CHAPTER

1

Pain Pathways

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Pain is produced by the noxious stimuli perceived by specific sensory receptors called nociceptors which are there at the free nerve endings of primary afferent terminals of Aδ and C fibres. An action potential is generated at this nociceptor (transduction) which is then further carried by the Aδ and C fibres towards the higher centre (transmission) and make us feel pain (perception).

There are two important aspects which are unique to pain signal. First, whenever sensory cortex is stimulated, limbic system which controls our emotions are stimulated simultaneously. Thus emotions are the integral components of pain. Second, pain is a unique sensory signal as it is maximally changed on its way towards the higher cortical centres (modulation). The action potential generated in the periphery and the action potential that reaches the somatosensory cortex are not the same. The action potentials are either decreased (mostly in healthy individuals) or increased (anxious and chronic pain patients). Thus, the action potential that is generated at the periphery and the amount of pain that we feel do not match.

Pain: Transduction, Transmission, Modulation and Perception.

There are sequences of events which are involved in the neural processing of noxious stimuli which leads to the perception of pain (Fig. 1.1). These are:

1. ***Transduction:*** It is a process of conversion of a noxious stimuli by the nociceptors into electrical signals or action potentials. Various mechanical, thermal or chemical stimuli are responsible for the generation of these action potentials.
2. ***Transmission:*** It is a process by which the action potential generated at the nociceptor is propagated along the axon of the primary afferent neuron.

Types of afferent fibres that carry pain:

- ***Aδ fibres*** are lightly myelinated with the conduction velocity of 5–15 m/sec which is faster than C fibres. They transmit rapid and sharp pain which is well localised.
- ***C fibres*** are unmyelinated with the slowest conduction velocity of <2 m/sec. They carry slow, diffuse and dull pain.

The primary afferent neurons have their cell body located in the dorsal root ganglion and their central processes enter the dorsal horn in the lateral division of the dorsal root. The first order neurons synapse with the second order neurons whose axon crosses the midline and the fibres ascend in the contralateral spinothalamic tract. They synapse with the third order neurons in the thalamus and their axons project into the somatosensory cortex.

Some of the fibres project into the contralateral periaqueductal grey matter (same side of tissue damage). From periaqueductal grey matter descending

