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Pathophysiology of Paresthesia

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1. Introduction

Neuropathic pain arises from a lesion in the somatosensory system, which includes peripheral nerves, spinal dorsal horn, ascending projection tracts, thalamus, the somatosensory cortex and other pain- processing brain region. Patients with neuropathic pain have neurosensory defecits as a consequence of their direct neural injury with positivesensory phenomena (i.e., hyperalgesia, allodyneia, dysthesia and paresthesia). Paresthesia is a variety of neuropathic pain arises as a spontaneous and abnormal sensation. The problem may arise from an abnormality anywhere along the sensory pathway from the peripheral nerves to the sensory cortex. Paresthesia are often described as pins-and-needle sensation. Particular kinds of paresthesias can be seen in the central nervous system (CNS) as follows: focal sensory seizures with cortical lesions, spontaneous pain in the thalamic syndrome, or bursts of paresthesia down the back or into the arms upon flexing the neck (Lhermitte's sign) in patients with multiple sclerosis (MS) or other disorders of the cervical spinal cord. Level lesions of the spinal cord may cause either a band sensation or a girdle sensation, a vague sense of awareness of altered sensation encircling the abdomen. Nerve root lesions or isolated peripheral nerve lesions may also cause paresthesia, but the most intense and annoying paresthesia is due to a multiple symmetric peripheral neuropathy (polyneuropathy). Dysesthesia or allodynia is the term for abnormal sensations ordinarily evoked by a non- noxious stimuli. Paresthesias may be transient (following a prolonged crossing of patients leg) and not associated with neurological abnormality; however, if paresthesias are persistent, sensory system abnormality should be ruled out. In recent years, there has been expanded insight in to the pathophysiology of neuropathic pain because of their multiple and complex pathophysiological mechanisms. Convincing evidence on the relationship between the underlying pathophysiological mechanisms and neuropathic pain symptoms now suggests that classifying neuropathic pain according to a mechanism-based rather than an etiology-based approach. So we will try to explain the mechanism of paresthesia in this chapter.

1.1 Anatomical consideration of sensory transducers

Sensory receptors by means of sensory transduction convert the stimulus from the environment to an action potential for transmission to the brain. The anatomy and classification of these cutaneous sensory nerves has been extensively reviewed by

(Winkelmann, 1988, and Ropper & Samuels, 2009). They are divided in to two groups: the epidermal and the dermal skin-nerve organs. The epidermal skin-nerve organs consist of "free" nerve endings or hederiform nerve organs (e.g., Merkel cells). The term free terminal nerve ending refers to a slight axon expansion that still contains perineural cells including cytoplasm of Schwann cells and multiple cell organelles. In the dermal part, we have free sensory nerve endings, the hair nervous network (Pinkus discs), and the encapsulated endings [Ruffini, Meissner, Krause, Vater-Pacini (vibration), mucocutaneous end organ. Neurophysiological studies have led to a more advanced functional classification of sensory nerves based on the type of cutaneous mechanoreceptor responses. Sensory nerves can be subdivided into four groups: Aα fibers (12–22 mm) are highly myelinated with fast conduction velocity (70–120 m/s), and are associated with muscular spindles and tendon organs. Aß fibers are moderately myelinated (6–12 mm) and capture touch receptors. Aδ fibers constitute a thin myelin sheath (1–5 mm), an intermediate conduction velocity (4–30 m/s), and are generally polymodal. The slow-conducting C fibers (0.5–2m/s) are unmyelinated and small (0.2–1.5 mm). Aδ fibers constitutes almost 80% of primary sensory nerves sprouting from dorsal root ganglia, whereas C fibers make up to almost 20% of the primary afferents. Moreover, the activation threshold of Aδ fibers is higher than that of C fibers. On the molecular level, specific receptor distribution seems to be important for the various functions of sensory nerve subtypes. For example, mechanoreceptors exclusively express the T-type calcium channel Ca (v) 3.2 in the dorsal root ganglion (DRG) of D-hair receptors. Pharmacological blockade indicates that this receptor is important for normal D-hair receptor excitability including mechanosensitivity. However, different mechanisms seem to underlie mechanosensory function in various tissues. The skin is innervated by afferent somatic nerves with fine unmyelinated (C) or myelinated Aδ primary afferent nerve fibers transmitting sensory stimuli (temperature changes, chemicals, inflammatory mediators, pH changes) via dorsal root ganglia and the spinal cord to specific areas of the CNS, resulting in the perception of pain, burning, burning pain, or itching. Thus the skin "talks" to the brain via primary afferents thereby revealing information about the status of peripherally derived pain, pruritus, and local inflammation (Roosterman, et al., 2006).

1.1.1 Normal processing of pain

The study of the complex pathophysiological processes that trigger neuropathic pain comes from animal models of peripheral nerve injuries that was largely designed to mimic human diseases. Several etiological factors were used in these studies such as total nerve transaction or ligation to simulate the clinical conditions of amputation, partial peripheral nerve injury was stimulated by partial nerve ligation. Spinal nerve ligation effectively simulates spinal root damage owing to a lumbar disk herniation. Vincristine, paclitaxel and cisplatin have been used in animal models to mimic polyneuropathy caused by tumor chemotherapy. Finally, experimental model of diabetic neuropathy was produced by induction of damage to pancreatic insulin-producing cells in rats b streptozocin (Leone, et al. 2011). Following peripheral nerve injury, the generation ectopic discharges at the site of stump neuromas due to regenerating sprouts of primary afferent nociceptors has been well documented by microneurography study. There is also formation of abnormal electrical connections between adjacent axons that have been demyelinated. These connections may be responsible for the so-called ephaptic (cross-talk) phenomenon and the crossed after-discharge phenomenon, which occur because the sprouts of primary afferent neurons with damaged

