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REVIEW ARTICLE

Neuronal Cell Mechanisms of Pain

Mécanismes Cellulaires Neuronaux de la Douleur

[1]*C. N. S. Nwonu

ABSTRACT

BACKGROUND: Pain is a distressful feeling that is frequently caused by intense or damaging chemical, thermal or mechanical stimuli. It can also occur without tissue damage or injury, although the patient makes reference to it. Pain is one of the body's most important communication tools, and a protective mechanism by which the body responds to noxious or harmful stimuli. The cascade of molecular events that culminate in the experience of pain in an individual is a complex neural phenomenon in which inordinate (excess) noxious peripheral stimuli are processed.

OBJECTIVE: The work discussed comprehensively the current knowledge and the mechanistic understanding that underlies pain and analgesia, as well as the clinical correlations.

METHOD: The strategy for the narrative review was carried out in works published in journals and other materials using original research articles, review articles, case reports, and standard pharmacology and pain text books. Electronic databases *viz*. scopus, science direct, pubmed, medline, and directory of open access journals were searched for relevant articles. Research works on the mechanisms of pain were identified for selection. Articles and works identified were those written in English and published between the period (1999 – 2020). Literature searches also included the scanning of references of journal articles.

RESULT: Over one hundred and seventy-five journal articles and other works were identified. Many of the studies had the same titles. Eleven materials consulted were non-journal articles and text books, while 22 articles were extracted and reviewed after screening of the titles and abstracts, and in consonance with the selection criteria.The multi-stage biochemical and physiological processes transform nociceptive information (excess energy) generated from the primary afferent nerve fibres (first order neurones) - nociceptors (C-fibres and Aδ-fibres) in the periphery into electrical energy or pain impulses. The electrical impulses are then conducted by the axons of the first order neurones and terminate (or synapse) with intrinsic dorsal horn neurones (the first relay station in the transmission of nociceptive signals from the periphery to the brain), and the upper part of the spinal cord (substantia gelatinosa), from where axons of the second order neurones in the Rexed laminae receive the primary afferent input, and further propagate the signals to the higher brain centres (e.g., sub-cortical and cortical structures) by crossing the midline at the anterior white commissure to the contralateral (opposite) side of the spinal cord *via* the spinothalamic tracts and other ascending pathways (e.g., spinoreticular and spinomesencephalic tracts). The second order neurones synapse in the ventral posterolateral nucleus of the thalamus, from where third order neurones arise and transmit the nociceptive signals to various anatomical regions of the cortex. The third order neurones project *via* the posterior limb of the internal capsule to terminate in the ipsilateral (on the same side) post-central gyrus (primary somatosensory cortex). The generation, transduction, transmission and ascent of these neuronal impulses to the higher centres are modulated by the descending control pain pathway (otherwise known as the efferent analgesic system), which is both inhibitory and facilitatory in function, and ultimately results in the experience of pain. Terminal nerve endings located at sites of tissue injury (or inflammation) exhibit exaggerated neuronal responses that cause increased cell membrane excitability, a condition referred to as peripheral sensitisation, as well as a heightened activity of the pain circuitry and pain signal processing in the central nervous system. These phenomena are responsible for the abnormal transmission of pain impulses and experience (e.g., hyperalgesia and allodynia) that accompany certain clinical conditions.

CONCLUSION: Clinical pain is a serious public health concern, and has a multiplicity of causes. The mechanistic understanding of pain is a step-wise complex biological event, which has provided insight to explore better therapeutic options with a view to improving the quality of life and living in individuals with clinical pain conditions. **WAJM 2022; 39(10): 1075–972.**

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Keywords: Pain circuitry, Pain perception, Pain signal, Peripheral nociceptors, Transmission of pain impulse.

RÉSUMÉ

CONTEXTE: La douleur est une sensation pénible qui est souvent causée par des stimuli chimiques, thermiques ou mécaniques intenses ou dommageables. Elle peut également survenir sans lésion ou dommage tissulaire, même si le patient y fait référence. La douleur est l'un des outils de communication les plus importants de l'organisme et un mécanisme de protection auquel le corps répond aux stimuli nocifs ou nuisibles. La cascade d'événements moléculaires qui aboutit à l'expérience de la douleur chez un individu est un phénomène neuronal complexe, dans lequel des stimuli périphériques nocifs excessifs sont traités.

