Anatomy of the nervous system

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Introduction

The international association for study of pain defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage." The term nociception, which is derived from noci (Latin for harm or injury), is used to describe the neural response to traumatic or noxious stimuli. Nociception involves four physiologic processes: transduction, transmission, modulation, and perception.

Transduction

Transduction refers to the process by which noxious stimuli are transformed into electric signals at the sensory nerve endings. The primary afferent fibers concerned with nociception are termed nociceptors. Most nociceptors are free nerve endings of Aδ and C fibers while some nociceptors have special structure such as pacinian corpuscles for touch. Peripheral nerve fibers can be classified according to conductive velocity, diameter, and degree of myelination. (Table 1.1) [1].

Nociceptors

Most nociceptors are free nerve endings that sense heat, mechanical, and chemical tissue damage. Several types of nociceptors are described:

1. **Mechanoceptors:** receptors that respond to pinch and pin prick sensations.
2. **Silent nociceptors:** receptors that are activated only in presence of inflammation.
3. **Polymodal mechano-heat nociceptors:** the most prevalent receptors. These receptors respond to excessive pressure, extremes of temperature, and alogens (pain-producing substances). Alogens include substance P, bradykinin, histamine, serotonin, H^+, K^+, some prostaglandins, and possibly adenosine triphosphate (ATP).

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Table 1.1 Classification of peripheral nerve fibers

Fiber group	Myelination	Diameter (μm)	Conduction	Function
A α	**Yes**	**12–20**	**70–120**	Motor nerves Proprioception
A ß	**Yes**	**5–12**	**30–70**	Light touch Pressure
A γ	**Yes**	**3–6**	**15–30**	Skeletal muscle tone Proprioception
A δ	**Yes**	**2–5**	**12–30**	Fast pain Touch Temperature
B	**Yes**	**<3**	**3–15**	Preganglionic autonomic fibers.
C	**No**	**0.5–1.5**	**0.5–2.6**	Slow pain Touch Temperature Postganglionic autonomic fibers

Table 1.2 Major neurotransmitters mediating or modulating pain

Excitatory neurotransmitters	Receptor	Inhibitory neurotransmitters	Receptor
Glutamate	NMDA, AMPA, Kainate	GABA	$GABA_A$, $GABA_B$
Aspartate	NMDA, AMPA, Kainate	Glycine	Glycine
Substance P	NK-1	Serotonin	5-HT_1 (5HT_3)
Adenosine triphosphate	P_1, P_2	Norepinephrine	α_2
CGRP		ß endorphins	μ, δ, K
VIP		Enkephalins	μ, δ, K
Cholecystokinin		Acetylcholine	Muscarinic

Central Neurochemistry and Important Transmitters of Pain Processing

The activation of nociceptors results in generalized activity in finely myelinated A-delta and unmyelinated C-fibers that project to dorsal horn of the spinal cord. Several excitatory and inhibitory neuropeptides as well as amino-acids function as neurotransmitters for afferent neurons (Table 1.2). Many, if not most, neurons contain more than one neurotransmitter involved in signal transmission. The most important of these peptides are substance P (SP) and calcitonin gene related peptides (CGRP). Substance P is released in the spinal cord following noxious stimulation and it excites interneurons and other second order neurons. Substance P sensitizes nociceptors, degranulates histamine from mast cells and serotonin from platelets, and is a potent vasodilator and chemoattractant for leucocytes. Glutamate is the most excitatory amino acid.

Transmission of Pain

Pain Pathway

Pain is conducted along a three-neuron pathway that transmits noxious stimuli from the periphery to the cerebral cortex (Fig. 1.1).