peripheral axons can be made to discharge by the discharge of other afferents. Also, locally demyelinated axons can give rise to reflected impulses, which propagate both ortho-and antidromically. This is likely able to produce a dysesthetic buzzing sensation (Sindou, et al. 2001) This process is referred to as peripheral sensitization. The mechanism behind this initially involves the synthesis of arachidonic acid as a result of the action of phospholipase A2 on membrane lipids. Arachidonic acid is then acted upon by cyclo-oxygenase to synthesize prostaglandin that in-turn directly lowers the activation threshold for A-delta and C-fibres.These (Neil, 2011). At the site of injury, inflammatory mediators such as histamine, bradykinin and leukotrienes are released in addition to prostaglandins. These factors are collectively regarded as the 'inflammatory soup' that surrounds peripheral nociceptors resulting in a further reduction in their membrane threshold and activation of dormant receptors. Sensitized receptors display an increased basal (unstimulated) rate of discharge and a supra-normal increase in discharge strength in response to any increase in stimulus. This is easily demonstrated clinically as an area of hyperalgesia extending beyond the boundary of a surgical incision (Neil, 2011). Sodium channel activation underpins the initiation of an action potential and ultimately the perception of acute pain. Following nerve damage, voltage-gated sodium channel expression undergoes marked changes. Abnormal sodium channel Nav1.3, Nav1.7, Nav1.8 and Nav1.9 expression were demonstrated by many studies(Black JA, et al. 2008, Wood JN, et al. 2004, in Leone C, et al. 2011) leading to primary afferent hyperexcitability (a lowered threshold and higher firing rat). The cell body of the sensory afferent fibers lies in the dorsal root ganglia (DRG). Different sodium channels accumulate also within the intact DRG (Amir R 2002, Leone C, et al. 2011). The type III embryonic sodium channel (Nav1.3) might play a key role in the development of neuropathic pain. It is present at low levels in adult afferent nociceptive pathways and after an experimental nerve injury its expression markedly increases (Dib-Hajj, et al. 2009, Leone, et al. 2011). Two human-inherited pain syndromes, inherited erythromelalgia and paroxysmal extreme pain disorder have been linked to the mutations in **SCN9A**, the gene that encodes Nav1.7, whereas loss-of-function mutations in **SCN9A** have been linked to complete insensitivity to pain (Dib-Hajj & Drenth, 2007, Leone, et al., 2011).

1.1.1.1 The role of the cytokines

Proinflammatory cytokines (PICs) such as interleukin-1 β (IL- 1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF α) are an important group of inflammatory mediators and play an essential role in pain sensitization f cytokines. Peripherally, PICs enhance the activity of TRPV1 (transient receptor potential subtype V1) (Nicol et al., 1997; Opree and Kress, 2000; Jin & Gereau, 2006; Kawasaki et al., 2008), induced the expression of pronociceptive genes in dorsal root ganglion (DRG) neurons (Fehrenbacher et al., 2005; von Banchet et al., 2005 in Kawasaki et.al, 2008), and further increase spontaneous activity in DRG neurons (Schafers et al., 2003; Kawasaki et.al, 2008). PICs also enhance pain via central mechanisms. First, PICs are induced in the spinal cord, especially in glial cells (e.g., microglia and astrocytes), in different chronic pain conditions. Second, intrathecal injection of the PICs was shown to enhance pain. Third, spinal blockade of PIC signaling attenuates chronic pain. The study of Kawasaki et al., 2008, have demonstrated that PICs induce central sensitization and hyperalgesia via distinct and overlapping synaptic mechanisms in superficial dorsal horn neurons either by increasing excitatory synaptic transmission or by decreasing inhibitory synaptic transmission. PICs may further induce long-term synaptic plasticity through cAMP response element-binding protein (CREB)-mediated gene

transcription. Blockade of PIC signaling could be an effective way to suppress central sensitization and alleviate chronic pain. Various protein regulation is seen in peripheral sensitization, peripheral nerve injury induced by various animal studies changes transient receptor potential (TRP) channel expression. TRP channels are a family of nonselective cation-permeable channels that are known to be important for sensory signaling in the peripheral nervous system. Vanilloid receptor 1 (TRPV1), a member of the TRP family, was investigated for their role in the development of neuropathic pain. Total or partial sciatic nerve transection, or spinal nerve ligation, reduce TRPV1 expression in the somata of all damaged dorsal root ganglia. Following partial nerve lesion or spinal nerve ligation, TRPV1 expression is greater in the undamaged dorsal root ganglion somata than in controls. TRPV1-deficient mice lack hyperalgesia and TRPV1 antagonists reduce pain behavior in mice after spinal nerve ligation. This is a strong evidence that TRPV1 plays a crucial role in the development of neuropathic pain (Staaf et al., 2009, Hudson, et al. 2001, Baron & Caterina, et al., 2000, Leone et al., 2011). The physiological changes seen within inflamed or infected tissue (i.e. heat and acidic pH) are known to activate the TPRV-1 receptor and enhance pain sensitivity. Other molecules within nociceptors that are known to enhance pain transmission include substance-P and calcitonin gene related peptide (CGRP). These two factors are often released simultaneously within the cell. Substance P activates second order neurons that send a 'pain' signal to the brain while CGRP contributes to neurogenic inflammation by causing vasodilation and hence warmth, redness and swelling (Neil, 2011). Normally, the DRG cell body receives via the nerve terminal signal substances, which modify gene transcription and protein synthesis. After nerve damage, these molecules will be lost. So, nerve damage, through complex signaling mechanisms (cAMP-dependent PKA and Ca2+/phospholipid-dependent PKC) modulate gene transcription. Also, it was demonstrated by animal study that after nerve damage, there is an induction of c-jun, p-38 and ERK. The encoded proteins of these genes are involved in the inflammatory responses, neuronal degeneration and neuronal plasticity, which maintain pain sensation. Therefore, the importance of genetic factors in neuropathic pain remains an interesting question for further research, especially for their possible use as targets for new, more selective drugs (Hudmon et al., 2008, Stamboulian et al., 2010, Leon , et al., 2011).

1.1.1.2 Central sensitization

The cell bodies of the peripheral afferent pain fibers of both A- δ and C types are placed in the dorsal root ganglia; central extensions of these nerve cells project via the dorsal root to the dorsal horn of the spinal cord (or, in the case of cranial pain afferents, to the nucleus of the trigeminal nerve, the medullary analogue of the dorsal horn). The pain afferents occupy mainly the lateral part of the root entry zone. Within the spinal cord, many of the thinnest fibers (C fibers) form a discrete bundle, the tract of Lissauer (Ropper & Samuels, 2009).

1.1.1.3 The dorsal horn

The afferent pain fibers, after traversing the tract of Lissauer, terminate in the posterior gray matter or dorsal horn, predominantly in the marginal zone. Most of the fibers terminate within the segment of their entry into the cord; some extend ipsilaterally to one or two adjacent rostral and caudal segments; and some project via the anterior commissure to the contralateral dorsal horn. Second-order neurons, the sites of synapse of afferent sensory fibers in the dorsal horn, are arranged in a series of six layers known as Rexed's laminae (Fig.1). Rexed's laminae I, II, and V play a role in modulating nociceptive transmission. A-δ

