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Research Article

Pathophysiology of Pain

Siniša Franjić*

Independent Researcher, Europe

***Corresponding author:** Siniša Franjić, Independent Researcher, Europe.

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Abstract

Pain can be caused by stimulation of receptors on any part of the sensory nervous system only if the stimulus is strong enough to activate a series of pathophysiological changes in the body as part of the response to stress and trauma. Apart from stimuli, pain can occur spontaneously, for no apparent reason. Under normal circumstances, pain indicates a bodily injury or pathological process, but is also absent when large areas of the body are damaged. Therefore, it is disproportionate in intensity to the severity of the injury, and sometimes lags behind after complete tissue healing. The feeling of pain is unequivocally an unpleasant experience, but its value is immeasurable, so this warning encourages a protective attitude towards the injured or sick part of the body.

Keywords: Pain; Human body; Neuralgia; Tissue damage

Introduction

Pathophysiologic responses and adaptive changes to extensive tissue injuries function to keep up hemodynamics, minimize tissue injury, and promote healing [1]. However, the exact same neural and hormonal catecholamine responses that promote recovery in healthy young adults worsen pain intensity, promote cardiovascular instability and pulmonary dysfunction and increase infection risk in American Society of Anesthesia highrisk patients. Anesthesiologists have traditionally been the physician specialists most aware of pain physiology and pathophysiology and play the key role in initiating highly effective neuraxial, regional, and multimodal analgesia. Findings from randomized controlled trials and meta-analyses suggest that continuous epidural analgesia and regional analgesia can significantly reduce pain intensity scores, sympathoadrenal responses, and pulmonary complications. Although these techniques are more expensive, time-consuming, technically difficult to initiate and need continuous follow-up, their application in high-risk patients has been shown to reduce postsurgical morbidity, mortality, and time to hospital discharge.

Pain

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience related to actual or potential tissue damage, or described in terms of such damage" [2]. From this definition, it might seem reasonable to think that pain could be a pretty simple concept to understand; however, understanding pain pathophysiology is extremely complicated. Let's say you're preparing dinner in your kitchen, cutting up vegetables when the knife you're using slips and you're feeling this incredible painful sensation on your finger. You quickly drop the knife and pull your hand away. There's blood running from your finger and you're feeling a throbbing pain. Some people even feel light headed and nauseous. this complete process-the painful sensation of cutting your finger-was a really complex phenomenon. Pain is one amongst the body's defense mechanisms warning the brain that there could also be potential tissue damage about to occur, although pain could also be triggered with none physical damage to the body's tissues.

Our nervous system is related to everything our body does so as to function-from regulating your breathing, to controlling your muscles, to sensing pain. The system is split into the peripheral nervous system and therefore the central nervous system and both are involved within the pathophysiology of pain. The central nervous system consists of the brain, spinal cord, and optic nerves; the peripheral nervous system consists of sensory and motor nerves. The sensory nerves carry information from external stimuli to the spinal cord, brain, and motor nerves, then carry the information from the brain and spinal cord to organs, muscles, and glands. Motor nerves is subdivided into the somatic nervous system and also the autonomic nervous system.

Categorization

Pain can be Pathophysiologically categorized as nociceptive, neuropathic, sympathetically mediated, neuralgia, radicular, central, psychogenic, and referred [3]. However, most clinicians specifically focus on somatic, visceral, psychogenic, neuropathic, and referred pain when determining the diagnosis of patient's underlying pain.

Somatic and visceral pains are categorized as nociceptive pain, with the degree of pain experienced proportional to activation of afferent pain fibers. Superficial somatic pain is caused by injury to the skin or superficial tissues and produces a sharp, well-defined, localized pain of short duration. Deep somatic pain originates from ligaments, tendons, bones, blood vessels, fascia, or muscles and produces a dull, aching, poorly localized pain of longer duration than cutaneous pain. Visceral pain originates from bodys viscera, or organs, with pain usually more aching and cramping and will have longer duration than somatic pain. Visceral pain is usually extremely difficult to localize and will exhibit pain, where the feeling is localized to an unrelated site. Common manifestations of referred pain include cutaneous and deep hyperalgesia, autonomic hyperactivity, tenderness, and muscular contractions.