First Order Neurons

Primary afferent neurons are located in the dorsal root ganglia. Each neuron has a single axon that bifurcates, sending one end to the peripheral tissues it innervates, and the other into the dorsal horn of the spinal cord where it synapses with the

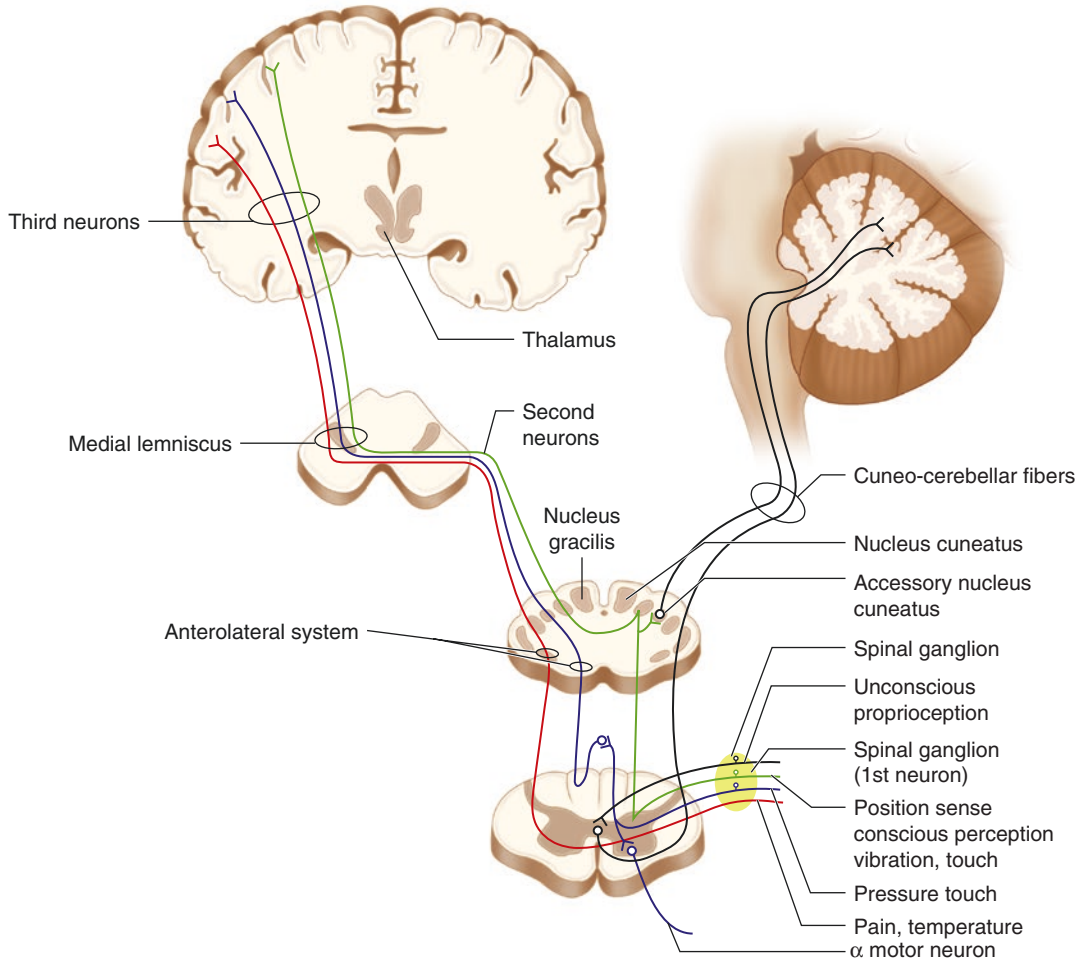

Fig. 1.1 Pain pathways

second order neuron. Afferent fibers enter the spinal cord segregates into medial large myelinated fibers and lateral small unmyelinated fibers [1].

Second Order Neurons

Afferent pain fibers may ascend several segments in Lissauer's tract before synapsing with second order neurons in the grey matter of ipsilateral dorsal horn. Spinal cord grey matter is divided into 10 laminae (Fig. 1.2). The first six laminae which make up the dorsal horn receive all afferent neural activity and represent the principal site of modulation of pain by ascending and descending neural pathways. Most nociceptive C fibers send collaterals to or terminate on second order neurons in lamina I, II, and to a lesser extent in lamina V. In contrast, nociceptive Aδ fibers synapse mainly in lamina I, V, and to a lesser extent in lamina X [2].