fibers terminate principally in lamina I of Rexed (marginal cell layer of Waldeyer) and also in the outermost part of lamina II; some A- δ pain fibers penetrate the dorsal gray matter and terminate in the lateral part of lamina V . Unmyelinated (C) fibers terminate in lamina II (substantia gelatinosa). Yet other cells that respond to painful cutaneous stimulation are located in ventral horn laminae VII and VIII. The latter neurons are responsive to descending impulses from brainstem nuclei as well as segmental sensory impulses. From` these cells of termination, second-order axons connect with ventral and lateral horn cells in the same and adjacent spinal segments and subserve both somatic and autonomic reflexes. The main bundle of secondary neurons subserving pain sensation projects contralaterally (and to a lesser extent ipsilaterally) to higher levels; this constitutes the spinothalamic tract. Most of the spinothalamic neurons ultimately ascend to the ventroposterolateral nucleus of the thalamus, though they may branch to provide input to these brain stem targets. However, some axons terminate solely in these bulbar regions, which then send projections to thalamic nuclei (Ropper & Samuels, 2009).
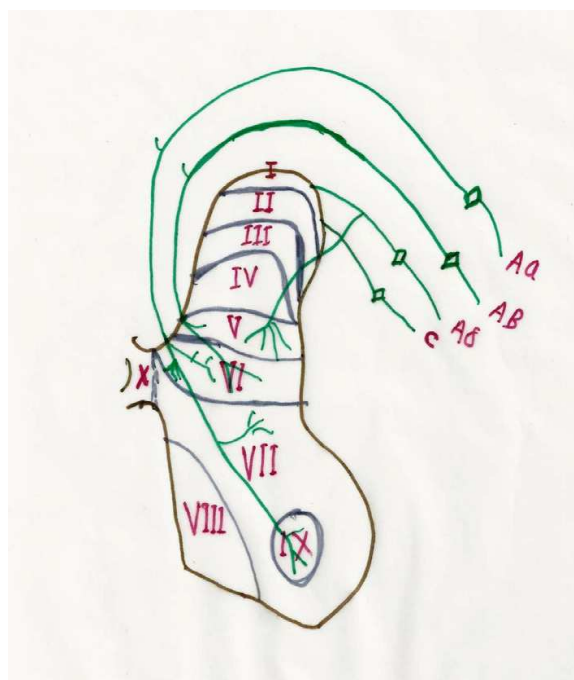

Fig. 1. Diagramatic representation of Rexed's laminae.

Information about this pathway in humans has been derived from the study of postmortem material and from the examination of patients subjected to anterolateral cordotomy for intractable pain. The clinical relevance is seen with the unilateral section of the anterolateral funiculus, which produces a relatively complete loss of pain and thermal sense on the opposite side of the body, extending to a level two or three segments below the lesion as noted earlier. Usually, the pain sensibility returns after a variable period of time, probably being conducted by pathways that lie outside the anterolateral quadrants of the spinal cord that gradually increases their capacity to conduct pain impulses. One of these is a longitudinal polysynaptic bundle of small myelinated fibers in the center of the dorsal horn (the dorsal intracornual tract); another consists of axons of lamina I cells that travel in the dorsal part of the lateral funiculus (Ropper & Samuels, 2009). The second-order nociceptive neurons consist of nociceptive-specific neurons and wide dynamic range neurons (Craig,

2006, D'Mello, 2008, Leone, et al., 2011). Nociceptive-specific neurons are located in the outer layers (laminae I–II) of the dorsal horn; wide dynamic range neurons lie in deeper laminae (most of lamina V neurons are wide dynamic neurons). Nociceptive-specific neurons respond selectively to noxious stimuli conveyed by Aδ- and C-fibers. Wide dynamic range neurons excited both by noxious and non-noxious stimuli, receive both large-myelinated Aβ-fibers as well as Aδ- and C-fibers. Wide dynamic range neurons can encode and project different types of sensory information, nociceptive and non-nociceptive, varying their firing rate (higher for noxious and lower for non-noxious stimuli).

Nociceptive neurons usually have a localized receptive field and probably plays an important role in spatially detecting nociceptive stimuli. By contrast, wide dynamic range neurons have a large receptive field and a stimulus-response function (the higher the stimulus intensity, the higher the firing rate of their output), their main function is to detect and discriminate the intensity of noxious stimuli (Dubner 1985, Sessle 1991, Leone, et al., 2011). The fundamental process of central sensitization is the release of the primary afferent neuron that binds to the NMDA receptor resulting in an influx of calcium and potassium. This leads to nerve depolarization and heightened sensitivity to circulating neurotransmitter. The N-methyl, D-adenine (NMDA) receptor is found widely within the CNS but features prominently in the DRG. At the molecular level, nociception induces alteration in second order neurone such as phosphorylation of NMDA and AMPA receptors. These processes contribute to the process of central sensitization (Neil, 2011). At the dorsal horn usually two processes occur, which are designated "windup" and "central sensitization. Central sensitization has been described earlier, the "windup" results from repetitive C-fiber firing at low frequencies that results in a progressive buildup of the amplitude of the response of the dorsal horn neuron, only during the repetitive train. Both can be blocked by NMDA receptor antagonists. Central sensitization can result from windup. This is a result of the calcium influx through the NMDA receptor following depolarization of the dorsal horn membrane. The intracellular calcium activates a number of kinase among which protein kinase C (PKC) is likely important. PKC enhances the NMDA receptor, which results in subsequent glutamate binding of the NMDA receptor generating an inward current. Though windup can result in central sensitization, it is not necessary for central sensitization to occur (Brannagan,2010). The neurotransmitters on activiation of NMDA receptor-channel produce an increase of intracellular Ca^{2+} and cAMP concentrations, which activates protein kinase. Protein kinase consist of the signaling cascade that modulates gene transcription (i.e. c-fos, c-jun) (Ji et al., 2003, Willis et al., 2002, Leone et al., 2011).

1.1.1.4 Role of calcium currents in the genesis of neuropathic pain

Cytoplasmic Ca^{2+} regulates numerous cellular processes in neurons. The pathogenic contribution of altered inward Ca^{2+} flux (ICa) through voltage gated Ca^{2+} channels in sensory neurons after peripheral nerve injury was examine by Hogan (2007). Primary sensory neurons isolated from animals after peripheral nerve injury with partial ligation show a decrease in high-voltage activated ICa by approximately one third. Low voltage-activated ICa is nearly eliminated by peripheral nerve injury. Loss of ICa leads to decreased activation of Ca^{2+}-activated K^+ currents, which are also directly reduced in traumatized neurons. As a result of these changes in membrane currents, membrane voltage recordings show increased action potential duration and diminished after hyperpolarization.

Excitability is elevated, as indicated by resting membrane potential depolarization and a decreased current threshold for action potential initiation. Traumatized nociceptive neurons develop increased repetitive firing during sustained depolarization after axotomy. Concurrently, cytoplasmic Ca2+ transients are diminished. In conclusions, axotomized neurons, especially pain-conducting ones, develop instability and elevated excitability after peripheral injury. DRG neurons expressed a variety of voltage-gated Ca2+ channels (VGCCs). High voltage activated (HVA) are distinguished by their voltage dependency, kinetics, and pharmacology. Low voltage activated (LVA) currents, or T currents inactivate rapidly during sustained depolarization but close (deactivate) slowly after repolarization of the membrane. Because of these features, T-currents account for up to 50% of Ca2+ entry. DRG neurons show definite heterogeneity with respect to HVA Ca2+ channels. Nerve injury, particularly axotomy, results in a loss of ICa in primary sensory neurons, which is present after different types of injury and their role in generating neuropathic pain. Axotomized Aδ neurons develop increased repetitive firing during sustained depolarization after axotomy , whereas Aα/β neurons does not. Thus, axotomized neurons, especially pain-conducting ones, develop instability and elevated excitability. Altered function of other ionic membrane channels contributes to the disordered membrane biophysics observed after nerve injury, including substantial changes in voltage-gated Na+ and K+ channels (Hogan, 2007).