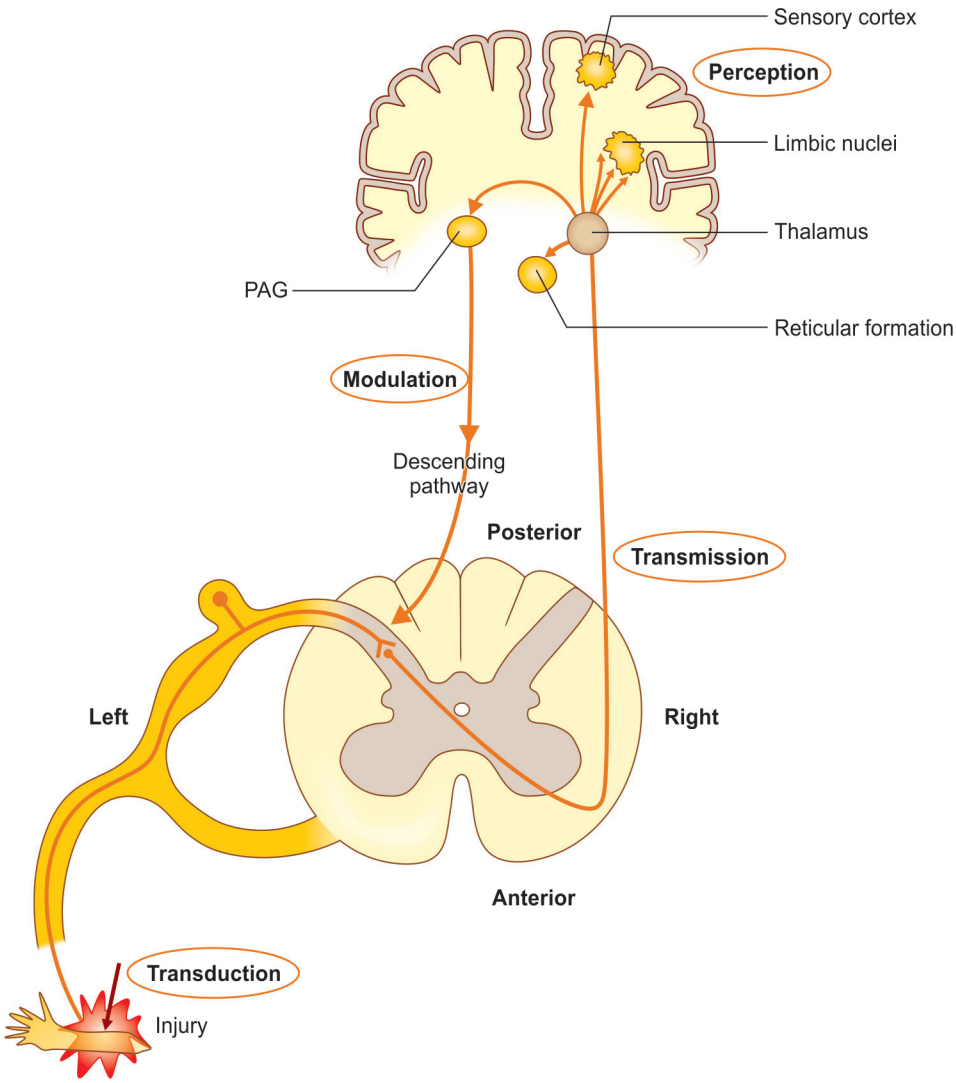

Fig. 1.1: Afferent pain pathway

inhibitory fibres (bulbospinal tract) start and some of the fibres project into different limbic nuclei.

3. ***Perception:*** The somatosensory cortex is associated with sensory and discriminative aspects of nociception, while the deeper limbic structures are associated with the affective motivation (emotional) component of the pain.
4. ***Modulation:*** It is a neural process that acts specifically to reduce the activity in the pain transmission system and reduce the perception of pain in healthy individuals. Some of the modulation systems are described below, among all of them descending inhibitory pathway plays a very important role in modulation of pain signals.

   a. Endogenous pain modulation system: Endogenous opioids like endorphins, enkephalins and dynorphins act on the opioid receptors present in the dorsal horn and result in presynaptic inhibition.

b. *Segmental inhibition:* Local inhibition in the dorsal horn is mediated by the release of inhibitory neurotransmitters like glycine and GABA.
c. *Gate control theory of pain:* It states that activating the larger diameter Aβ fibres leads to inhibition of pain signals transmitted via smaller diameter Aδ and C fibres. An inhibitory interneuron acts as a physiological gate which is closed by stimulation of Aβ fibres. It is a historical event when Melzack and Wall proposed gate control theory in 1965. Transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation, and peripheral nerve stimulation were established based on this principle.
d. *Descending inhibitory pathways:* Periaqueductal grey (PAG) and the rostral ventromedial medulla in the midbrain send descending fibres which project into the dorsal horn of the same side of tissue damage. These inhibitory neurons are activated by serotonin (5-HT) and norepinephrine (NE). They send an inhibitory signal in the dorsal horn and reduce the intensity of the signal which is transmitted from first order neuron to the second order neuron. Antidepressant medications activate this system and increase the level of 5-HT and NE and help in reducing the intensity of pain.

Autonomic Nervous System

The autonomic nervous system (ANS) plays an important role in different kinds of pain. For example, pain signals from thoracic or abdominal viscera and intervertebral disc or vertebral body are carried by afferent sympathetic fibres. Efferent sympathetic fibres also involved in some kinds of pain.

ANS can be defined as the neurological substrate that acts to maintain homeostasis in the body. It consists of two main divisions—parasympathetic and sympathetic nervous system. They are functionally and anatomically distinct.

Sympathetic outflow originates in the thoracolumbar region of the spinal cord and exits through spinal nerve T1–L2.

Parasympathetic nervous system, also called cranial-sacral, exits through cranial nerve 3rd (oculomotor), 7th (facial), 9th (glossopharyngeal), 10th (vagus) and S2–S3 sacral nerves.

Sympathetic Nervous System: Different configuration of the preganglionic and postganglionic fibres (Fig. 1.2)

Travel with spinal nerve: Efferent sympathetic outflow originates in the lateral horn of the spinal cord from segments T1–L2.The preganglionic neurons exit the spinal cord via the ventral horn along with the somatic motor fibres, then through ventral root and reaches up to the mixed spinal nerve. These fibres then join the sympathetic chain situated at the anterolateral border of the spine via the white ramus communicans. Sympathetic chain or trunk contains sympathetic ganglion or paravertebral ganglion and extends from the base of the skull to the coccyx.