OBJECTIF: L'ouvrage examine de manière exhaustive les connaissances actuelles et la compréhension mécaniste qui sous-tendent la douleur et l'analgésie, ainsi que les corrélations cliniques.

MÉTHODES: La stratégie de l'examen narratif a été menée dans des travaux publiés dans des revues et d'autres documents en utilisant des articles de recherche originaux, des articles de synthèse, des rapports de cas et des manuels standard de pharmacologie et de douleur. Des bases de données électroniques, à savoir scopus, science direct, pubmed, medline et le répertoire des revues à accès libre, ont été consultées pour trouver des articles pertinents. Les travaux de recherche sur les mécanismes de la douleur ont été identifiés pour être sélectionnés. Les articles et travaux identifiés étaient ceux écrits en anglais et publiés entre 1999 et 2020. La recherche documentaire comprenait également le balayage des références des articles de journaux.

RÉSULTATS: Plus de cent soixante-quinze articles de journaux et autres travaux ont été identifiés. Beaucoup d'études avaient les mêmes titres. Les processus biochimiques et physiologiques à plusieurs étapes transforment les informations nociceptives (excès d'énergie) générées par les fibres nerveuses afférentes primaires (neurones de premier ordre) - nocicepteurs (fibres C et fibres A?) dans la périphérie en énergie électrique ou en impulsions de douleur. Les impulsions électriques sont ensuite conduites par les axones des neurones de premier ordre et se terminent (ou font synapse) avec les neurones intrinsèques de la corne dorsale (la première station de relais dans la transmission des signaux nociceptifs de la périphérie au cerveau), et la partie supérieure de la moelle épinière (substantia gelatinosa), d'où les axones du neurone de second ordre dans les lamines Rexed reçoivent l'entrée afférente primaire, et propagent ensuite les signaux aux centres cérébraux supérieurs (par ex, structures sous-corticales et corticales) en traversant la ligne médiane au niveau de la commissure blanche antérieure jusqu'au côté contralatéral (opposé) de la moelle épinière via les voies spinothalamiques et d'autres voies ascendantes (par exemple, les voies spinoréticulaires et spinomésencéphaliques). Les neurones de deuxième ordre font synapse dans le noyau ventral postérolatéral du thalamus, d'où naissent les neurones de troisième ordre qui transmettent les signaux nociceptifs à diverses régions anatomiques du cortex. Les neurones de troisième ordre se projettent via le membre postérieur de la capsule interne pour se terminer dans le gyrus post-central ipsilatéral (du même côté) (cortex somatosensoriel primaire). La génération, la transduction, la transmission et la remontée de ces impulsions neuronales vers les centres supérieurs sont modulées par la voie descendante de contrôle de la douleur (également appelée système analgésique efférent), dont la fonction est à la fois inhibitrice et facilitatrice, et qui aboutit finalement à l'expérience de la douleur. Les terminaisons nerveuses situées sur les sites de lésions tissulaires (ou d'inflammation) présentent des réponses neuronales exagérées qui provoquent une augmentation de l'excitabilité de la membrane cellulaire, une condition appelée sensibilisation périphérique, ainsi qu'une activité accrue des circuits de la douleur et du traitement du signal de la douleur dans le système nerveux central. Ces phénomènes sont responsables de la transmission anormale des impulsions et de l'expérience de la douleur (par exemple, l'hyperalgésie et l'allodynie) qui accompagnent certaines conditions cliniques.

CONCLUSION: La douleur clinique est un grave problème de santé publique, et ses causes sont multiples. La compréhension mécaniste de la douleur est un événement biologique complexe et progressif, qui a permis d'explorer de meilleures options thérapeutiques en vue d'améliorer la qualité de vie des personnes souffrant de douleurs cliniques. **WAJM 2022; 39(10): 1075–972.**

Mots clés: Circuit de la douleur, Perception de la douleur, Signal de la douleur, Nocicepteurs périphériques, Transmission de l'impulsion douloureuse.

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Abbreviations: CNS, Central Nervous System; **SG,** Substantia Gelatinosa; IL, Interleukin; **IFN,** Interferon; **GPCR,** G-Protein Coupled Receptor; **NMDA,** N-Methyl-D-Aspartate; **PAG,** Peri-Aqueductal Gray; **RVM,** Rostral Ventromedial Medulla.