1.1.1.5 The role of glial cells in neuropathic pain

Glial cells, including microglia and astrocytes, are non-neuronal cells that have various functions in the spinal cord. They act as physical support, release mediators that modulate neuronal activity and alter axonal and dendritic growth. Usually they account for 70% of CNS cells under normal conditions. Uncontrolled glial cell activation under neuropathic pain conditions induces the release of proinflammatory cytokines and other substances that facilitate pain transmission (Watkins 2009, Mika 2008, Song 2001, Leone et al., 2011). In addition, glial cells enhance release of substance P and excitatory amino acids from nerve terminals, including primary afferents in the spinal cord (Malcangio 1996, Inoue 1999, Leone, et al., 2011). Their activation can also lead to altered opioid system activity (Watkins 2009, Mika 2008, Song 2001, Leone et al., 2011). Neuropathic pain can also induce a protein named fractalkine, which is expressed by neuron (Abbadie 2009, Leone et al., 2011). The soluble portion of fractalkine diffuses away and binds to and activates glial cells (Chapman 2000, Leone et al., 2011). Intrathecal fractalkine creates both thermal hyperalgesia and mechanical allodynia, and fractalkine receptor blockade blocks inflammatory neuropathy-induced pain (Milligan, 2004, Leone et al., 2011).

1.1.1.6 Thalamic projection of pain fibers

The lateral division of the spinothalamic tract terminates in the ventrobasal and posterior groups of nuclei, the most important of which is the VPL nucleus. The medial portion terminates mainly in the intralaminar complex of nuclei and in the nucleus submedius. Spinoreticulothalamic (paleospinothalamic) fibers project onto the medial intralaminar (primarily parafascicular and centrolateral) thalamic nuclei. Projections from the dorsal column nuclei, which have a modulating influence on pain transmission, are mainly terminated in the ventrobasal and ventroposterior group of nuclei (Ropper & Samuels, 2009).

1.1.1.7 Thalamocortical projections

The ventrobasal thalamic complex and the ventroposterior group of nuclei project to two main cortical areas: the primary sensory (postcentral) cortex (a small number terminate in the precentral cortex) and the upper bank of the Sylvian fissure. They are concerned mainly with the reception of tactile and proprioceptive stimuli and with all discriminative sensory functions including pain (Ropper & Samuels, 2009).

1.1.1.8 Descending pain-modulating systems

The descending fibers play an important role to modulate activity in nociceptive pathways and inhibition of neuropathic pain. The endogenous pain control system decend from the frontal cortex and hypothalamus and projects to cells in the peri-aqueductal region of the midbrain and then passes to the ventromedial medulla. From there it descends in the dorsal part of the lateral fasciculus of the spinal cord to the posterior horns (laminae I, II, and V). Several other descending pathways, noradrenergic and serotonergic, arise in the locus ceruleus, dorsal raphe nucleus, and nucleus reticularis. Gigantocellularis are also important modifiers of the nociceptive response. The descending pain-control systems mainly acting via noradrenergic and serotonergic, as well as opiate pathway. A descending norepinephrine- pathway, also has been traced from the locus ceruleus in the dorsolateral pons to the spinal cord, and its activation blocks spinal nociceptive neurons. The rostroventral medulla contains a large number of serotonergic neurons from which descending fibers inhibit dorsal horn cells concerned with pain transmission, this provide a rationale for the use of serotonin agonists antidepression medications in patients with chronic pain (Ropper & Samuels, 2009).

1.1.1.9 Genetic inheritance of neuropathic pain

Genetic risk factors play as an important factor in various clinical neuropathic pain conditions. Various genetic diseases are reported to be associated with an increased risk for the development of neuropathic pain. For example, Fabry disease, which is a rare X-linked recessive (inherited) lysosomal storage disease that causes painful neuropathy (Zarate et al., 2008, Leone, et al., 2011). Mutations in SCN9A, the gene that encodes Nav1.7 caused two extremely rare inherited neuropathic pain conditions, erythromelalgia and paroxysmal extreme pain disorder (Dib-Hajj et al., 2007, Leone et al., 2011). Following nervous system damage, gene mutations can lead to the genetic risk of developing neuropathic pain. To highlight the role of genetic susceptibility in neuropathic pain, a recent study investigates a single nucleotide polymorphism association of the potassium channel α subunit, KCNS1, in humans with neuropathic pain. They found that a common amino acid changing-allele, the 'valine risk allele', was significantly associated with higher pain scores (Costigan et al., 2010, Leone et al., 2011). Other studies investigated catechol-O-methyltransferase polymorphisms that modulate nociceptive and dysfunctional temporomandibular joint disorder pain (Diatchenko et al., 2005, Nackley et al., 2006, Leone et al., 2011). A single nucleotide polymorphism in SCN9A is demonstrated by recent study to increase the firing frequency of DRG neurons, another study demonstrates that this single nucleotide polymorphism was subsequently shown to be associated with chronic pain (Reimann et al., 2010, Estacion et al., Leone et al. 2011). So, a new future approach to neuropathic pain should include genetic analysis among the more conventional diagnostic tools.

