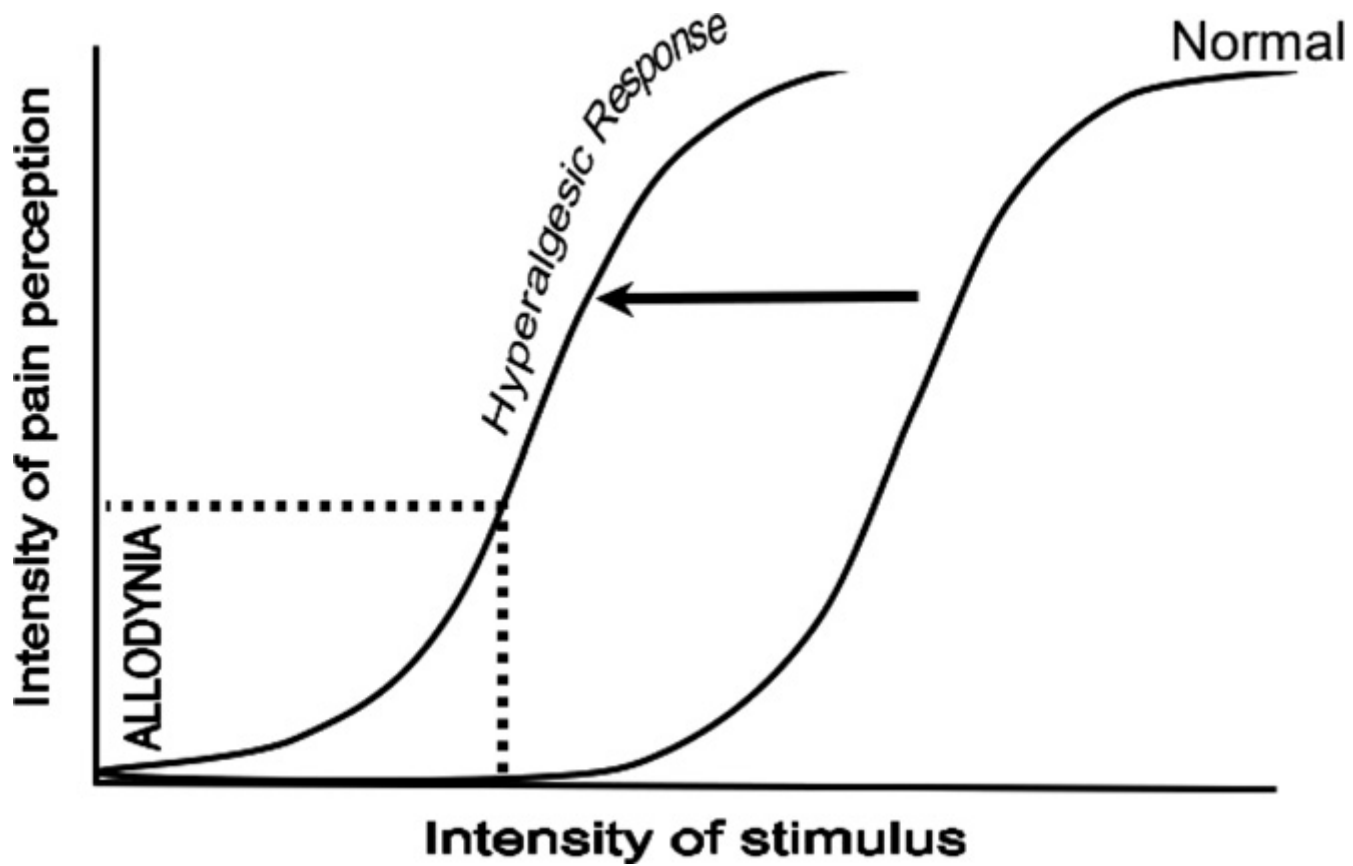


**Figure 1-11** Synaptic transmission of brief, acute pain.

## **Phase 2: Chronic Nociceptive Pain**

- Nociceptive spinal cord neurons modify their responses, moving to more excitable state.
- In this phase of pain, the subject experiences spontaneous pain, evoked from stimulation of the injured area and pain from undamaged surrounding area.

