6 Segmental and Brain Stem Mechanisms

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Introduction

Even though nociceptors and the afferent sensory pathways detect and transmit noxious stimuli, modification occurs at multiple levels. Modulation of pain occurs peripherally at the nociceptors or centrally in the spinal cord or supraspinal structures. This modulation can either inhibit or facilitate pain (Figs. 6.1 and 6.2).

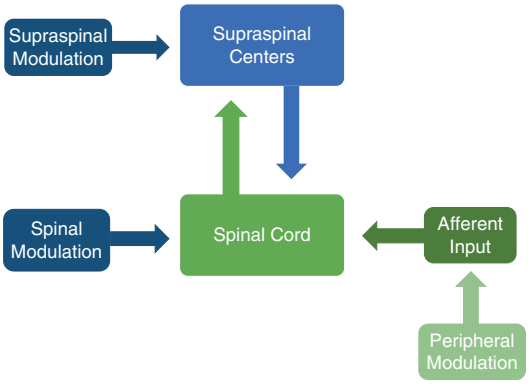

Fig. 6.1 Summary of modulation of nociceptive input

Modulation of Nociception

Peripheral Modulation

Nociceptors and their neurons display sensitization following repeated stimulation. This sensitization is manifested by enhanced response to noxious stimulation or by newly acquired responses to a wider range of stimuli, including non-noxious stimuli (Figs. 6.1 and 6.2) [1].

Primary Hyperalgesia

Sensitization of nociceptors results in decreased pain threshold, increased frequency of response to the same stimulus, decreased receptor latency, and spontaneous firing even after cessation of the stimulus (after discharge). Primary hyperalgesia is mediated by release of alogens from damaged

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A. Abd-Elsayed (ed.), *Pain*, https://doi.org/10.1007/978-3-319-99124-5_6

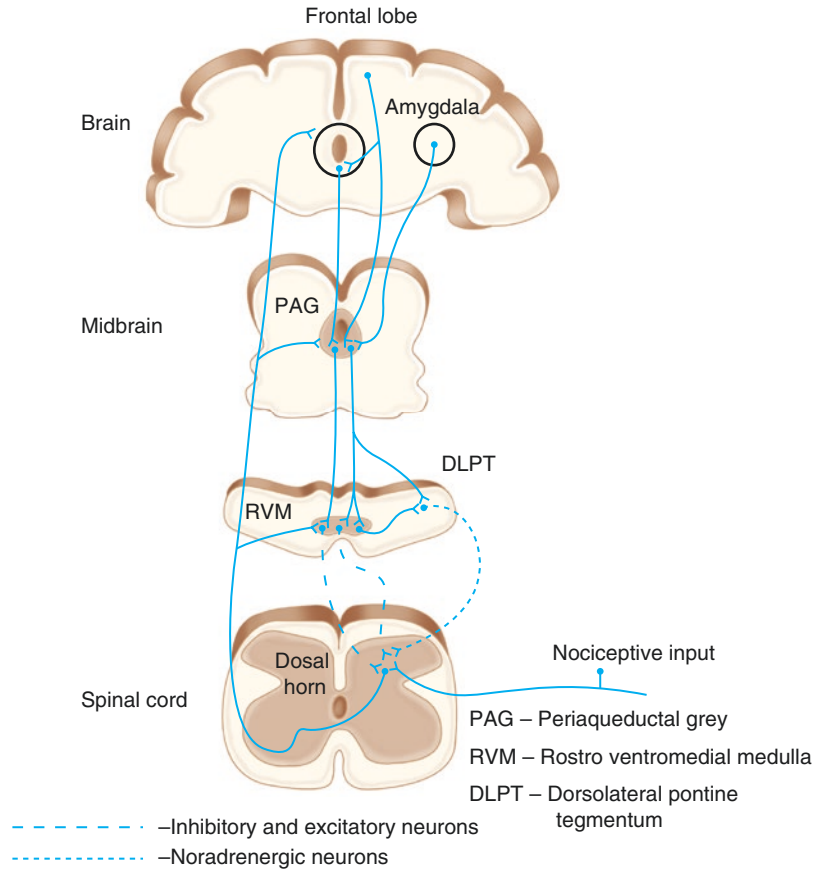

Fig. 6.2 Pain modulation

tissues. Histamine and serotonin are released from mast cells and platelets in that order. Bradykinin is released from tissues following factor XII activation. Bradykinin activates free nerve endings via specific receptors ß$_1$ and ß$_2$. Prostaglandins are produced following tissue damage by the action of phospholipase A_2 on phospholipids released from the cell membrane to form arachidonic acid. Arachidonic acid is converted to endoperoxides by the cyclooxygenase pathway. Endoperoxides are then transformed into prostacyclin and prostaglandin E_2 (PGE_2). PGE_2 directly activates free nerve endings while prostacyclin potentiates the edema formation from bradykinin. The lipooxygenase pathway converts arachidonic acid into hydroperoxyl compounds, which are converted into leukotriens. Leukotriens appear to potentiate certain types of pain. Pharmacologic agents such as acetyl salicylic acid, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs) produce analgesia by inhibition of cyclooxygenase while corticosteroids produce analgesia by inhibition of phospholipase A_2 activation [2].