In contrast, neuropathic pain results from injury or disease to the peripheral or central nervous system and is characterized by pain out of proportion to tissue injury, dysesthesia, and signs of nerve injury detected during neurologic examination. As mentioned previously, psychogenic pain is characterized by pain existing with no apparent organic pathology despite extensive evaluation and commonly presents with pain inconsistent with the likely anatomic distribution.

Many disease processes present with pain, thus associated pain syndromes should be a part of the physician's differential diagnosis. Diabetic neuropathy may be a frequently encountered pain, characterized by burning, muscle cramps, lancinating pain, metatarsalgia, hyperalgesia, allodynia, loss of proprioception, tingling, and numbness in lower extremities. Human immunodeficiency virus (HIV) patients present with pain including neuropathic, somatic, visceral, and headache symptoms. Patients full of autoimmune disorder will often present with joint pain related to inflammation, achiness, and stiffness. Post-surgical pain is usually encountered and is sometimes somatic or visceral in nature. Infectious processes involving intra-abdominal organs are more likely to present with visceral pain while infectious processes involving the skin (e.g., herpes zoster) will present with somatic or neuropathic pain.

Pathophysiological Mechanisms

It is beyond the scope to explain thoroughly the complicated pathophysiological mechanisms involved in acute and, particularly, chronic pain [4]. To an outsized extent, most mechanisms are still unknown. However, it should be helpful to possess some understanding of the known basic mechanisms. The feeling of acute pain is that the results of activation of normal (not sensitized) nociceptors classified as Ad- or C-nociceptors, in keeping with the peripheral nerve fiber transmitting the neural impulses. Several classes of C-nociceptors in humans are identified by the technique of microneurography. Of special importance for pathophysiological mechanisms is also the discovery of mechanoinsensitive or silent nociceptors, i.e. nociceptors that don't seem to be activated by normal noxious stimuli but become active in an exceedingly state of injury, particularly following inflammation.

If a peripheral injury occurs, the C-nociceptors may become sensitized as a results of the effect of an outsized number of inflammatory substances released at the location of the injury. Sensitization of C-nociceptors may produce sensory changes that are restricted to the current site. The sensory changes that are produced are, first and foremost, a lowering of the warmth absolute threshold or allodynia to heat (allodynia is defined as pain produced by a nonpainful stimulus) and, second, hyperalgesia to heat (hyperalgesia is defined as an increased response to a stimulus that's normally painful). It's important to notice that sensory changes thanks to nociceptor sensitization are detectable within the positioning of injury alone, and not within the surrounding tissue.

In the event of acute pain, the incoming stimuli to the spinal cord are processed normally, and also the nociceptive impulses are omitted to second-order neurons and transmitted in central projection pathways. If sustained peripheral injury (or an injury to a peripheral nerve) occurs, an increased barrage of nociceptive impulses reaches the dorsal horn of the spinal cord and central sensitization may occur. This general term includes a sophisticated series of events in neurons within the dorsal horn. Windup, a cumulative increase of action potentials caused by nociceptive stimulation, is taken into account to be a possible first initial step that's mediated by the activation of N-methyl-D-aspartate (NMDA) receptors. A state of central hyperexcitability is produced, which is characterized in animal experiments by allodynia to light mechanical stimulation and a rise within the size of the peripheral receptive fields of the central neurons. It should not yet be possible to clarify all of the clinical symptoms, findings, and sensory abnormalities in patients with chronic pain using the speculation of central sensitization, but the demonstration of central hyperexcitability has had an amazing impact on the understanding of a number of the phenomena observed in patients with chronic pain. as an example,

allodynia to mechanical stimulation, which is usually encountered in neuropathic pain patients, and therefore the increase (over time) within the extent of the areas of pain are accredited to central hyperexcitability. Whether the occurrence of spontaneous and paroxysmal pain is also explained entirely or partly by the identical mechanisms remains an unresolved question. In general, a considerable amount of research is still needed to know fully the various aspects of clinical pain.