- The relevant clinical phenomena are:
  - (a) **Hyperalgesia** - increased response (increased pain) to a stimulus which is normally painful, but much less
  - (b) **Allodynia** - which is pain evoked by a stimulus that does not normally produce pain.
- This enhancement of the response of the nociceptive pathways after prolonged input of stimuli of certain intensity is called **sensitization**.



**Figure 1-12** Increased responsiveness with allodynia and hyperalgesia in chronic pain states.

- Both peripheral and central mechanisms contribute.
- A similar phenomenon, known as **long-term potentiation**, is seen in the hippocampus and is associated with memory and learning.

# Peripheral Mechanisms of Sensitization(phase 2)

- Cutaneous tissue damage or inflammation is associated with two zones of pain:
- 1. Area of primary hyperalgesia  
Located over the area of the original tissue damage itself. It is characterized by spontaneous pain and increased sensitivity to mechanical, thermal, and chemical stimuli.
- 2. Area of secondary hyperalgesia  
An increased sensitivity to mechanical stimuli, but not to thermal stimuli in an undamaged area surrounding the first zone.

## Peripheral Mechanisms of Sensitization(phase 2)

Primary hyperalgesia is produced mainly by

- Events and mechanisms occurring in the periphery, at the level of the primary afferent nociceptive fibers.

Secondary hyperalgesia

- Is mediated by predominantly central mechanisms.

## Peripheral Mechanisms of Sensitization(phase 2)

- The primary hyperalgesia has specific mechanisms very complex and include:
- 1. Direct stimulation of nociceptive primary afferents by
  - Kinins, such as bradykinin and kallidin
  - Prostaglandins and leukotrienes
  - ATP from tumor cells, endothelial cells, and/or platelets
  - Serotonin (5-HT), histamine, excitatory amino acids, tachykinins, Norepinephrine



## Peripheral Mechanisms of Sensitization(phase 2)

- 2. **Antidromic activation** of nociceptive primary afferents further enhance the activity of the nociceptors by a positive feedback mechanism and elicit vascular effects.
- 3. **Synergistic actions and sensitization of nociceptors** by the engagement of intracellular transduction systems. Previously “silent” nociceptors are recruited by this mechanism.

## Peripheral Mechanisms of Sensitization(phase 2)

- 4. **Modulatory events interactions** amongst primary afferents, glial cells, immunocompetent cells, sympathetic terminals, etc.
- 5. **Altered phenotype** of primary afferents. Increase in primary afferent levels of sP, CGRP, nitric oxide and glutamate, and other changes.

## Central mechanism of sensitisation(phase 2)

- Increased responsiveness of the spinal cord after prolonged, intense nociceptive input.
- This includes the dorsal horn neurons, interneurons, and ventral horn neurons.
- The thalamus, cortex, and other brain areas also develop relevant changes.
- As a consequence of the central sensitization, low intensity or normal input of stimuli can produce an inappropriately greater response

## Central mechanism of sensitisation(phase 2)

Three general electrophysiological characteristics at the cellular level:

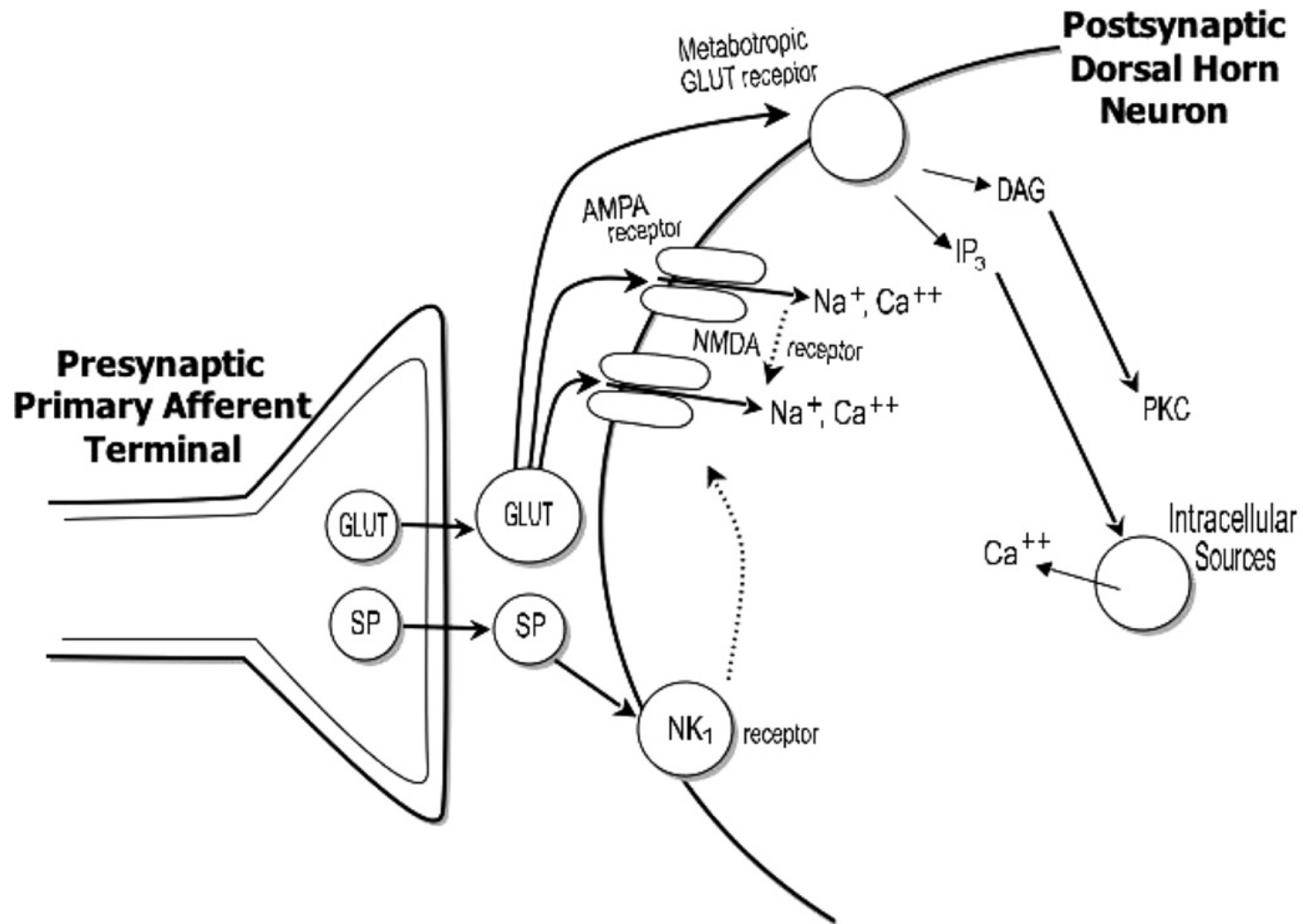
- A stimulus provokes a response with greater number of generated action potentials (hyperalgesia).
- Receptive fields expand previously ineffective in eliciting firing (area of secondary hyperalgesia).
- There is also appearance of novel responses to A $\beta$  fibers (allodynia).

## Central mechanism of sensitisation(phase 2)

- Two relevant events are recognized:
- 1. Progressive increase in the number of the action potentials generated by dorsal horn cells. This phenomenon is called wind-up and constitutes model of pain sensitization at the CNS level.
- 2. Heterosynaptic facilitation  
Progressive increase in neuronal excitability leads to an increased responsiveness to other inputs, specifically A $\beta$  fibers.

## Central mechanism of sensitisation(phase 2)

- There is role of **excitatory Amino Acids and tachykinins** in the sensitization of dorsal horn neurons.
- **Activation of NMDA receptors and increases in intracellular Ca<sup>++</sup>** level play role in triggering and maintaining neuronal sensitization in the dorsal horns.
- NMDA receptor antagonists (ketamine) potentiate the analgesic effect of opioids and may play a role in preventing central hypersensitive states.



**Figure 1-14 Central role of activation of NMDA receptor, calcium influx, and intracellular signaling in chronic pain states.**

## Central mechanism of sensitisation(phase 2)

- Another way is associated with the relatively slower transport of chemical substances called **neurotrophins**.
- Transient, **functional reduction of the tonic GABA-ergic and glycinergic** inhibitory interneuronal activity can accentuate processes of dorsal horn sensitization, contributing to the allodynia and hyperalgesia



## Central mechanism of sensitisation(phase 2)

- Any reduction of A $\beta$  fiber mediated stimulation of the inhibitory interneurons might disinhibit and further sensitize nociceptive neurons in the dorsal horns.