1.1.2 Pathophysiologic characteristic of paresthesia

Human microneurography experiments have demonstrated that tingling paresthesia results from the aberrant activity of mechanosensitive neurons (Ochoa and Torebjork 1980, Nordin et al., 1984, Lennertz et al., 2010), but little is known about the molecular mechanisms underlying this abnormal sensation. So Hydroxy-sanshool (sanshool), which is a natural plant alkylamide that induces numbing and robust tingling paresthesia in humans (Bryant and Mezine, 1999; Sugai et al., 2005, in Lennertz, et al., 2010) has been used to provide insight into the cellular and molecular mechanisms underlying tingling paresthesia. Nearly 52% of cultured dorsal root ganglion neurons are excited by sanshool in vitro, including a: subset of large-diameter, putative light-touch mechanoreceptors (Bautista et al., 2008, Lennertz, et al., 2010)). Lingual nerve (Bryant and Mezine, 1999 , Lennertz, et al., 2010) and dorsal horn neurons recording (Sawyer et al., 2009, Lennertz, et al., 2010) confirm that sanshool does activate light-touch receptors. Interestingly, it was found that sanshool may discriminate between subtypes of mechanosensitive fibers. Using the saphenous skin–nerve preparation to record from primary afferent nerve fibers ex vivo, it was demonstrated that sanshool excites specific subtypes of cutaneous mechanoreceptors. Sanshool potently activates all ultrasensitive D-hair fibers and, to a lesser extent, unique populations of pressure-sensitive Aß fibers and low conduction velocity C fibers. In all fiber types, sanshool evokes action potential bursting, reminiscent of the activity observed in myelinated fibers of human subjects experiencing tingling paresthesia. In addition, sanshool-evoked avoidance behavior is distinct from pain-evoked behaviors and is consistent with the robust activation of low threshold mechanoreceptors. Moreover, it was proved that sanshool is an invaluable tool for delineating the function of novel mechanosensitive neuron subtypes (Lennertz et al., 2010). Thus, the majority of fibers activated by sanshool are $A\beta$ and D-hair neurons that mediate the detection of light-touch rather than noxious stimuli. However, there is a subset of C fibers that do respond robustly to sanshool. In a subset of fibers, sanshool evoked a burst pattern of action potential firing. Bursting was most prevalent among sanshool-sensitive C fibers and D-hair fibers, occurring in 73 and 26% of sanshool-sensitive fibers, respectively. Large myelinated $A\beta$ fibers were the least likely to show bursting because only one RA- $A\beta$ fiber exhibited bursting and none of the SA- $A\beta$ fibers displayed bursting Interestingly, the rapidly adapting D-hair fibers and slowly adapting C fibers displayed distinct patterns of burst firing. Rapidly adapting D-hair fibers (and the RA- $A\beta$ fiber) issued quick bursts of action potentials with short intervals, whereas the slowly adapting C fibers issued significantly longer duration bursts of action potentials at less frequent intevals. Consequently, the average number of action potentials per burst was considerably higher in C fibers than in D-hair or RA- $A\beta$ fibers. Sanshool is the first pharmacological agent identified that can discriminate between subsets of mechanosensory neurons which often leads to tingling paresthesia in patients . Among $A\delta$ fibers, virtually all D-hair afferents were vigorously excited by sanshool, whereas adrenomedullin (AM) nociceptors were completely unresponsive. D-hair afferents are the most sensitive of all mechanoreceptors, with mechanical thresholds below the measurable limit D-hairs have also been implicated in diabetic peripheral neuropathy (Shin et al., 2003; Jagodic et al., 2007, Lennerts et al., 2010), which often leads to tingling paresthesia in patients(Lennertz et al., 2010).

Sanshool activates rapidly adapting mylinated more better than slowly adapting fibers. Spontaneous activity in rapidly adapting myelinated fibers has been implicated in both

injury- and disease-evoked paresthesia, as well as in post ischemic paresthesia; however, the exact neuronal subtypes that mediate tingling paresthesia have not been characterized (Ochoa and Torebjrko, 1980; Nordin et al., 1984, Lennertz, et al., 2010). A subset of slowly adapting Aβ fibers also responded to sanshool, two findings support the idea that the sanshool-sensitive slowly adapting Aβ fibers are SA-II type skin stretch sensors. First, the proportion of sanshool-sensitive slowly adapting Aβ fibers (36%) is consistent with the proportion of SA-II type skin stretch sensors. Second, the sanshool-sensitive SA- Aβ fibers were approximately fivefold less sensitive to sustained force than the sanshool-insensitive population. Sanshool activated a unique subset of C fibers that has an intrinsically slower conduction velocity than other C fibers (Lennertz et al., 2010). Previous studies of tingling paresthesia in humans have failed to report aberrant activity of Aδ or C fibers (Ochoa and Torebjork, 1980; Nordin et al., 1984, Lennertz, et al., 2010). However, this may be attributable to technical difficulties in recording from patients experiencing tingling paresthesia. Knowing that sanshool elicits tingling paresthesia through selective activation of mechanosensitive somatosensory neurons. Also, sanshool consumption fails to elicit the nocifensive responses of nose rubbing and wiping that are commonly observed after consumption of capsaicin or mustard oil (our unpublished observations)(Lennertz et al., 2010).Thus, sanshool evoked behaviors is more likely to be resulted from tingling paresthesia rather than painful irritation and this is consistent with the activation pattern of Aδ and Aβ fibers by sanshool, as well as with results from human psychophysical studies demonstrating that sanshool does not elicit pain sensations (Bryant and Mezine, 1999; Sugai et al., 2005, Lennertz et al., 2010). Although sanshool also activates a subset of C fibers, it is unclear whether these C fibers actually transmit pain signals. Several studies have demonstrated the existence of C fibers that transmit information other than pain, such as the study by (Loken et al., 2009, Lennertz, et al., 2010), who demonstrates the existence of unmyelinated C fibers that code for pleasant touch sensations in humans. In addition, C fibers that transmit sensations of brushing and itch have also been reported (Zotterman, 1939, Lennertz, et al., 2010). Specific labeling of neurons that express a mass-related G-protein-coupled receptor, MrgprB4, revealed a unique subpopulation of C fibers that specifically innervate the skin but not the viscera. These fibers are hypothesized to function as touch receptors rather than nociceptors (Liu et al., 2007, Lennertz, et al., 2010). Common among all subtypes of sanshool-sensitive fibers is the presence of action potential bursting, which we observed in 29% of fibers. Bursting is also associated with tingling paresthesia. Microelectrode recordings show robust bursting of sensory afferents in normal human subjects experiencing tingling paresthesia (Ochoa and Torebjork, 1980, Lennertz et al., 2010). Neuronal recordings from patients suffering from activity-dependent tingling paresthesia showed that robust bursting of myelinated, rapidly adapting mechanoreceptors increased with the degree of paresthesia. Also, it was found in a rat models of diabetic neuropathy, robust bursting of medium-diameter fibers increased in diabetic neurons compared with wild-type neurons (Jagodic et al., 2007, Lennertz, et al., 2010). Bursting is exhibited by many neurons within the CNS, as well as some peripheral neurons. In the peripheral nervous system, bursting has been described in trigeminal afferents in the brainstem that are thought to play a key role in the central pattern generator circuit regulating mastication in rodents (Brocard et al., 2006; Hsiao et al., 2009, Lennertz, et al., 2010). In addition, neuronal recordings from patients suffering from activity-dependent tingling paresthesia showed robust bursting of myelinated, rapidly adapting mechanoreceptors that increased with the

degree of paresthesia. Finally, in rat models of diabetic neuropathy, robust bursting of medium-diameter fibers increased in diabetic neurons compared with wild-type neurons (Jagodic et al., 2007, Lennertz, et al., 2010). It has been demonstrated that sanshool-evoked fiber responses are of similar prevalence and amplitude in the presence or absence of TRPA1 and TRPV1 selective antagonists. These data suggest that neither TRPA1 nor TRPV1 mediate the excitatory effects of sanshool (Lennertz et al., 2010). Sanshool may act directly on two pore potassium channel (KCNK) in sensory neurons as well as in keratinocytes, which are known to modulate sensory neuron function (Koizumi et al., 2004; Lumpkin and Caterina, 2007; Lennertz et al., 2010) to induce tingling paresthesia, and that is because in somatosensory neurons, expression and electrophysiological studies show the presence of KCNK18 channels (Dobler et al., 2007; Kang et al., 2008, Lennertz et al., 2010), and expression of KCNK3 and KCNK9 have not been demonstrated. However, KCNK3 and KCNK9 are expressed by keratinocytes in the skin (Kang and Kim, 2006, Lennertz, et al., 2010). Bursting in trigeminal neurons has been linked to the activity of Kv1 channels (Hsiao et al., 2009). Characterization of sanshool-sensitive mechanoreceptors represents an essential first step in identifying the cellular and molecular mechanisms underlying tingling paresthesia that accompanies peripheral neuropathy and injury (Lennertz, et al., 2010).