Traditionally, clinical pain syndromes are treated in keeping with the etiology of the pain (e.g. postherpetic neuralgia, painful diabetic neuropathy). thanks to the present knowledge of the possible common neurophysiological mechanisms involved in different pain entities, It's recently been suggested that, rather than that specialize in the various etiologies, it would be possible to assess and treat pain in keeping with the underlying neurophysiological mechanisms involved, i.e. mechanism-based classification of pain.

Spinal Mapping

The anatomy of the spine can undergo numerous changes that lead to pain [5]. Various styles of chronic pain, including pain of the neck, back, or extremities, may indicate one or more spinal pathologies. Differing treatments is also used depending on the pain generator, including radiofrequency neurotomy, corticosteroid injection, decompression, and neurostimulation. Utilizing an appropriate treatment is also challenging, given frequently comorbid spinal pathologies and potentially overlapping symptoms. Spinal mapping enables the identification and treatment of the suitable pain generator. Most spinal mapping techniques and associated interventional procedures tend to be minimally invasive, with low risk, but like any spinal intervention, each patient must be carefully examined for any associated pathophysiological conditions or other contraindications to their use:

a. Coagulopathy, platelet count of less than 100,000

b. Implants (pacemaker, neural implants, etc.)

c. Skin infection over placement site

d. Allergic reaction to local anesthetics or the other medication provided during procedure

e. Malignancy near placement site

f. Hypovolemia

g. Sepsis

h. Spinal abnormalities or decreased spinal stability

i. Pregnancy

j. Renal insufficiency

k. Chronic liver dysfunction

l. Cerebrovascular disease

m. Increased intracranial pressure

n. Patient refusal

Pathway

The pain pathway starts within the periphery with nociceptors within the type of free nerve endings [6]. The afferent nerve fibres from nociceptors are either non-myelinated C-fibres or within the myelinated A-delta group. They travel in peripheral nerves via dorsal roots to the spinal cord or via portions of the cranial nerves V, VII, IX and X to the medulla oblongata, where they synapse within the superficial layers and cross over within some segments to ascend within the anterolateral compartment to the thalamus (spinothalamic tract) or to the brain stem (spino-tectal tract). The relatively smaller component of the spino-tectal fraction terminates within the intermediate and deep layers of the superior colliculus whereas the larger mesencephalic proportion also includes spinal projections to the periaqueductal grey substance (spinoperiaqueductal fibres). The periaqueductal grey is that the site of a high concentration of μ-receptors activating powerful descending inhibition on the pain pathway. The spinothalamic tract terminates within the ventroposterolateral nucleus (VPL) of the thalamus. Corresponding anatomy applies to the sensory fraction of the cranial nerves with termination within the ventroposteromedial nucleus (VPM). Third order neurones from the thalamus hook up with variety of cortical and sub-cortical areas, including the somatosensory areas SI and SII, the cingulate cortex, the hypothalamus, and other areas. The somatosensory area SI is found on the postcentral gyrus where the contralateral half the body is represented within the variety of the homunculus. In chronic pain, many other areas of the brain also are involved during a complex manner that's not always fully understood.

At each synaptic level there's the potential for modulation which has been well described at the level of the dorsal horn.

Nociceptive free nerve endings are excitable by stimuli that are likely to damage tissue, leading to the discharge of intracellular substances into the extracellular environment. Receptors are either modality specific like heat receptors or pressure receptors or they'll respond to a variety of noxious stimuli (polymodal nociceptors). Low pH, as observed during ischaemia, may be a powerful stimulus for nociceptors. A separate category contains the so-called silent nociceptors which can be activated by inflammation. Distension may be a powerful stimulus for nociception in hollow organs.

Heat sensitive nociceptor-neurones contain the TRPV1 receptor in their cell membranes. Capsaicin binds closely to the current receptor and elicits a sensation of burning pain. At sufficiently high concentration, topically applied capsaicin will, after initial strong burning sensation, inactivate TRPV1 receptors, leading to alleviation of pain in conditions like postherpetic neuralgia, diabetic neuropathy, or neuropathic pain in HIV.