Secondary Hyperalgesia

The role of neurogenic inflammation (secondary hyperalgesia) in peripheral sensitization following tissue injury is manifested by the triple response of red flush around the site of injury (flare), local tissue edema, and sensitization to noxious stimuli. Secondary hyperalgesia is primarily due to the release of substance P from collateral axons of primary afferent neurons. This response can be produced by antidormic stimulation of a sensory nerve. It can be diminished by local injection of lidocaine and is absent in denervated skin. The compound capsaicin degranu-

lates and depletes substance P and it appears to be useful for some patients with post-herpetic neuralgia when topically applied [3].

Central Modulation

Facilitation

Modulation in the spinal cord results from the action of neurotransmitters in the dorsal horn or from spinal reflexes, which convey efferent impulses back to the peripheral nociceptive field.

Central Hypersensitization or Wind-up

Tissue trauma results in afferent barrage of nociceptive transmission that may alter the threshold for excitation as well as the magnitude of impulse generation in nociceptors. Such sensitization may occur in both peripheral and central nociceptors after peripheral trauma. This enhanced afferent transmission to the dorsal horn of the spinal cord may expand the receptive field of dorsal horn neurons [4] as well as induce a progressive facilitation of dorsal horn neuronal discharge, a process referred to as central hypersensitization or "Wind-up". Changes in neurochemistry of the dorsal horn due to repetitive stimulation, inhibition of interneurons, and recruitment of non-neuronal cells, such as astrocytes and microglial cells, are believed to play an important role in central sensitization. Sprouting of sympathetic fibers in the dorsal horn seems to also play a role in the sympathetic component of hyperalgesia [5].

Inhibition

Transmission of nociception in the spinal cord can be inhibited by segmental activity in the spinal cord itself or by descending neural activity from supraspinal sites.

I. *Segmental Inhibition*
   Activation of large diameter, low threshold $A_ß$ mechanoreceptors inhibit the response of dorsal horn cells to nociceptive inputs. This is known as the gate control theory of pain. This was the basis for the use of transcutaneous electric nerve stimulation (TENS) and dorsal column stimulation in pain relief.

   Glycine and GABA play an important role in segmental inhibition and their antagonism results in powerful facilitation of WDR neurons, which can produce allodynia and hypersensitivity. There are two subtypes of GABA receptors. $GABA_A$ receptor activity increases Cl^- conductance, while $GABA_B$ receptor activity increase K^+ conductance across the cell membrane. Benzodiazepines potentiate $GABA_A$ receptor activity. Activation of glycine receptors increases Cl^- conductance across neural cell membrane. Glycine also has a facilitatory (excitatory) effect on the NMDA receptor. Adenosine also modulates nociceptive activity in the spinal cord. Adenosine receptor A_1 mediates adenosine's antinociceptive action.

II. *Supraspinal Inhibition*
   The supraspinal structures that send fibers down the spinal cord to inhibit pain in the dorsal horn include the periaqueductal gray, reticular formation, and nucleus raphe magnus (NRM). Axons from these tracts act presynaptically on primary afferent neurons and postsynaptically on second order neurons (Fig. 6.2). These pathways mediate their antinociceptive action via α_2 adrenergic, serotoninergic, and opiate (μ, δ, and K) receptor mechanisms.

   The analgesic action of antidepressants is mediated through blocking the uptake of catecholamines and serotonin. The endogenous opiate system acts via methionine-enkephalin, leucine-enkephalin, and ß-endorphin which are antagonized by naloxone. They act both presynaptically and postsynaptically in contrast to exogenous opioids that act postsynaptically on the second order neurons in the substantia gelatinosa. The opioid and the α_2 receptors share such a common mechanism of action at the cellular level that these receptors appear to belong to a family of receptors that are coupled with a G protein which exerts its

membrane function through a secondary messenger protein capable of converting guanosine triphosphate to guanosine diphosphate. When the receptor is occupied, modulation of cellular function occurs resulting in hyperpolarization of the nerve with subsequent decreased transmission of the action potential and decreased release of stored neurotransmitter. This hyperpolarization of the nerve most likely occurs because of the opening of potassium channels and the inhibition of calcium movement [6].

High Yield Points

- Primary hyperalgesia is characterized by decreased pain threshold, increased frequency of response to the same stimulus, decreased receptor latency, as well as spontaneous firing even after cessation of the stimulus (after discharge).
- Secondary hyperalgesia is characterized by the triple response of red flush around the site of injury, local tissue edema, and sensitization to noxious stimuli. Secondary hyperalgesia is primarily due to release of substance P from collateral axons of primary afferent neurons.
- Changes in neurochemistry of the dorsal horn due to repetitive stimulation, inhibitions of interneuron, as well as recruitment of non-neuronal cells, such as astrocytes and microglial cells, are believed to play an important role in central sensitization.
- Segmental inhibition occurs at the level of the spinal cord due to simultaneous activation of large myelinated A_{β} fibers (gate control theory) as well as release of inhibitory neurotransmitters.
- The periaqueductal gray, reticular formation, and nucleus raphe magnus send descending inhibitory pathways to inhibit nociception in the dorsal horn.

Questions

1. Secondary hyperalgesia develops
   A. In the area of injury
   B. Around area of injury
   C. Far from area of injury
   D. None of the above
   Answer: B
2. Allodynia and hyperalgesia develop due to facilitation of
   A. WDR neurons
   B. Large fibers
   C. Delta fibers
   D. None of the above
   Answer: B
3. Segmental inhibition can be explained by
   A. Sprouting
   B. Demyelination
   C. Gate control theory
   D. Wind-up theory
   Answer: C

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