INTRODUCTION

Pain is a subjective and an unpleasant sensory and emotional experience associated with actual or potential tissue damage (IASP, 2005; Swieboda *et al*., 2013). Experience of pain is dependent on the strength of the stimulus, individual susceptibility and resistance to pain. The process leading to pain is a complex step-wise biological phenomenon, involving neuro-transmitters and inflammatory mediators. Nociception is the perception of a noxious stimulus (i.e., transmission of a noxious peripheral stimulus to the spinal cord and the brain). Nerve injury and inflammation can induce the appearance of macrophages and lymphocytes. When these cells are activated, they release significant amounts of cytokines (e.g., IL-4, IL-10, IL-17 and IFN-γ). Nociceptors (free nerve endings that detect painful stimuli) are sensory receptor proteins that are sensitive to actual or potential tissue damage or trauma. These receptors are the free endings (primary afferent) of nerve fibers that are widely distributed in the peripheral tissues and organs, and have high thresholds for stimulation (Schug *et al*., 2011). Pain receptors are sensitive to mechanical, thermal or chemical stimuli. The application of noxious stimulus to these receptors results in the processing into an electrical signal. This impulse is conducted by nerve fibres into the spinal cord and then to the brain (Swieboda *et al*., 2013). Nociception, therefore, propagates signal regarding tissue damage to the CNS (i.e., transmission of a noxious peripheral stimulus to the spinal cord and the brain). Precisely how this signal is ultimately perceived as pain by the individual is obscure. For instance, there can be pain without nociception (e.g., phantom pain following surgical amputation of a limb) and nociception without pain. On the other hand, perception refers to the interpretation of sensory information. Nociceptors (free nerve endings that detect painful stimuli) are sensory receptor proteins that are sensitive to actual or potential tissue damage or trauma. These receptors are the free endings (primary afferent) of nerve fibers that are widely distributed in the peripheral tissues and organs, and have high thresholds for stimulation (Schug *et al*., 2011). Nociceptors do not respond to non-painful stimuli and have no inherent adaptive mechanisms. In other words, constant application of nociceptive stimuli to a nociceptor results in repetitive firing, and in certain circumstances, the continuous stimulation may decrease the threshold for response. Nociceptors are of two major types:

1. High threshold mechanoreceptors (nociceptors that respond to mechanical stimuli, such as pin-prick and pinch) which activate larger myelinated fast conducting Aδ-fibres (3–8 μ) and transmit a well-localised sharp or pricking sensation (or pain) at 15–20 metres *per* second (Swamy, 2005; Barar, 2006; Schug *et al*., 2011).

2. Polymodal nociceptors (a sub-type of peripheral sensory neuron) stimulate smaller non-myelinated slowly conducting C-fibres (<1.5 μ). The polymodal nociceptors not only respond to mechanical stimuli, but are also activated by thermal and chemical stimuli, e.g., hydrogen ions, potassium ions, bradykinin, serotonin, adenosine triphosphate and prostaglandins (Barar, 2006; Schug *et al*., 2011; Rang *et al*., 2019). These nociceptors respond to excessive pressure, extremes of temperatures (>42 °C and <18 °C), and algogenic (pain producing) substances. Polymodal nociceptors are slow to adapt to strong and intense pressure, and display thermal sensitisation (Swamy, 2005). The C-fibres transmit a less well-localised persistent aching or burning sensation at 1–2 metres *per* second that outlasts the initial (trigger) stimulus (Schug *et al*., 2011).
3. Silent nociceptor is a pain (nociceptive) receptor that responds to stimuli only during inflammatory states (Swamy, 2005).

OBJECTIVE

The work discussed comprehensively the current knowledge and the mechanistic understanding that underlies pain and analgesia, as well as the clinical correlations.

METHODS

The strategy for the narrative review was carried out in works published in journals and other materials using original research articles, review articles, case reports, and standard pharmacology and pain text books. Electronic databases *viz.* scopus, science direct, pubmed, medline, and directory of open access journals were searched for relevant articles. Research works on the mechanisms of pain were identified for selection. Articles and works identified were those written in English and published between the period (1999 – 2020). Literature searches also included the scanning of references of journal articles.