Second order neurons are either nociceptive-specific or wide dynamic range (WDR) neurons. Nociceptive-specific neurons recieve only noxious stimuli, while WDR neurons receive also non-noxious afferent input from Aß, Aδ and C fibers. Nociceptive-specific neurons are normally silent and respond only to high threshold noxious stimulation. WDR neurons are the most

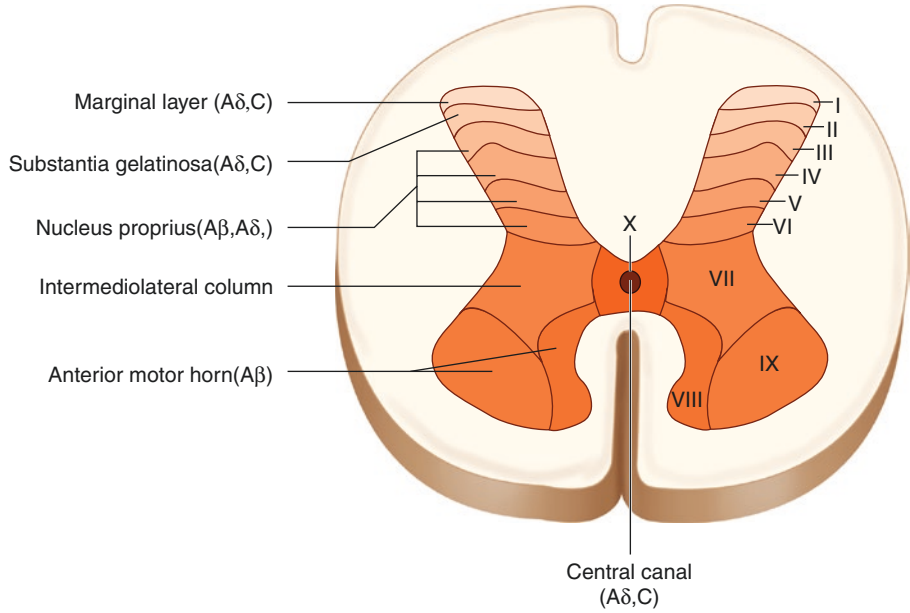

Fig. 1.2 Rexed Laminae of the spinal cord

prevalent cell type in the dorsal horn and most abundant in lamina V. They typically increase their firing rate exponentially in a graded fashion, even with the same stimulus intensity. They also have large receptive fields compared to nociceptive-specific neurons.

The Spinothalmic Tract (STT)

The spinothalamic tract (Fig. 1.3), which is considered the major pain pathway, lays anterolaterally in the white matter of the spinal cord. The cell bodies of spinothalamic tract are located in laminae I, V (mainly), and VII of the spinal cord. The axons of the second order neurons ascend few segments in the dorsal column before they cross to the contralateral side to form the spinothalamic tract where they end in the thalamus.

The spinothalamic tract is divided into lateral spinothalamic (neospinothalamic) and medial (ventral) spinothalamic (palaeo-spinothalamic) tracts. The lateral spinothalamic tract projects mainly to the ventral posterolateral (VPL) nucleus of the thalamus and carries discriminative aspects of pain, such as location, intensity, and duration. The medial (ventral) spinothalamic tract projects to the medial thalamus and is responsible for mediating the autonomic and unpleasant emotional perception of pain [3].

Alternate Pain Pathways

The spinoreticular tract is thought to mediate arousal and autonomic responses to pain. The spinomesencephalic tract may be important in activating anti-nociceptive descending pathways because it has some projections to periaqueductal grey matter. The spinohypothalamic and spinotelencephalic tracts activate the hypothalamus and evoke emotional behaviour. The spinocervical tract ascends uncrossed to the lateral cervical nucleus, which relays fibers to the contralateral thalamus.

Integration with the Sympathetic and Motor Systems

Somatic and visceral afferents are fully integrated within the skeletal motor and sympathetic systems in the spinal cord, brain stem, and higher centers. Afferent dorsal horn neurons synapse both directly and indirectly with anterior horn motor neurons. These synapses are responsible

