

INTRODUCTION

Neuropathic pain is caused by functional abnormalities of structural lesions in the peripheral or central nervous system, and occurs without peripheral nociceptor stimulation. Many common diseases, such as postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, spinal cord injury, cancer, stroke, and degenerative neurological diseases may produce neuropathic pain. Recently, theories have been proposed that state there are specific cellular and molecular changes that affect membrane excitability and induce new gene expression after nerve injury, thereby allowing for enhanced responses to future stimulation. In addition, the ectopic impulses of neuroma, changes of sodium and calcium channels in injured nerves, sympathetic activation, and deficient central inhibitory pathway contribute to the mechanisms of neuropathic pain (*Chang, 2005*).

Currently, treatment of neuropathic pain is still a challenge. Pharmacotherapies (antidepressants, antiepileptics) remain the basis of neuropathic pain management. However, patient satisfaction in the results of the treatment of neuropathic pain is still

disappointing. Since it has been established that intense noxious stimulation produces a sensitization of central nervous neurons, it may be possible to direct treatments not only at the site of peripheral nerve injury, but also at the target of central changes. In order to provide better pain control, the mechanism-based approach in treating neuropathic pain should be familiar to physicians. In the future, it is hoped that a combination of new pharmacotherapeutic developments, careful clinical trials, and an increased understanding of the contribution and mechanisms of neuroplasticity will lead to an improvement in the results of clinical treatments and prevention of neuropathic pain (*Chong et al., 2003*).



ANATOMY OF PAIN

Pain pathways:

Pain is conducted along three neuron pathways that transmit noxious stimuli from the periphery to the cerebral cortex. Primary afferent neurons are located in the dorsal root ganglia, which lie in the vertebral foramina at each spinal cord level. 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. In the dorsal horn, the primary afferent neuron synapses with a second order neuron whose axons cross the midline and ascend in the contralateral spinothalamic tract to reach the thalamus. Second-order neuron synapses in the thalamic nuclei with the third order neuron, which in turn send projections through the internal capsule and corona radiata to the post central gyrus of the cerebral cortex (*Wall et al., 2002*).

First order neurons:

Sensory afferent neurons have a unipolar cell body located in the dorsal root ganglion and are classified by fiber size into three major groups(A, B,



C). Group A is further sub classified into four subgroups ($A\alpha$, $A\beta$, $A\gamma$, $A\delta$) (**Table 1**). Sensory afferents that responds to noxious stimulation include small caliber myelinated ($A\delta$) or fine unmyelinated(C) fibers from epidermal and internal receptive fields including periosteum, joints, muscles and viscera (*Raj, 2000*). The majority of first order neurons send the proximal end of their axons into the spinal cord via the dorsal (sensory) spinal root at each cervical, thoracic and sacral level. Some unmyelinated afferent c-fibers have been shown to enter the spinal cord via the ventral nerve (motor) root, accounting for the observation that some patients continue to feel pain even after transection of the dorsal nerve root (rhizotomy) (*Morgan et al., 2006*). Once in the dorsal horn, in addition to synapsing with second order neurons, the axons of the first-order neuron may synapse with interneurons, sympathetic neurons, and ventral horn motor neurons.



Table (1): Erlanger/Gasser Classification of peripheral nerve fibers (*Raj, 2000*)

Fiber group	Innervation	Mean diameter (nm)	Mean conduction velocity (m/sec)
A α (M)	Primary muscle spindle, motor to skeletal muscles	15	100
A β (M)	Cutaneous touch and pressure afferents	8	50
A γ (M)	Motor to muscle spindles	6	20
A δ (M)	Mechanoreceptors and nociceptors	<3	15
B (M)	Sympathetic preganglionic	3	7
C (UM)	Mechanoreceptor, nociceptors, and sympathetic preganglionic fibers	1	1

M : myelinated
UM : unmyelinated

Second order neurons:

As afferent fibers enter the spinal cord, they segregate according to size, with large myelinated fibers becoming medial, and small unmyelinated fibers becoming lateral. Pain fibers may ascend or descend one to three spinal cord segments in lissauer's tract before synapsing with second order neurons in the gray matter of the ipsilateral dorsal horn. In many instances they communicate with second order neurons through interneurons (*Willis et al., 1997*).



Spinal cord grey matter divided into 10 laminae by Rexed (**Table 2, Fig. 1**). The first six lamina, which make up the dorsal horn, receive all afferent neural activity, and represent the principle site of modulation of pain by ascending and descending neural pathways (*Dennis et al., 2001*).