RESULTS AND DISCUSSION

Over one hundred and seventy-five journal articles and other works were identified. Many of the studies had the same titles. Eleven materials consulted were non-journal articles and text books, while 22 articles were extracted and reviewed after screening of the titles and abstracts, and in consonance with the selection criteria.The multi-stage biochemical and physiological processes transform nociceptive information (excess energy) generated from the primary afferent nerve fibres (first order neurone) - nociceptors (C-fibres and Aδ-fibres) in the periphery into electrical energy or pain impulses. The electrical impulses are then conducted by the axons of the first order neurones and terminate (or synapse) with intrinsic dorsal horn neurones (the first relay station in the transmission of nociceptive signals from the periphery to the brain), and the upper part of the spinal cord (substantia gelatinosa), from where axons of the second order neurone in the Rexed laminae receive the primary afferent input, and further propagate the signals to the higher brain centres (e.g., sub-cortical and cortical structures) by crossing the midline at the anterior white commissure to the contralateral (opposite) side of the spinal cord *via* the spinothalamic tracts and other ascending pathways (e.g., spinoreticular and spinomesencephalic

tracts). The second order neurones synapse in the ventral posterolateral nucleus of the thalamus, from where third order neurones arise and transmit the nociceptive signals to various anatomical regions of the cortex. The third order neurones project *via* the posterior limb of the internal capsule to terminate in the ipsilateral (on the same side) post-central gyrus (primary somatosensory cortex). The generation, transduction, transmission and ascent of these neuronal impulses to the higher centres are modulated by the descending control pain pathway (otherwise known as the efferent analgesic system), which is both inhibitory and facilitatory in function, and ultimately results in the experience of pain. Terminal nerve endings located at sites of tissue injury (or inflammation) exhibit exaggerated neuronal responses that cause increased cell membrane excitability, a condition referred to as peripheral sensitisation, as well as a heightened activity of the pain circuitry and pain signal processing in the CNS. These phenomena are responsible for the abnormal transmission of pain impulses and experience (e.g., hyperalgesia and allodynia) that accompany certain clinical conditions.

A. Cellular Mechanisms of Pain

Neurones are the primary component that connect, receive and process all the nociceptive information generated from transduction, transmission and modulation in both the peripheral and central nervous systems (Yam, *et al*., 2018). Three types of neurone exist in the body; sensory neurones (afferent neurones), interneurone (functions to relay the signals between afferent and efferent neurones), and the motor neurones (efferent neurones). All neurones are electrically excitable and consist of the same division of parts: soma, axon (either myelinated or unmyelinated), and dendrites (Yam *et al*., 2018). Neurones are connected with each other to form complex neural networks (circuitry) in the body, where the chemical and electrical signals are transmitted *via* specialised connections known as synapses. The synaptic signals sent from a neurone are received by the dendrites and soma (synaptic transmission) of another neurone (Yam *et al*., 2018). The series of activity that culminate in the experience of pain in an individual is a complex biological multi-stage neural event, in which inordinate noxious peripheral stimulus is processed. Pain is produced by tissue damage or injury which liberates chemicals (e.g., bradykinin, histamine, prostaglandins, acetylcholine, lactic acid, serotonin and potassium) adjacent to nerve endings. These chemicals initiate electrical (pain) impulses, an indication that stimulation of nociceptive endings in chemically mediated. Excessive stimulation by nociceptive stimuli (heat or mechanical) can cause acute pain. However, persistence of the pain post removal of the stimulus, or the pain resulting from inflammation or ischaemic changes in tissues demonstrates alteration in the chemical *milieu* of the pain afferents (McMahon *et al*., 2006). The perception of pain involves receptors (nociceptors), conductors and integrative cerebral mechanisms (Barar, 2006). These multi-stage processes include:

1. ***Transduction***

   This is the initial step (stage I) in the processing of pain signals and involves the activation and sensitisation of nociceptors. Transduction converts the energy from a noxious (harmful) thermal, mechanical, or chemical stimulus into electrical energy (nerve impulses or signals) by nociceptors. It is the conversion of noxious peripheral stimuli into electrical signals by sensory receptors known as nociceptors. Pain is associated with impulse activity in small diameter primary afferent fibres (C- and A-delta) of the peripheral nerves (Barar, 2006; Rang *et al*., 2019). These nerves have endings or terminals in the peripheral tissues and are activated by various nociceptive stimuli (Julius and Basbaum, 2001; Julius and McCleskey, 2006). The signals from the nociceptors travel along these two fibers: a slow conducting unmyelinated C-fibers and a myelinated, and more rapidly conducting A-delta fibers. When there is injury to the tissues, cells are broken down, and subsequently the liberation of tissue by-products and inflammatory mediators *viz*. prostaglandins, substance P, bradykinin, histamine, serotonin, cytokines (Byers and Bonica, 2001). Many of these mediators activate the nociceptors to generate nerve impulse, and then sensitise the nociceptors by increasing their excitability and frequency of discharge. Activation of the nociceptors may cause nociceptive pain. A third type of primary afferent fibre, the Aβ-fibre conducts low intensity mechanical stimuli which convey tactile (touch) sensation, and not pain. However, in pathological conditions associated with chronic pain, they become involved in the transmission of pain (Schug *et al*., 2011). Peripheral (nociceptor) sensitisation amplifies neurotransmission (signal propagation), and thus contributes to central sensitisation and clinical pain. The unmyelinated C-fibers convey dull, poorly localised (diffuse), burning pain while the myelinated A-delta fibers convey sharp, well-localised pain. Both fibers convey nociceptive signals from the skin, muscle, and the viscera. The spinal cord is the first relay station in the transmission of nociceptive information from the periphery to the brain. Pain is transmitted by primary afferents (first order neurones), which have their cell bodies in the dorsal root ganglion (DRG), and terminate in the dorsal horn of the spinal cord (Schug *et al*., 2011). The neurotransmitters produced in cell bodies are the same at the peripheral and central nerve endings, and are released at both terminals to participate in the production of pain signals peripherally and to facilitate processes that further lead to pain perception centrally (Schmelz and Petersen, 2001). Neurotransmitter substances released from the peripheral nerve terminals of afferent fibres exert a physiological effect on the afferent neurones. Peripheral release of neurotransmitters triggers

axon reflex which induces peripheral changes that clinically indicates pain (e.g., erythema or redness, swelling, and tenderness) (Schmelz and Petersen, 2001). Studies have shown that opioid receptors located on peripheral nerve endings when activated by endogenous opioid peptides (e.g. enkephalins) or exogenous opioids (e.g. morphine) cause inhibition of afferent neuronal firing (Vanderah, 2007). For instance, morphine acting on opioid receptors, a G-protein coupled receptor (GPCR) indirectly opens K^+ channels while blocking voltage-gated Ca^{2+} channels (N-type), and inhibiting Ca^{2+} conductance. As a consequence, there is efflux of K^+ (with associated influx of Cl^- into the nerve cell), thereby creating a state of negativity within the cell membrane (nociceptor). This increased negative state of the cell induces intracellular (nociceptor) hyperpolarisation, decreases nociceptor activity (firing of action potential), and ultimately leads to analgesia (i.e., the reduction, elimination, or prevention of pain). Hyperpolarisation alters the cell membrane potential and makes it more negative (Pack, 2013). It is the opposite of a depolarisation. Hyperpolarisation is often caused by the efflux of K^+ (a cation) through the K^+ channels, or the influx of Cl^- (an anion) through the Cl^- channels. During hyperpolarisation, the neurone is in a refractory state (during which the neurone is unable to generate subsequent action potentials), and lasts for about two milliseconds (Pack, 2013).

Clinical Correlates

Non-steroidal anti-inflammatory drugs – NSAIDs (e.g., aspirin or acetyl salicylic acid), which are anti-inflammatory therapeutic drugs are employed in the treatment of inflammatory conditions, including chronic pain states, that predispose to sensitisation. Anti-seizure medicines (e.g., carbamazepine) and local anaesthetic agents (e.g., lidocaine or lignocaine) are also used in specific clinical pain states either to block or modulate ion channel activity, thereby inhibiting the generation of nociceptive impulses in the neurones.