Repeated noxious stimulation damages cells within the vicinity of nociceptors entailing the discharge of intracellular material into the extracellular space. The resulting inflammation causes peripheral sensitization, meaning that there'll be an increased number of action potentials within the primary afferent nerve fibre supplying a nociceptor in response to stimulation. Clinically,

peripheral sensitization expresses itself as Allodynia (increased response of neurones following normally non-painful stimuli) or Hyperalgesia (enhanced pain response). Peripheral sensitization has been described for nociceptors within the skin in addition as visceral, muscle, and joint nociceptors.

Neuralgia

The pathophysiology regarding tic douloureux continues to be debated [7]. Originally, TN was attributed to abnormal central nervous system discharges like seizures as antiepileptic drugs were the primary successful treatment. Currently, the foremost commonly advanced mechanism of TN involves vascular compression of the nerve at the dorsal root entry zone to the pons, where central oligodendrocytes cede to Schwann cells for production of myelin. Evidence for the compression is provided by the curative benefit many patients experience with microvascular decompression of the trigeminal nerve. Biopsies from the trigeminal nerve dorsal root entry zone (DREZ) have shown compression of the nerve with loss of myelin.

Trigeminal neuralgia (TN) must be distinguished into two subsets: typical or TN1, which is that the more common form, involving intermittent intense lancinating pain for brief moments, and atypical or TN2, which shares symptoms with the standard form, but patients also develop a constant burning pain at baseline. TN type 2 has been described as a chronic sort of TN type 1, as a natural history study shows progression of intermittent pain to constant burning pain with intermittent eruptions. Patients with TN2 were found to possess increased central processing from stimulation than TN1 patients, likely representing overstimulation at the level of the medulla. This study implies central plasticity at wide-dynamic range second-order neurons or third-order neurons.

V2 and V3 dermatomes contain the foremost common trigger points and are the areas of greatest symptomology, and superior cerebellar artery is that the presumably culprit of compression at the dorsal root entry zone. Anatomical studies demonstrate the rostral, superior projection of alpha fibers from V2 and V3 to the most trigeminal sensory nucleus within the pons, which might be the positioning of compression for superior cerebellar artery. The upper density of Aδ fibers at this location may explain the lancinating pain of typical TN. C fibers mostly project to the caudal medulla, which can be associated with the increased central processing in atypical TN.

Other causes of trigeminal neuralgia exist beyond the idiopathic form discussed above like cerebellopontine angle tumors and multiple sclerosis|sclerosis|induration|degenerative disorder. TN caused by CPA tumors is assumed to possess an identical mechanism to neurovascular compression, as resection of tumor can provide relief of symptoms. multiple sclerosis is a demyelinating disease, so it causes TN via an axonopathy that's witnessed with chronic compression in vascular compression. MS plaques are shown to involve the trigeminal nerve at the DREZ.

Glossopharyngeal neuralgia may be a condition of hyperactivity of the glossopharyngeal nerve; therefore the identical theories of pathophysiology apply here as in TN. It consists of intermittent, severe sharp pain affecting the sensory distribution of the ninth and tenth cranial nerve, particularly the throat, oropharynx, base of the tongue, ear canal, and areas inferior to the angle of the mandible. Many cases of GPN are found to possess vascular compression of the ninth nerve at the dorsal root entry zone to the medulla. Other kinds of neuronal damage and compression, including post-traumatic, Eagle's syndrome, postradiation, tumor compression, and multiple sclerosis, can produce symptoms of glossopharyngeal neuralgia.

Occipital neuralgia can present with strikingly similar symptoms to TN but covering the superior and inferior occipital nerves. Nerve dysfunction, mostly from compression, is that the cardinal etiology of the disease process. Pathophysiology can include vascular compression from aberrant courses of the posterior inferior cerebellar artery or vertebral artery of the C1 and C2 nerve root, multiple sclerosis, C2 myelitis, tumor, or spondylosis of the C1/2 joint with tonic contraction and compression. Postherpetic neuralgia is sustained pain after acute varicella zoster viral (VZV) infection and resolution of the rash. VZV can remain latent within the trigeminal ganglion of patients who have experienced chicken pox within the past.