Second order neurons are either nociceptive, specific or wide dynamic range (WDR) neurons. Nociceptive specific neurons serve only noxious stimuli, but WDR neurons also receive non noxious afferent input from A β , A δ , and C fibers. Nociceptive specific neurons are arranged somatotopically in lamina I and have discrete, somatic receptive fields. They are normally silent and respond only to high threshold noxious stimulation, poorly encoding stimulus intensity. WDR neurons are the most prevalent cell type in the dorsal horn. Although they are found throughout the dorsal horn, WDR neurons are most abundant in lamina V. During repeated stimulation WDR neurons characteristically increase their firing rate exponentially in a graded fashion (wind-up), even with the same stimulus intensity. They also have large receptive fields compared with nociceptive specific neurons (*Zhang et al., 1997*)



Most nociceptive C fibers send collaterals to, or terminate on, second-order neurons in lamina I, II, and to lesser extent lamina V. In contrast, nociceptive A δ fibers synapse mainly in lamina I, V, and to a lesser degree lamina X. Lamina I response primarily to noxious nociceptive stimuli from cutaneous and deep somatic tissues. Lamina II, also called the substantia gelatinosa, contains many interneurons and is believed to play a major role in processing and modulating nociceptive input from cutaneous nociceptors. It is also of special interest because it is believed to be a major site of action for opioids. Lamina III, IV receive primarily non-nociceptive sensory input. Lamina VII, IX make up the anterior(motor)horn. Lamina VII is called the intermediolateral column and contains the cell bodies of preganglionic sympathetic neurons (*Morgan et al., 2006*).

Visceral afferents terminate primarily in lamina V, and to a lesser extent lamina I. These two lamina represent points of central convergence between somatic and visceral inputs. Lamina V responds to both noxious and non noxious sensory input and receives both visceral and somatic pain afferents. The



phenomenon of convergence between visceral and somatic sensory input is manifested clinically as referred pain (Wall et al., 2002).

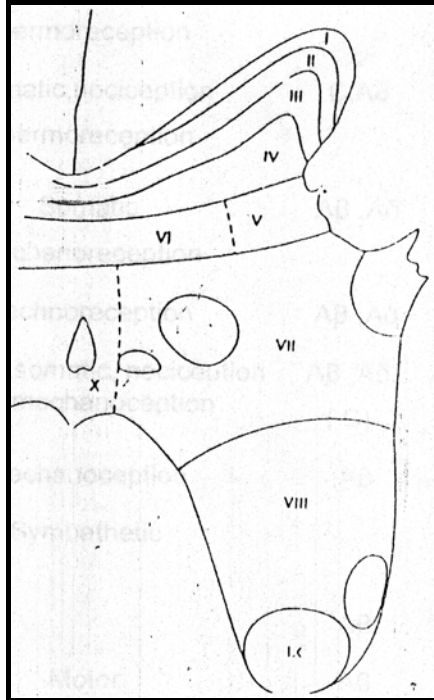


Fig. (1):
Rexed's spinal cord lamina
(Morgan et al., 2006)

Table (2): Spinal cord laminae

Lamina	Predominant function	Input	Name
I	Somatic, nociceptive Thermoreception	A δ , C	Marginal layer
II	Somatic, nociception Thermoreception	C, A δ	Substantia gelatinosa
III	Somatic Mechanoreception	A β , A δ	Nucleus proprius
IV	Mechnoreception,	A β , A δ	Nucleus proprius
V	Visceral., somatic, nociception and mechanoception	A β , A δ , (C)	Nucleus proprius WDR neurons
VI	mechanoception	A β	Nucleus proprius
VII	Sympathetic		Intermediolateral column
VIII		A β	Motor horn
IX Motor	A β		Motor horn
X		A δ	Central canal



Ascending pathways:

The spinothalamic tract:

The axons of most second-order neurons cross the midline close to their level of origin at the anterior commissure to the contra lateral side of the spinal cord before they form the spinothalamic tract and send their fibers to the thalamus, the reticular formation, the nucleus raphe Magnus, and the periaquiductal gray. The spinothalamic tract which is classically considered the major pain pathway lie anteriolaterally in the white matter of the spinal cord. This ascending tract is divided into lateral and medial. The lateral spinothalamic (neospinothalamic) tract projects mainly to the ventral posterolateral nucleus of the thalamus and carries discriminative aspects of pain such as intensity, location, duration *(Willis et al., 1997)*.

The medial spinothalamic (paleospinothalamic) tract projects to the medial thalamus and is responsible for mediating the autonomic and unpleasant emotional perception of pain *(Willis et al., 1997)*.

Alternate pain pathway:



As with epicritic sensation, pain fibers ascend diffusely, ipsilaterally, and contra laterally, hence some patients continue to perceive pain following ablation of the spinothalamic tract. Thus, other ascending pain pathways are also important. The spinoreticular tract is thought to mediate arousal and autonomic response to pain. The spinomesencephalic tract may be important in activating antinociceptive, descending pathways, because it has some projections to periaquiductal gray. The spinohypothalamic and the spinotelencephalic tract activate the hypothalamus and evoke emotional behavior. The spinocervical tract ascends uncrossed to the lateral cervical nucleus, which relays the fibers to the contralateral thalamus; this tract is likely a major alternative pain pathway (*Macintyre et al., 2001*).