2. *Transmission*

The propagation of neural signals from the site of transduction at the periphery to the CNS (spinal cord and brain) is referred to as transmission, and is the stage II in the cascade of processing pain signals. Sensory nerve impulses (electrical stimuli) are transmitted *via* the axons of primary afferent neurone to the dorsal horn of the spinal cord and synapse at the second order neurone. Noxious signals generated from the periphery are relayed through dual primary afferent nociceptive neurones (C- and Aδ-fibres) to the dorsal horn, from where ascending nerve axons travel in the contralateral spinothalamic nuclei and synapse on neurones in the ventral and medial parts of the thalamus, and then finally project to the somatosensory cortex. Repetitive C-fiber activity facilitates transmission through the dorsal horn (wind-up) by mechanisms that involves the activation of NMDA and substance P receptors (Rang *et al*., 2019). Primary afferent nociceptive neurone conduct noxious information to the dorsal horn *via* the release of excitatory amino acid (e.g. glutamate, aspartate) and neuropeptide (e.g., substance P) transmitters at the synapses (Terman and Bonica, 2001). The spinal interneurones release inhibitory neurotransmitters (e.g., GABA; γ-aminobutyric acid) and neuropeptides (endogenous opioids-enkephalins), which bind to receptors on primary afferent and dorsal horn neurones, and inhibit nociceptive transmission both at the pre- and post-synaptic neuronal cell

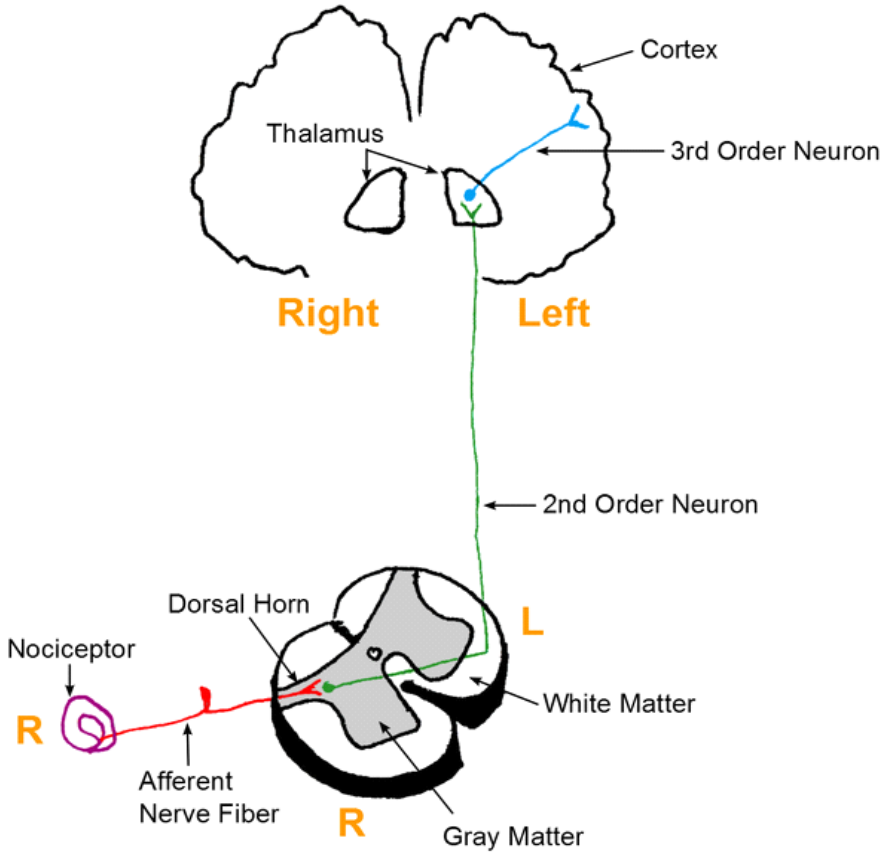

Fig. 1: Schematic Representation of the Pain Pathway
Source: **Dudley, 2020.**

(Terman and Bonica, 2001). The descending control pain pathway (DCPP) otherwise referred to as the efferent analgesic system (EAS) from the higher brain centres inhibits nociceptive neurotransmission ('nociceptive gate') in the spinal dorsal horn (Millan, 2002), an indication that not all the biochemical and physiological processes that occur in the dorsal horn facilitate nociception (perception of noxious stimuli). The DCPP is believed to be a critical site of action for opioid analgesics (Rang *et al*., 2019).

B. Abnormal Transmission of Pain and Pain Perception: Hyperaesthesia

Hyperaesthesia is a clinical condition that results from abnormal pain transmission and perception, and refers to both hyperalgesia and allodynia.