## Phase 3: Neuropathic Pain

- Abnormal pain states develop as the consequence of disease or damage to peripheral nerves or to the CNS itself.
- Lack of correlation between injury and pain
- Spontaneous or evoked, triggered by innocuous stimuli or associated with exaggerated responses to minor noxious stimuli.
- May involve genetic, cognitive, or emotional factors.

- Neuropathic pain :
  1. Spontaneous pain with burning quality or intermittent, sharp stabbing, or lancinating pain
  2. Thermal hyperalgesia, to both cold and hot stimuli
  3. Mechanical allodynia, elicited by touch or brushing. This is a very common neuropathic manifestation, considered a hallmark of the neuropathic pain.

# Peripheral mechanism(phase 3)

- 1. Acute injury to the nerve leads to an “afferent barrage.”
- This includes the rapid, intense central discharge of both A $\beta$  and C fibers for a period of minutes, and even several days for some fibers.

# Peripheral mechanism(phase 3)

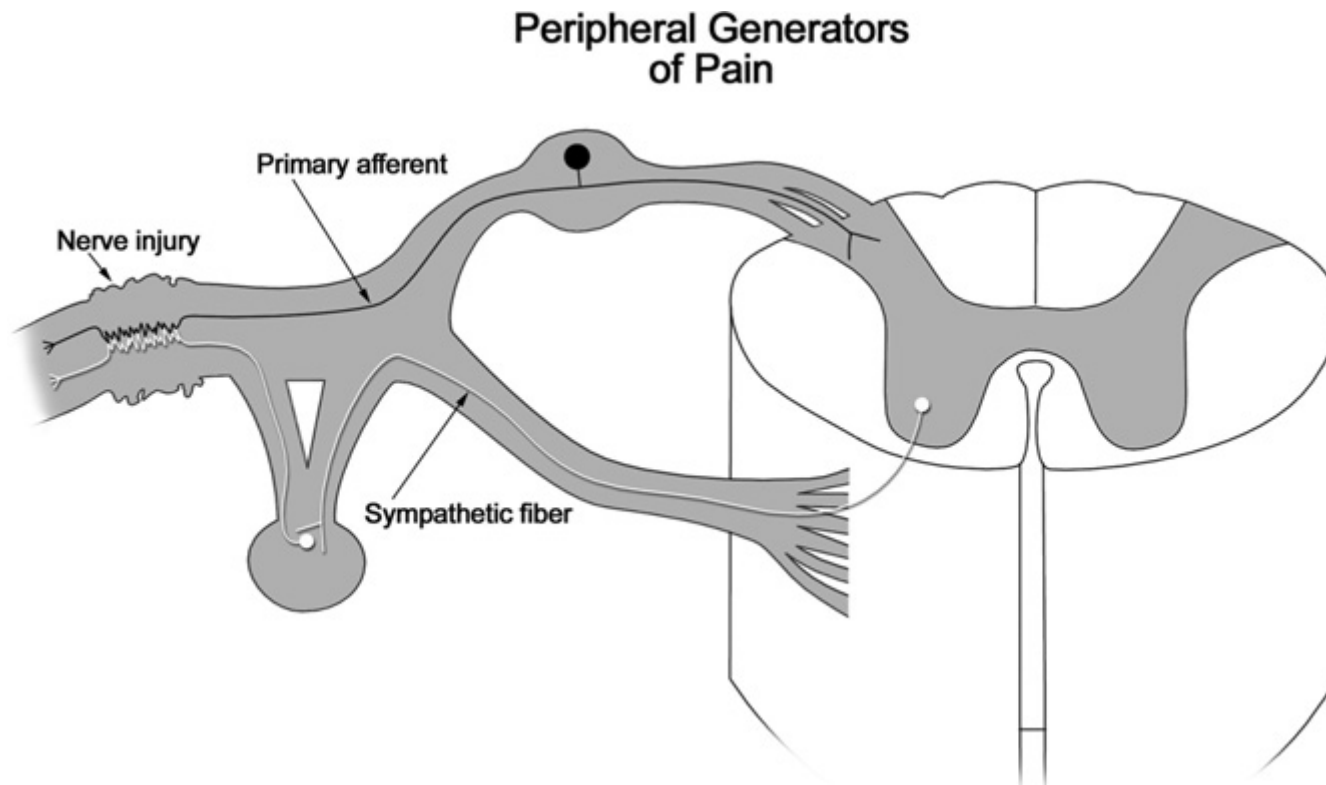
- 2. The injured axons begin to sprout growth cone (neuroma)
- They are hyperexcitable to stimuli, and have increased sensitivity to humoral and mechanical factors.
- Spontaneous ectopic firing and ectopic mechanosensitivity have been shown.