Third order neuron:

Third order neurons are located in the thalamus and send fibers to somatosensory area 1 and 2 in the post-central gyrus of the parietal cortex and the superior wall of the sylvian fissure, respectively. Perception and discrete localization of pain take place in these cortical areas (*Wall et al., 2002*).



Physiology of Pain

Physiology of nociception:

Receptors that transduce noxious stimuli are called nociceptors. They are characterized by a high threshold for activation and encode the intensity of stimulation by increasing their discharge rates in a graded fashion. Following repeated stimulation, they characteristically display delayed adaptation, sensitization and after discharge (*Enrich et al., 2001*).

Noxious stimulation can often be broken down into two components: a fast, sharp and well localized sensation (first pain) which is conducted with a short latency (0.1s) by A δ fibers (tested by pinprick) and a duller slower onset and after a poorly localized sensation (second pain) which is conducted by C fibers (*Morgan et al., 2006*).

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

1. Mechano nociceptors that respond to pinch and pinprick.
2. Silent nociceptors that respond only to inflammation.



3. Polymodal mechano- heat nociceptors, they are the most prevalent and respond to excessive pressure, extreme of temperature ($>42^{\circ}\text{C}$ and $<18^{\circ}\text{C}$) and Alogens (pain producing substance).

Alogens include Bradykinin, serotonin, histamine, K^+ , some prostaglandins, and possibly adenosine triphosphate. Polymodal nociceptors are slowly to adapt to strong pressure. Specialized heat, cold and chemical nociceptors have been described but appear to be rare (*Enrich et al., 2001*).

Somatic nociceptors:

- Cutaneous nociceptors are present in the skin.
- Deep nociceptors are present in muscles, joints, bone, they are less sensitive to noxious stimulation than cutaneous nociceptors, but are easily sensitized by inflammation. The pain arising from them is dull and poorly localized. Specific nociceptors may exist in muscles and joint capsules, they respond to mechanical thermal and chemical stimuli.

(*Grubb, 1998*)

Visceral nociceptors:



Visceral organs are insensitive tissues that contain silent nociceptors. Some organs appear to have specific nociceptors such as heart, lung, testis and bile ducts. Most other organs such as the intestine are innervated by poly modal nociceptors that respond to smooth muscle spasm, ischemia and inflammation (allogens). These receptors do not respond to cutting, burning or crushing that occur during surgery. The brain lack nociceptors, however, the meningeal covering do contain nociceptors (*Grubb, 1998*).

Chemical Mediators of pain

Several neuropeptides and excitatory amino acids function as neurotransmitters for afferent neurons sub serving pain (**Table 3**). Many if not most neurons contain more than one neuro-transmitter which is simultaneously coreleased. The most important of these peptides are substance P and calcitonin gene-related peptide (CGRP). Glutamate is the most important excitatory amino acid (*Park et al., 2000*).

Anatomy and pathophysiology of neuropathic pain



Table (3): Major neurotransmitters mediating or modulating pain

Neurotransmitter	Receptor	Effect on Nociception
Substance P	NK-1	Excitatory
Calcitonin gene-related peptide		Excitatory
Glutamate	NMDA, AMPA, kainite, quisqualate	Excitatory
Aspartate		Excitatory
Adenosine triphosphate (ATP)	NMDA, AMPA, kainite, quisqualate	Excitatory
Somatostatin	P ₁ , P ₂	Inhibitory
Acetylcholine	Muscarinic	Inhibitory
Enkephalins	μ, δ, κ	Inhibitory
β-Endorphin	μ, δ, κ	Inhibitory
Norepinephrine	α ₂	Inhibitory
Adenosine	A ₁	Inhibitory
Serotonin	5-HT ₁ , (5-HT ₃)	Inhibitory
γ-Aminobutyric acid (GABA)	A, B	Inhibitory
Glycine		Inhibitory

(Morgan et al., 2006)

Substance P is an 11 amino acid peptide that is synthesized and released by first order neurons both peripherally and in the dorsal horn. Substance P facilitates transmission in pain pathways via NK-1 receptor activation. In the periphery, substance P neurons send collaterals that are closely associated



with blood vessels, sweat glands, hair follicles, and mast cell in the dermis. Substance P sensitizes nociceptors, degranulates histamine from mast cells and serotonin (5-HT) from platelets, and is a potent vasodilator and chemotactant for the leucocytes (*Morgan et al., 2006*).

Modulation of pain:

Modulation of pain occurs peripherally at the nociceptors, in the spinal cord or in supraspinal structure. This modulation can either inhibit (suppress) or facilitate (aggravate) pain (*Sinatra et al., 1998*).

Peripheral modulation:

Nociceptors and their neurons display sensitization following repeated stimulation. Sensitization may be manifested as an enhanced response to noxious stimulation or a newly acquired responsiveness to a wider range of stimuli, including non-noxious stimuli (*Loser et al., 2001*).

A. Primary hyperalgesia:

Sensitization of nociceptors results in a decrease in threshold, an increase in frequency response to the