In sympathetic ganglia, the preganglionic neurons synapse with the postganglionic neurons and leave through the grey ramus communicants to join the spinal nerve and follow it to supply the target effector organs.

Preganglionic fibres do not necessarily end at the same level, some fibres ascend up and end at different cervical levels and similarly some fibres descend down and end at different lumbar and sacral levels. Thus, every spinal nerve root gets sympathetic fibres via grey rami communicantes. Therefore, we can say that grey rami communicantes are there in all spinal nerve roots; however, white rami communicantes are there only between T1 and L2.

These sympathetic fibres spread and reach periphery via blood vessels or somatic nerves. They are of different types—vasomotor, pilomotor or sudomotor. Vasomotor fibres release catecholamines and regulate blood pressure; sudomotor and pilomotor fibres

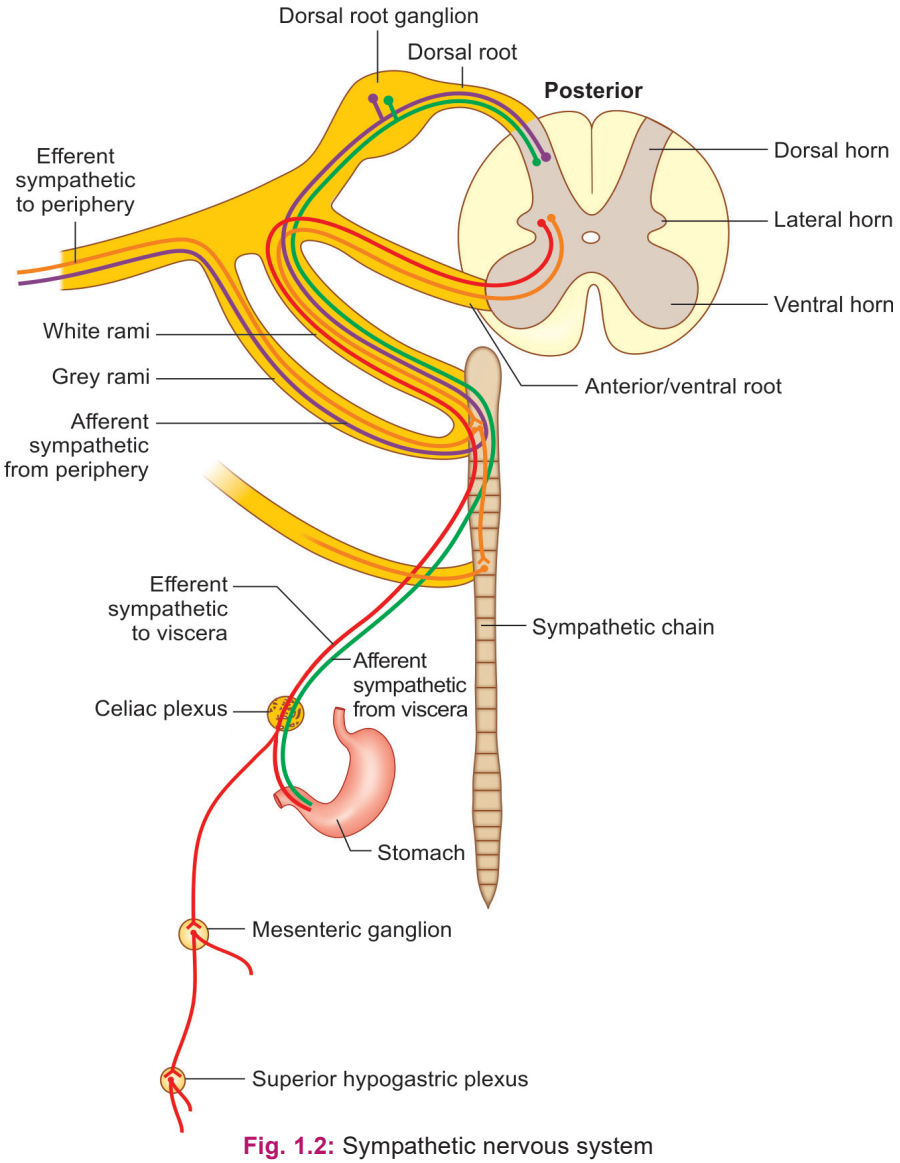

Fig. 1.2: Sympathetic nervous system

release acetylcholine and control sweating and erection of hail follicle, respectively.