1. ***Hyperalgesia***

It is an increased or severe pain arising from a tactile stimulus or sensation that would ordinarily cause a minimal pain. Hyperalgesia can be primary or secondary. Primary hyperalgesia is caused by peripheral mechanisms (e.g., tissue injury) while secondary hyperalgesia extends beyond the anatomical site of injury to an uninjured tissue or organ. The nociceptive system enables and enforces protective behavioural responses such as withdrawal or avoidance from acutely painful stimuli. When injury occurs, the vulnerability of the affected tissue increases. The nociceptive system adapts to this enhanced vulnerability by locally lowering the nociceptive thresholds and by facilitation of nocifensive responses, and thus ensuring adequate tissue protection (Sandkühler, 2009). Elevated NGF production may be a mechanism by which nociceptive transmission becomes facilitated by tissue damage, thereby leading to hyperalgesia (Pezet and McMahon, 2006).

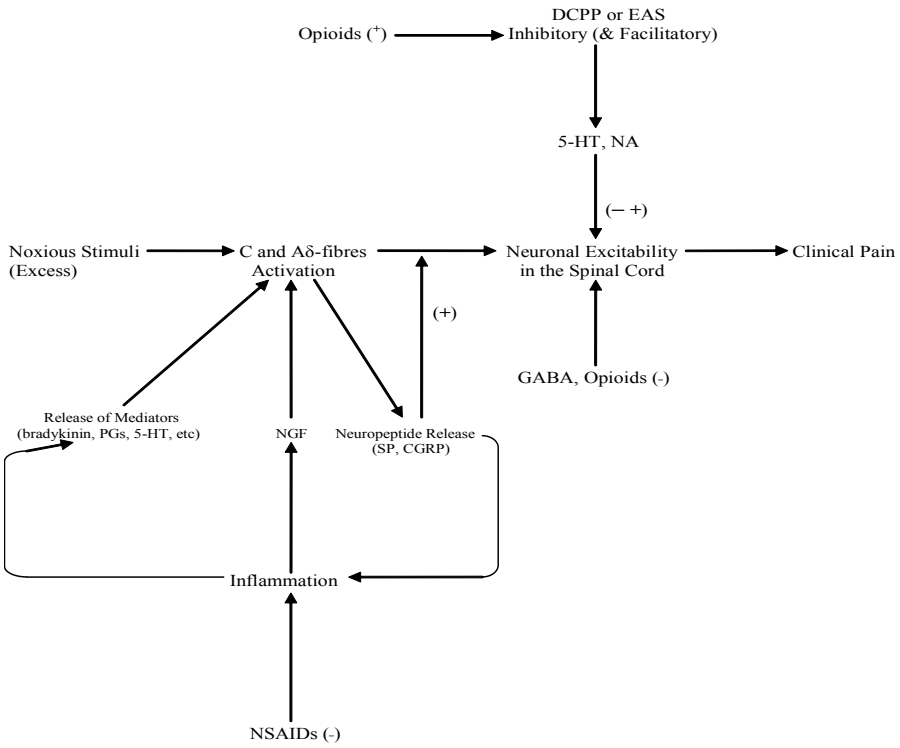

Fig. 2: The Pain Pathway and its Modulatory Mechanisms

DCPP, descending control pain pathway; EAS, efferent analgesic system; 5-HT, 5-hydroxytryptamine (serotonin); NA, noradrenaline (norepinephrine); PGs, prostaglandins; NGF, nerve growth factor; SP, substance P; CGRP, calcitonin gene-related peptide; GABA, γ-aminobutyric acid; (–), inhibitory; (+), excitatory.

Hyperalgesia involves a combination of two factors, a central and a peripheral component; peripheral sensitisation of nociceptive nerve terminals (endings) and central facilitation of neurotransmission at the level of the dorsal horn of the spinal cord and thalamus in the midbrain. These are referred to as neuroplasticity. Ankle sprain and burns are classical examples in which allodynia and hyperalgesia are experienced clinically. The peripheral component of the action is mediated by bradykinin and prostaglandins (PGs) acting on nerve terminals, while the central component facilitates synaptic neuro-transmission in the dorsal horn of the spinal cord (Yaksh, 1999). The synaptic responses of the dorsal horn neurones to nociceptive inputs demonstrate the 'wind-up' phenomenon (defined as sustained increase in the amplitude of synaptic potential with each stimulus when repetitive stimuli are administered at normal or physiological frequencies). This activity-dependent facilitation of neurotransmission has characteristics that are analogous to those of long-term potentiation, as well as their mechanistic basis (Ji *et al*., 2003).