# Peripheral mechanism(phase 3)

- 3. **Persistent spontaneous firing** from small afferent fibers at the site of the lesion (neuroma) to the DRG and neurons in the ipsilateral dorsal horn after the acute injury.
- 4. Activation of damaged and adjacent intact fibers by inflammatory mediators.

# Peripheral mechanism(phase 3)

- 5. Abnormal patterns of inter-neuronal communication in the DRG and/or neuroma, causing excitatory cross-talk between the fibers.



**Figure 1-15 Excitatory “cross-talk” between injured peripheral fibers.**



# Peripheral mechanism(phase 3)

- 6. Neuropathic, painful states are **sympathetically maintained**.
- 7. **Altered phenotype** of damaged fibers.
- 8. Surgical or traumatic lesions proximal to DRG produces spontaneous pain and increased responsiveness of dorsal horn neurons.

## Central Mechanisms(Phase 3)

- 1. Stimulation of A $\beta$  fibers mediates the mechanical allodynia
- 2. Afferent sprouting of the large afferents to more superficial dorsal horn laminae involved in nociception.
- 3. Reduction of A $\beta$  fiber input to inhibitory interneurons

# Central Mechanisms(Phase 3)

- 4. Functional reduction in the activity or physical degeneration of inhibitory interneurons.
- 5. Adaptive changes in the thalamus, cortex, and other higher centers.

# Why treat Acute pain?

Under treatment of severe acute pain has

- Number of harmful physiological and psychological effects
- Emotional and physical suffering;
- Sleep disturbance
- Cardiovascular effects
- Impaired bowel movement
- Effects on respiratory function
- Delayed mobilization, promotes thrombosis.
- Preoperative pain and poorly controlled acute postoperative pain are risk factors for chronic postsurgical pain (CPSP)development.
- Prolong stay in hospital
- Delay healing and recovery
- costs of extended length of hospital stay and readmissions.

# Why treat Acute pain?

- Improved pain relief may reduce the incidence of such complications.
- Epidural analgesia significantly decreases the risks of
  - postoperative pulmonary complications
  - myocardial infarction
  - the incidence of pneumonia
  - number of ventilator days in patients with multiple rib fractures
  - dysrhythmias and time to extubation in patients after coronary artery bypass surgery.

# Persistent postsurgical pain

- Acute postoperative pain is followed by persistent pain in 10–50% of individuals after common operations.
- Chronic pain can be severe in about 2–10% of these patients
- Iatrogenic neuropathic pain is probably the most important cause of long-term postsurgical pain

	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes (1000s)†
Amputation <sup>2</sup>	30-50%	5-10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy) <sup>3</sup>	20-30%	5-10%	479
Thoracotomy <sup>4,7</sup>	30-40%	10%	Unknown
Inguinal hernia repair <sup>8-10</sup>	10%	2-4%	609
Coronary artery bypass surgery <sup>11-13</sup>	30-50%	5-10%	598
Caesarean section <sup>14</sup>	10%	4%	220

\*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

**Table 1: Estimated incidence of chronic postoperative pain and disability after selected surgical procedures\***

	Neuropathic pain	Inflammatory pain
<b>Positive symptoms and signs</b>		
Spontaneous pain in damaged area	Yes	Yes
Heat hyperalgesia	Rarely	Often
Cold allodynia	Often	Rarely
Hyperpathia (increased threshold and explosive suprathreshold pains)	Often	Never
Aftersensations	Often	Rarely
Paroxysms	Often	Rarely
Burning pain	Often	Rarely
Throbbing pain	Rarely	Often
<b>Negative symptoms and signs</b>		
Sensory loss in damaged nerve territory	Yes	No
Motor deficit in damaged nerve territory	Often	No