Visceral efferent sympathetic nerves: Preganglionic fibres join the sympathetic chain via white rami communicantes in the same way as efferent sympathetic nerves that reach the periphery via somatic nerves. These preganglionic efferent sympathetic fibres neither end in sympathetic chain nor do they join grey rami communicantes.

These fibres extend up to the ganglion lying close to the visceral organs (celiac ganglion). Some of the fibres end there, rests extend to the other ganglions (mesenteric, superior hypogastric, etc.). Postganglionic fibres arise from this ganglion and supply the visceral organs.

Afferent sympathetic fibres: The afferent fibres travel along with the somatic nerves and blood vessel and enter the sympathetic chain through the grey rami communicantes and leave the sympathetic chain via white rami communicantes and join the mixed spinal nerve. Then through the dorsal root along with the somatic sensory fibres enter the dorsal horn and end there. The afferent sympathetic system has one nerve and its cell body is situated in the dorsal root ganglion. Second order neurons are spinothalamic tract which is same for both somatic and sympathetic systems.

Visceral afferent sympathetic nerves: Visceral painful stimulus is carried by the afferent sympathetic fibres in a direction opposite to that of efferent fibres. Pain signals travel via these fibres, then pass through the celiac ganglion without relaying there. These fibres via splanchnic nerves join the sympathetic chain and finally mixed spinal nerve by white rami communicantes. Then through the dorsal root enter the dorsal horn.

Sympathetic Nervous System Distribution and Functions

Somatic: It supplies body wall and the skin. Each spinal nerve has got a contribution from grey ramus and supplies one spinal segmental area along with sympathetic fibres and provides three functions to the skin—vasomotor (vasoconstriction of the arterioles), pilomotor (erector pilli muscle) and sudomotor (sweat glands).

Visceral: It supplies the internal organs of head and neck, abdomen and pelvis.

- ***Head and neck:*** Postganglionic fibres arise from the sympathetic ganglion and travel along the segmental nerve and the blood vessel and supply the skin, eye.
- ***Thorax:*** Postganglionic fibres from the cardiopulmonary and oesophageal plexuses supply the heart, lung and oesophagus.
- ***Abdomen and pelvis:*** *Preganglionic fibres project into the ganglion:* Unlike head/neck and thoracic viscera, here preganglionic fibres from white rami after joining sympathetic trunk project via splanchnic nerves into abdomen and form several visceral ganglions like: Celiac, superior mesenteric, inferior mesenteric, superior hypogastric and inferior hypogastric ganglions located in front of the vertebra along the branches the aorta.

Splanchnic: Greater T5–T9: Celiac ganglion—supplies foregut. Lesser T10–T11: Superior mesenteric—supplies midgut. Least T12: Aortic renal—supplies hindgut.

Somatic Sympathetic Coupling and Mechanisms of Sympathetically Mediated Pain

Somatic and sympathetic nerves are well insulated with no cross talks in between them. But with pathological conditions, it may change and there is a connection between somatic and sympathetic signals.

It occurs at three sites:

1. DRG (dorsal root ganglion): Cross talk is possible here.
2. Peripheral nerve injury/neurolysis may be followed by regeneration and sprouting which results in the exchange of signals between the somatic and sympathetic fibres. It is mostly the afferent sympathetic fibres which are mainly involved.
3. Sympathetic efferent fibres: Sympathetic efferent fibres release catecholamines, which instead of acting on sympathetic receptors may stimulate the nociceptors, which normally are stimulated by mechanical, chemical and thermal stimuli. These nociceptors then generate action potentials which are carried by somatic nerves. The classical example is CRPS.

Sympathetic Blockade and its Significance in Pain Management

Sympathetic blockade results in the interruption of transmission by both efferent and afferent fibres. It does not result in sensory and motor loss as seen in somatic blockade.

Examples of sympathetic blockade at various levels:

1. Stellate ganglion and lumbar sympathetic blockade for CRPS of upper and lower limbs.
2. Splanchnic and celiac plexus block for upper abdominal malignancy and chronic benign pain.
3. Superior hypogastric plexus block: Cancer and non-cancer chronic pelvic pain.

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