1.1.3 Paresthesia and entrapment neuropathy

Paresthesia are reported in many different conditions of entrapment neuropathies (Lewis, 2010). In our study of surgical outcome of thoracic outlet compression syndrome, paresthesia was the second most common syndrome (30%) after pain (86.7%), two-thirds of the patient were operated (Al Luwimi &Al Awami, 2009). Recently symptoms of paresthesia and signs of numbness were recorded by (Hann et al., 2010) to establish the changes in nerve excitability and symptom generation associated with the application of focal nerve compression (FNC). The aim of the study was to investigate the changes in sensory nerve excitability and thereby resting membrane potential that develops with focal nerve compression (FNC). FNC was applied by means of a custom-designed, novel compression device (Fig 2).

Paraesthesia developed in response to application of FNC. Their intensity increased as the FNC continued reaching the end of FNC (Fig. 3A). Following the release of FNC, paraesthesia continued and the duration required for complete resolution of symptoms varied between individuals, ranging from 3 to 11 min. Numbness was quantitatively assessed using von frey filaments(VFFs). The levels of numbness, as indicated by normalized VFFs, paralleled the pattern of changes produced by paraesthesiae (Fig. 3B). During FNC, the mean tactile sensitivity deteriorated, followed by a gradual recovery with release of FNC.

1.1.3.1 Comparison to ischaemia

The ischemia change seen on release of compression was similar to that previously achieved with generalized limb ischaemia (Fig. 4A), similarly, the reduction in compound sensory action potential (CSAP) amplitude observed during compression was similar to that achieved with ischaemia (Fig. 4B), suggesting that the two maneuvres achieved comparable effects on the axons over similar time period. But, the rates of recovery on release of the different interventions were clearly different, the rate of compound sensory action potential

(CSAP) recovery was significantly faster following release of FNC (12.4 +/- 2.1% min−1) when compared to ischaemia (3.6 +/- 0.6% min−1; P <0.005). Accordingly, full recovery of CSAP was achieved in a shorter time frame with release of FNC (3.3 +/- 0.5min) than ischaemia (8.8 +/- 2.1min; P <0.05(Hann, et al., 2010)**.**
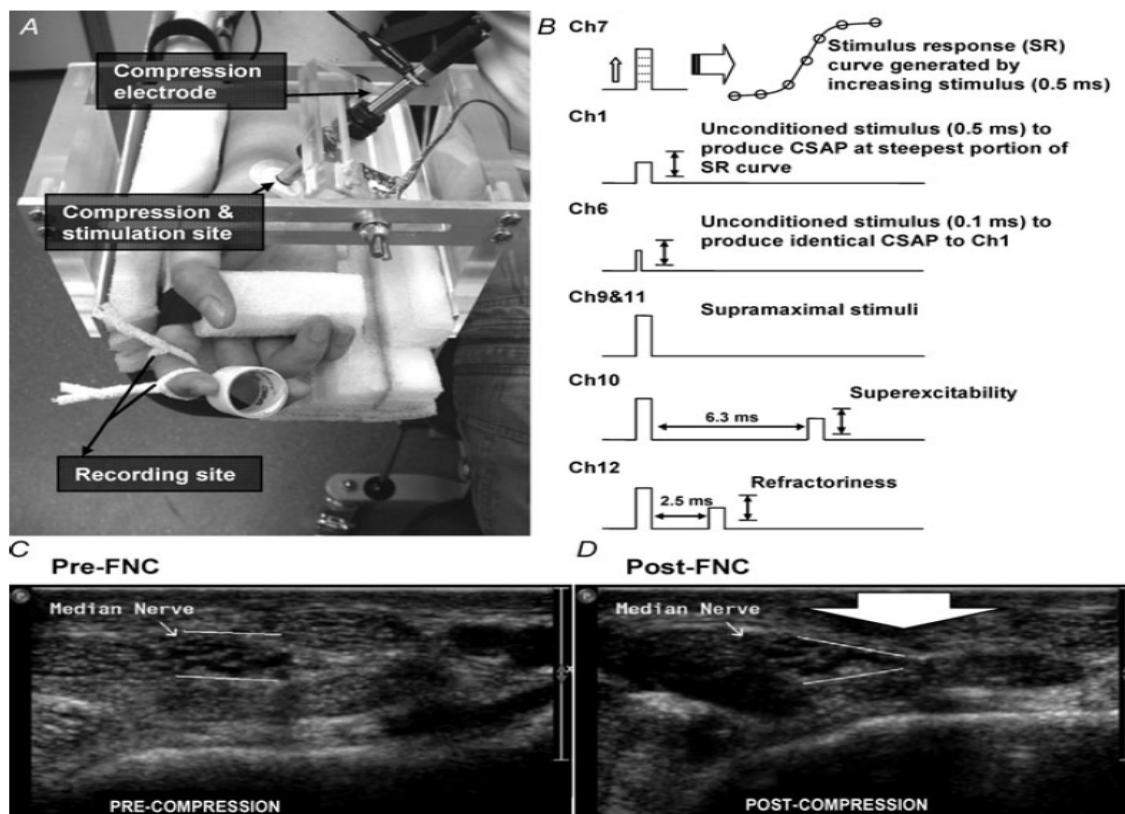

Fig. 2. Experimental paradigm and structural changes to the median nerve achieved via FNC. **A**, experimental protocol. The median nerve was stimulated at the wrist and the resultant compound sensory action potential (CSAP) was recorded from the second digit. A custom designed and built compression device was utilized for delivering both electrical stimulation and focal nerve compression. **B**, configuration of stimulation channels. Vertical arrows in channels 1, 6, 10 and 12 indicate threshold tracking of the test stimulus, aiming to generate a CSAP amplitude corresponding to the steepest portion of SR curve in channel 7. **C**, a representative cross-sectional ultrasound (US) image of median nerve (MN) prior to FNC. **D**, cross-sectional US image of MN immediately after the application of FNC showing the changes in shape of MN. Open vertical arrow indicates the region of FNC application. Copy permission from publisher (John Wiley and Sons) via Copyright Clearance Center's Rights Link service from the article by Hann S.E, J Physiol 588.10 (2010) pp 1737–1745.