Postherpetic neuralgia exists within the same dermatome of the acute zoster infection and causes allodynia, hyperalgesia, constant burning, and intermittent lancinating common to other neuropathic diseases. The inflammatory process of reactivation presumably creates peripheral and central sensitization leading to unpleasant symptoms. Of cranial herpes zoster, 75% occur within the V1 (ophthalmic) division due to an unknown predilection for the latent VZV to settle within the ophthalmic portion of the gasserian ganglion. the variability of symptoms is also explained best by the inconsistent proportional destruction of Aβ, Aδ, or C fibers.

Traumatic injuries to the afferent sensory nerves of the face and head can cause neuropathic pain. After transection of peripheral sensory nerves, the transected axons begin Wallerian degeneration and form neuromas. Neuromas may also form after any damaging process including compression, stretch, postsurgical scar, and irritation. Neuromas are implicated in creating neuropathic pain. At the location of neuromas, the axons are highly disorganized in shape and myelinations. Several adjacent axons might not be myelinated by Schwann cells which may result in ectopic discharge and ephaptic cross-talk, producing the symptoms of neuropathic pain. Also, inflammatory results from traumatic nerve injuries may end up in peripheral and central sensitization as discussed above.

Tissue Damage

Acute pain reflects potential or established tissue damage [8]. It's now recognized that acute pain is mediated by peripheral nociceptors, which are stimulated by traumatic and inflammatory mechanisms. the most effective way to treat acute pain is to attenuate tissue injury and forestall or reduce the inflammatory and neuropathic stimulation. Administration of nonopioid analgesics/adjuvants can reduce inflammatory responses and peripheral

neuropathic sensitization, thereby minimizing nociceptive pain and opioid dose requirements. Prophylactic, preventative measures designed to reduce tissue injury (noninvasive surgery) and inflammation (nonsteroiday antiinflammatory drugs [NSAIDs] and other anti-inflammatory agents) are important during this context. The importance of gentle and minimally traumatic surgery should even be mentioned; for instance, endoscopic procedures are related to significantly less tissue injury and are generally less painful than open invasive surgery. Also, nonpharmacological measures to further reduce tissue damage, inflammation, and nerve stimulation should be provided, particularly when the pain-provoking process is ongoing. Examples are limb elevation, compression, and localized cooling to scale back inflammation and edema.

Analgesics have variable sites of activity and might interact with receptors, local and humoral mediators in injured tissues, or on nerves and nerve endings that transmit nociceptive stimuli to the central nervous system. Analgesics also are effective to modulate the pain impulse at the level of the spinal cord and at cortical level.

Nociceptive pain is related to tissue damage or potential tissue damage and may be caused by a range of stimuli [9]. It's broken down into two types; somatic and visceral. The duration of symptoms determines if the pain is acute (generally present 3–6 months) or chronic (>6 months). Somatic and visceral pain have several defining characteristics that help distinguish each from the opposite which include localization, quality of pain and evocative stimuli.