**Table 2: Characteristic features of neuropathic and inflammatory pain**



# Risk Factors for Persistent Postsurgical Pain

- Genetic susceptibility - High COMT activity correlates with a risk of developing chronic temporomandibular joint pain.
- melanocortin-1 receptor gene associated with red hair and fair skin confers greater female-specific  $\kappa$ -opioid analgesia

# Risk Factors for Persistent Postsurgical Pain

- Preceding pain - Severe postherpetic neuralgia is preceded by severe zoster pain.
- Amputees with severen phantom limb pain have had intense preamputation pain than amputees with less intense phantom pain
- Psychosocial factors-In a study 66 of 70 lower-limb amputees, psychosocial variables, such as catastrophising—a tendency to exaggerated pessimism about outcome—perceived social support responding 1 month after amputation, predicted phantom pain up to 2 years after amputation

# Risk Factors for Persistent Postsurgical Pain

- Age and sex - In postherniorrhaphy pain, older patients have a reduced risk of developing chronic pain
- Women have higher postoperative pain than men.

**Table 1** Predisposing factors for chronic post-procedural pain

Preoperative pain at the site of surgery or other body regions

Psychosocial and mood factors

Coping skills

Surgical factors

1. Nerve damage (complicated aetiology likely than just nerve injury alone)
2. Factors predisposing to prolonged inflammatory states (foreign materials)
3. Volume of surgeries performed per year for given operation
4. Recurrence of operation
5. Type of surgery
6. Length of surgery

Genetic predisposition

Acuity of postoperative pain

Prolonged postoperative pain/inflammatory responses

Duration of postoperative pain treatment

Anaesthetic factors (general vs regional, type of general anaesthesia)

Gender (female)

Type of disease

Recurrence of malignancy

Adjuvant therapy: radiation, chemotherapy (conflicting reports)

Age (conflicting reports)

# Predicting postsurgical chronic pain

- The intensity of the acute postoperative pain correlates with the risk of chronic postsurgical pain.
- **A combined scoring system** based on age, sex, type of surgery, extent of preoperative pain, and level of anxiety has been developed in an attempt to predict the severity of early postoperative pain.
- **Preoperative tests**, including nociceptive responsiveness and detection of pain-protective or pain-enhancing gene haplotypes could predict patients at risk for developing persistent pain.

# Potential for prevention of postsurgical chronic pain

- Surgical technique - many of the operations that produce persistent pain are associated with risk of damage to major nerves.
- Laparoscopic herniorrhaphy can decrease the risk of nerve damage and pain compared with open surgery.
- Use of a lightweight mesh for repair of the inguinal hernia with less inflammatory response might reduce the risk of chronic pain.
- In mastectomy preservation of the intercostal brachial nerve could decrease chronic pain.

# Potential for prevention of postsurgical chronic pain

- Pre-emptive and aggressive multimodal analgesia - short blockade in the perioperative period, COX inhibitors, and opiates suitable for alleviating the inflammatory pain.
- Ketamine or other N-methyl-d-aspartate receptor antagonists gabapentin or pregabalin COX inhibitors, steroids, and afferent neural blockade prevent central neuroplasticity.

# Potential for prevention of postsurgical chronic pain

- Drugs
- Patient controlled analgesia (PCA)
- Neuraxial analgesia
- PNB (Brachial plexus/Lumbar Plexus/
- Continuous peripheral Nerve Block(CPNB)



# Role of Acute Pain Service

- Multidisciplinary committee comprising anesthesiologists, surgeons, nurses and pharmacists management.
- Regular pain assessment methods and guidelines to control pain within a defined time scale.
- Enroll patients specifically with risk factors for development of chronic pain.

# Conclusion

- Pre-emptive and aggressive multimodal analgesia for postoperative pain should be initiated.
- Avoid analgesic gaps.
- Identify patients with increased risk of developing chronic pain.
- Surgical techniques that avoid nerve damage should be applied whenever possible.
- Finally, the role of genetic factors should be studied.