When paraesthesia generation was compared between the process of FNC and ischemia it was continued to increase during the former process of FNC, and subsided after initial changes during the latter process (Fig. 3C) (Han et al., 2008, 2010). On the release of FNC, there was no increase in paraesthesia, in contrast with the release of ischaemia (of similar duration), where a large rebound in the intensity of paraesthesia developed. The pattern of change for numbness during and after FNC was similar to that observed with an ischaemic insult (Fig. 3D) (Han et al., 2008, 2010). There appeared apparent relationship between the

pattern of paraesthesia and corresponding changes in strength–duration time constant (SDTC). The pattern of paraesthesia generation observed in the present series was novel (Fig. 3A and C). The metabolic changes seen in the process of ischemia and FNC are different and that might explain the change in paresthesia generation in the two processes. The metabolic byproducts of ischaemia, such as H+, which accumulate and potentially interfere with parameters that determine axonal excitability, particularly the Na+/K+-ATPase and persistent Na+ conductance's. H+ ions and pH can modify channel gating (Wanke et al., 1980, 1983, Hann, et al. 2010), raised intracellular pH reduce Na+ channel inactivation (Brodwick & Eaton, 1978, Hann et al., 2010). Also, low pH may also alter the gating mode of persistent Na+ conductances (Baker & Bostock, 1999; Hann et al., 2010).
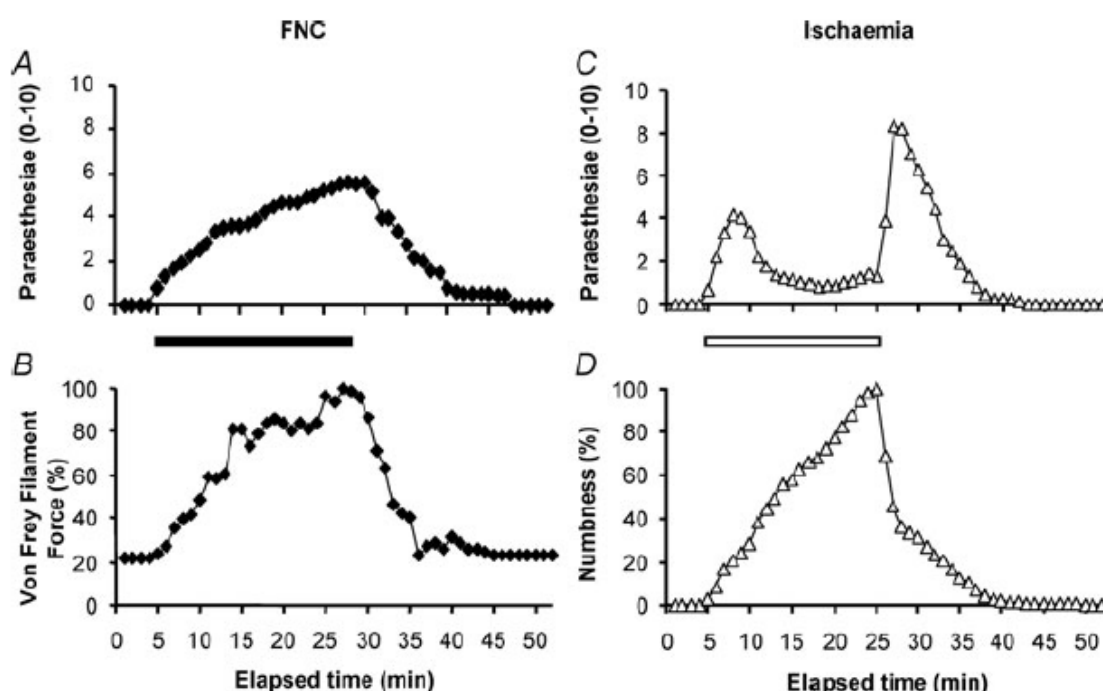
Fig. 3. Symptom rating before, during and after FNC (A and B), and compared to ischaemia (C and D). Copy permission from publisher (John Wiley and Sons) via Copyright Clearance Center's RightsLink service from the article by Hann S.E, J Physiol 588.10 (2010) pp 1737–1745.

Both processes can contribute to greater rate of paraesthesia generation during the initial phases of generalized ischaemia compared to FNC (Fig. 3A and C). But, during FNC where focal ischaemia appeared to be the underlying mechanism, metabolites exerted less significant effects. Such a view would also be supported by the rapid rate of CSAP recovery observed with release of FNC. Such differences in the secondary effects on axonal function, and persistent Na+ conductances, may also contribute to the relative differences in (SDTC) and symptom generation observed between FNC and ischaemia, particularly the relative absence of paraesthesia on release of FNC, in contrast to the more severe symptoms that follow generalized ischaemia (Fig. 5A). It is possible that metabolites associated with generalized ischaemia enhanced the accumulation of K+ ions during ischaemic depolarization, and it is possible that this mechanism dose not