Opioids

Opioids can be given by a large type of routes [10]. These include oral, intranasal, transbuccal (sublingual), transdermal, and rectal routes of administration. More common methods of opioid administration for acute pain, especially within the perioperative setting, are intramuscular, intravenous, and neuraxial (intrathecal and epidural). These methods offer rapid onset and better titratability. Emerging technologies for sublingual (sufentanil) and transdermal (fentanyl) administration appear promising. Opioid agonist analgesics are indicated within the treatment of mild, moderate, or severe acute pain. Mild acute pain is treated with oral opioids like hydrocodone, oxymorphone, and oxycodone. These drugs are frequently given after moderate to severe pain symptoms have subsided and discharge from the recovery room or facility is anticipated. they're often combined with an NSAID (Nonsteroidal anti-inflammatory drugs) like aspirin or acetaminophen and their dosing is usually limited by the nonopioid content. Oral opioids are subject to extensive first-pass effect within the liver and don't seem to be a first-line choice for moderate to severe acute pain because their bioavailability is low. Intramuscular injections (morphine, hydromorphone) are a preferred route of administering opioid analgesics. Serum concentrations of opioids may vary greatly with this modality as uptake is erratic and dependent on perfusion of the positioning. Despite these drawbacks, intramuscular injections of opioids are considered in select situations (lack of IV access). Intravenous opioids (morphine, hydromorphone, fentanyl) are commonly used perioperatively and in intensive care units to treat moderate to severe acute pain. The sedation related to morphine typically precedes its analgesic effect. this can be a crucial clinical consideration to avoid "stacking" doses which can end in oversedation and respiratory depression. Morphine is conjugated (metabolized) within the liver with glucuronic acid into morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) before renal excretion. M6G may be a potent mu receptor agonist, whereas M3G is pharmacologically inactive. the accumulation of M6G may produce respiratory embarrassment in patients with renal disease. Hydromorphone may be a logical choice for renal patients because its metabolism doesn't produce (M6G). Hydromorphone metabolism generates a vigorous metabolite (hydomorphone-3-glucuronide) which will exhibit excitatory properties. Patient-controlled analgesia (PCA) allows patient titration of the opioid against their own pain requirements and eliminates the drawbacks related to PRN dosing like staff availability and subjective staff interpretations of patient's pain. PCA requires patient cooperation and thus appropriate selection of candidates for PCA therapy is indicated. Patient acceptance of PCA has been high, and studies demonstrate less total drug consumption with improved postoperative respiratory function compared to patients receiving conventional as needed or scheduled dosing by trained staff. Continuous ("basal rate") PCA infusions are shown to supply a better incidence of respiratory depression particularly in opioid-naïve patients, and their use during this group isn't recommended. Morphine, hydromorphone, fentanyl, and sufentanil are all common choices for intravenous PCA. Fentanyl and sufentanil don't have any active metabolites and are used successfully in patients receiving intravenous PCA. Sufentanil provides better analgesia with less respiratory depression than fentanyl when used for intravenous PCA. Intrathecal and epidural opioids provide excellent analgesia and rapid onset. Morphine, fentanyl, and sufentanil are commonly used for this purpose. Morphine's lack of lipid solubility provides extended analgesia for 12–24 h. This property makes one-time dosing or repeat dosing through an epidural catheter with morphine convenient. Fentanyl and sufentanil provide analgesia for about 2 h when administered neuraxial. they're commonly given along with a local anesthetic (ropivacaine, lidocaine) to speed onset of spinal analgesia. Their short duration of effect compared with morphine limits their usefulness as primary modalities for postoperative analgesia when administered as a single-shot injection; however, epidural PCA with either sufentanil or fentanyl via an epidural catheter has been used successfully in patients requiring postoperative analgesia.

Conclusion

The pain can be superficial and deep, depending on the location of the painful stimulus. Acute pain is most often distinguished from chronic pain. Acute pain is relatively short-lived. Acute pain is a warning to a person to protect themselves from damage. chronic pain lasts for six months or more and is most often a sign of some chronic illness. The experienced intensity of pain is the result of a complex interaction of neurophysiological, psychological and sociocultural factors. The sensation of pain becomes an experience when the stimulus ends in the parietal part of the cerebral cortex,

but also in some other parts of the central nervous system. The mechanism of pain begins with the appearance of nerve impulses in free nerve endings due to certain intense stimulation. Free nerve endings are branches of sensory nerve fibers found in the superficial layers of the skin, hair follicles, artery walls, joint surfaces, and many tissues of internal organs. They are not specific pain receptors as they receive other qualities of sensation. With weaker stimulation, there is a feeling of warmth, cold, touch, pressure, and only strong intensities of stimulation lead to the appearance of painful impulses. It is very important to emphasize that these impulses travel through the nervous system, which is already influenced by past experience, culture, expectations and many other factors.

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Conflict of Interest

No Conflict of interest.

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