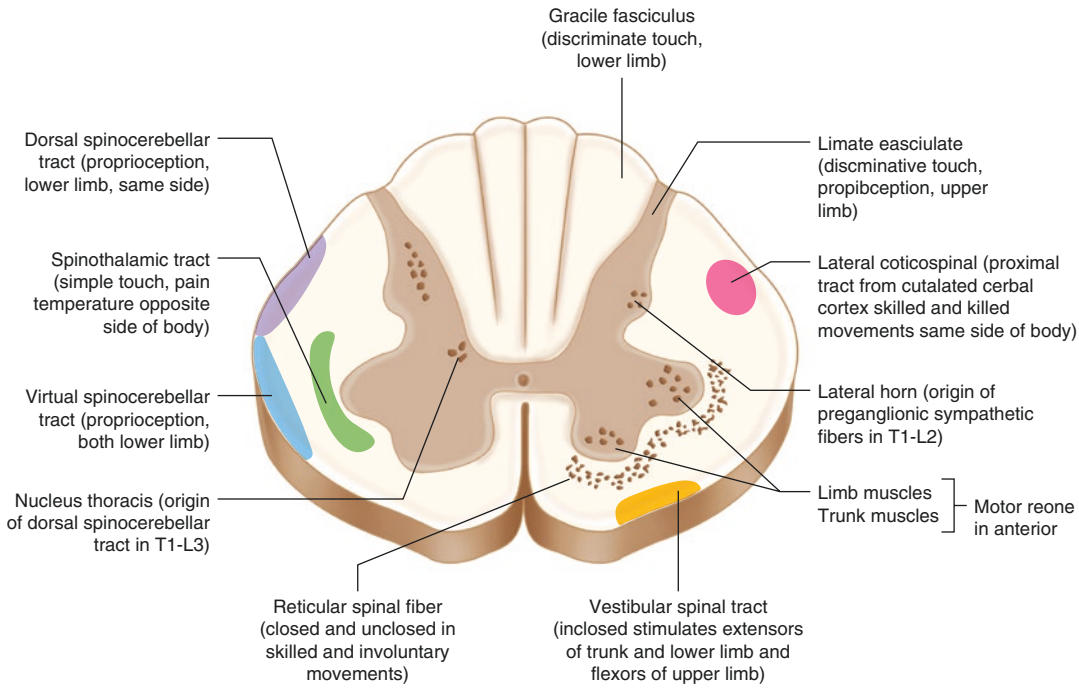

Fig. 1.3 Spinothalamic tract and other pain pathways

for reflex muscle activity that is associated with pain. Synapses between afferent nociceptive neurons and sympathetic neurons in the intermediolateral column result in reflex sympathetically mediated vasoconstriction, smooth muscle spasm, and the release of catecholamines locally and from the adrenal medulla [4].

Third Order Neurons

Third order neurons are located in the thalamus and send fibers through internal capsule to somatosensory areas I and II in the post-central gyrus of the parietal cortex and through corona radiata to the superior wall of the sylvian fissure.

High Yield Points

- Nociception involves four physiologic processes: transduction, transmission, modulation and perception.
- Most nociceptors are free nerve endings that sense heat, mechanical, and chemical tissue damage.
- Polymodal mechano-heat nociceptors are the most prevalent receptors; other types include mechanoreceptors and silent nociceptors.
- Most nociceptive C fibers terminate on second order neurons in lamina I, II, and to a lesser extent in lamina V. In contrast, nociceptive Aδ fibers synapse mainly in lamina I, V and to a lesser extent in lamina X.
- Second order neurons are either nociceptive-specific or wide dynamic range (WDR) neurons. Nociceptive-specific neurons serve only noxious stimuli, while WDR neurons receive non-noxious afferent input from Aß, Aδ and C fibers. WDR neurons are the most prevalent cell type in the dorsal horn.
- Afferent pain signals ascend in multiple pathways; the spinothalamic tract is considered the major pathway.
- The spinothalamic tract is located anterolaterally in the white matter of the spinal cord with its cell bodies in laminae I, V (mainly), and VII.

Questions

1. Lateral spinothalamic tract receives
   A. Pain and temperature from opposite side of the body
   B. Pressure from opposite side of the body
   C. Proprioception from opposite side of the body
   D. Pain and temperature from the same side of the body
   Answer: A
2. Fasiculus gracillis receives sensations from
   A. Lower half of the body
   B. Upper half of the body
   C. Both upper and lower halves of the body
   D. Upper and lower halves on the opposite side
   Answer: A
3. First order neurons usually present in
   A. Dorsal horn
   B. Anterior horn
   C. Dorsal root ganglia
   D. Supraspinal centers
   Answer: C

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