contribute in the process of FNC. So, Post-ischaemic paraesthesia is most likely due to regenerative potassium currents (Han et al.; Kuwabara, 2008; Hann et al., 2010). In addition, different mechanisms were described for the peak of paraesthesia during and after ischaemia, (Kuwabara, 2008). During ischaemia, paraesthesia appear to be of low frequency ('buzzing'), and have been attributed to persistent Na+ conductances (Kiernan & Bostock, 2000; Han et al., 2008, 2009, 2010). In the post-ischaemic period, the discharges are typically of high frequency, occurring in recurrent bursts, attributed to inward K+ currents. The origin of such activity appears to be rapidly adapting or Meissner's corpuscle mechanoreceptor fibres (Ochoa & Torebjork, 1980; Kuwabara, 2008; Hann et al., 2010). Additional modifying factors including stretch sensitive channels (Hamill, 2006; Hann et al., 2010) and morphological changes involving the axonal membrane (Clarke et al., 2007; Hann et al., 2010) cannot be excluded.
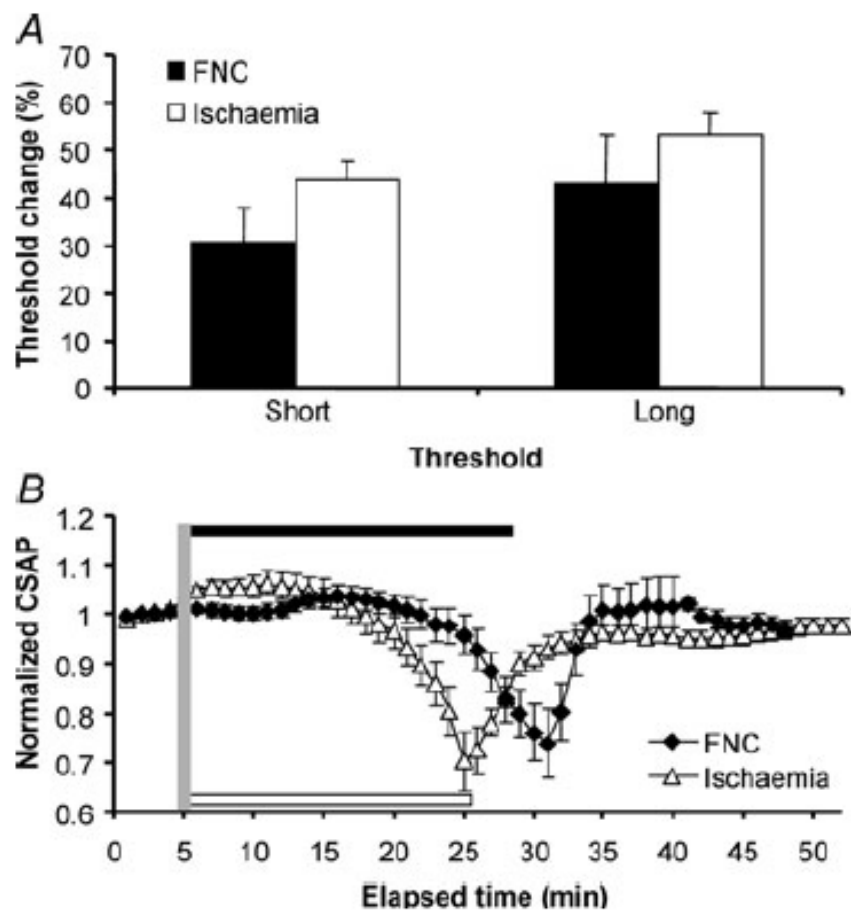
Fig. 4. Comparison between FNC applied to the wrist and ischaemia applied to the upper limb for associated threshold and supramaximal response. **A**, the maximal threshold change achieved following release of compression and ischaemia. **B**, normalized compound sensory action potential(CSAP) amplitude, with similar reductions achieved for both FNC (filled diamonds) and ischaemia (open diamonds). Horizontal bar indicates period of FNC (filled) or ischaemia (open), and grey vertical bar represents the period to achieve compression. Copy permission from publisher (John Wiley and Sons) via Copyright Clearance Center's RightsLink service from the article by Hann S.E, J Physiol 588.10 (2010) pp 1737–1745.

1.1.4 Mechanisms of paresthesia in dental procedures

The mechanism of paresthesia in dental procedure depend on the pharmacology of the dental local anesthetics and their local action. These local anesthetics are classified into esters and amides based on the bond hydrolyzed in metabolic degradation and elimination in the human body (Ritchie & Greene, 1985; Nickel, 1990). The hydrolysis of the ester or amide bond, which is joining the three parts of the local anesthetics molecule, the aromatic (hydrophobic), the alcoholic (hydrophilic) and tertiary amino groups, will results in the formation of an alcohol product which varies in structure and activity depending on the parent molecule (Morrison & Boyed, 1987; Nickel, 1990). This product is an active one, it will increase the length of the alcohol group and thus a greater anesthetic potency. The increase anesthetic potency of the alcohol group because of alcohol is neurotoxic, causing paresthesia (Littler, 1984; Shannon & Wiscott, 1974; Nickel, 1990).

1.1.5 Mechanisms of paresthesias arising from healthy axons

Paresthesia have been described to arise from healthy axons. Cutaneous afferents due to differences in their biophysical properties are more excitable than motor axons, such differences include more persistent Na (+) conductance which create a greater tendency to ectopic activity. These ectopic discharges have been described in normal afferents by different mechanisms such as hyperventilation, ischemia, release of ischemia, and prolonged tetanization. The alkaline shift produced by hyperventilation selectively increases the persistent Na (+) conductance, while the membrane depolarization produced by ischemia affects both transient and persistent Na (+) channels. Post-ischemic and post-tetanic paresthesia occur when hyperpolarization by the Na (+)/K (+) pump is transiently prevented by raised extracellular K (+). The electrochemical gradient for K (+) is reversed, and inward K(+) currents trigger regenerative depolarization. These mechanisms of paresthesia generation can account for paresthesia in normal subjects and may be relevant in some peripheral nerve disorders (Mogyoros et al., 2000).

2. Conclusion

Paresthesia as one of the presentation of neuropathic pain, had been shown to be caused by different mechanisms. Recent literature were able to elaborate more about the anatomical and physiological basis of paresthesia by using hydroxy-sanshool (sanshool), which is a natural plant alkylamide that induces numbing and robust tingling paresthesia in humans. Sanshool excites specific subtypes of cutaneous mechanoreceptors, it potently activates all ultrasensitive D-hair fibers and, to a lesser extent, unique populations of pressure-sensitive Aß fibers and low conduction velocity C fibers. Paresthesia was seen to be more apparent in rapidly adapting myelinated fibers than the slow one and that has been implicated in both injury- and disease-evoked paresthesia, as well as in post ischemic paresthesia. The cellular and molecular basis of paresthesia is most likely due to two pore potassium channel (KCNK), and not to transient receptor channels (TRPA1). Also, paresthesia generation in the two processes of ischemia and focal nerve compression (FNC) were different. In ischemia, the metabolic byproducts, such as H+, accumulate and potentially interfere with parameters that determine axonal excitability. But during FNC where focal ischaemia appeared to be the underlying mechanism, metabolites exerted less significant effects, as supported by the

rapid rate of CSAP recovery observed with release of FNC. More future study is needed in the field of molecular basis of paresthesia, as it seen to be the basis in normal axons in healthy human being.

3. Acknowledgement

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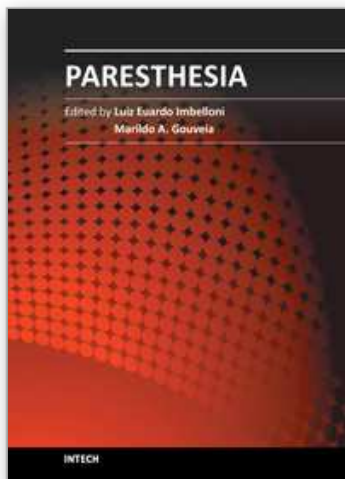
Paresthesia

Edited by Dr. Luiz Eduardo Imbelloni

Paresthesias are spontaneous or evoked abnormal sensations of tingling, burning, pricking, or numbness of a person's skin with no apparent long-term physical effect. Patients generally describe a lancinating or burning pain, often associated with allodynia and hyperalgesia. The manifestation of paresthesia can be transient or chronic. Transient paresthesia can be a symptom of hyperventilation syndrome or a panic attack, and chronic paresthesia can be a result of poor circulation, nerve irritation, neuropathy, or many other conditions and causes. This book is written by authors that are respected in their countries as well as worldwide. Each chapter is written so that everyone can understand, treat and improve the lives of each patient.

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