2. ***Allodynia***

This is the experience of pain due to a tactile stimulus that would ordinarily not cause pain. Allodynia has no biological importance *per se,* but may be an adaptive mechanism to protect the vulnerability of an injury (Sandkühler, 2009). It is classified by stimuli into dynamic mechanical, punctate and static *(*Jensen and Finnerup, 2014). In osteoarthritis, for instance, NGF has been implicated in allodynia (Lolignier *et al*., 2015). The extent and intensity of sensation can be evaluated by locating trigger points and the region of sensation, as well as the use of phantom maps *(*Jensen and Finnerup, 2014).

Clinical Correlates

Analgesics (e.g., morphine, an

opiate) inhibit nociceptive neurotransmission at the spinal level by binding to opioid receptors (μ, δ, and κ) at the primary afferent and dorsal horn neurones. The $GABA_B$ receptor agonist, baclofen binds to GABA receptors and mimics the inhibitory effects of GABA (one of the main inhibitory CNS transmitters), and thus results in the blocking of nociception.

3. ***Modulation***

Modulation is stage III in the cascade of processing pain signals. Modulation in the pain pathway occurs through CNS excitatory and inhibitory processes (Latremoliere and Woolf, 2009). It refers to the influence of descending inhibitory and facilitatory inputs (DCPP) from the brain on nociceptive afferents transmission at the spinal dorsal horn (Millan, 2002). Ascending facilitatory and descending inhibitory processes enhance or suppress the pain perception (experience) respectively (Latremoliere and Woolf, 2009). Modulation of nociceptive transmission to the higher centres occurs at multiple levels – peripheral, spinal, and supraspinal. The neural modulatory mechanisms are essentially inhibitory in nature and are activated by nociceptive signals with a view to relieving pain. Several neuroanatomical sites (cortical and sub-cortical) are involved in the DCPP, a system that controls impulse transmission in the dorsal horn (Millan, 2002). The DCPP is involved in the behavioural and psychological responses to pain, as well as modulation of pain sensation. A critical component of the DCPP is the peri-aqueductal gray (PAG) area of the midbrain, which is a small grey matter that surrounds the central canal (cerebral aqueduct of Sylvius). The PAG receives inputs from other brain regions (e.g., hypothalamus, amygdala and cortex), and is the major pathway through which other inputs act to modulate the nociceptive gate (neurones in the *substantia gelatinosa* – SG functions as 'gate' to regulate transmission of impulses to the CNS). The PAG projects to the rostral ventromedial medulla (RVM) and then *via* the dorsolateral furniculus of the spinal cord to the dorsal horn (Rang *et al*., 2019). Nerve fibers from these pathways largely release inhibitory substances (e.g., endogenous opioid peptides, 5-HT, nor-adrenaline, GABA) at synapses with other neurones (e.g., incoming primary afferent neurones, second-order transmission neurone or interneurones) in the dorsal horn (Doly *et al*., 2005; Bardin, 2011). These substances bind to receptors on primary afferent and/or dorsal horn neurones, and block nociceptive neurotransmission, especially the discharge from the spinothalamic neurones or second-order transmission neuronal cells. The blockade of nociceptive neurotransmission by endogenous pain modulating system, comprising intermediate neurones and DCPP inhibits the ascent of pain signal transmission to higher centres (Yaksh, 2006). This endogenously mediated modulation by DCPP probably contributes to the array of discrepancies in pain perception between and among patients who have similar injuries or the lack of perception of pain even in times of stress. The RVM plays a significant role in modulating the descending pain inhibitory pathway, but recent evidence indicates that RVM is the origin of descending facilitatory nociceptive inputs at the dorsal horn of the spinal cord. Application of electrical stimuli to the *nucleus raphe magnus* of RVM and other neighboring tissues evokes excitatory responses in the neurones of the dorsal horn. Stimulation of the RVM using very high currents inhibits behavioural and electrophysiological responses to noxious stimuli while stimulation at low currents facilitates nociceptive responses. Also, the administration of micro-amounts of glutamate, neurotensin, cholecystokinin into the RVM enhances a seemingly nociceptive behavioural response. There is ample evidence to demonstrate that the activation of the descending facilitatory inputs from the RVM is critically important in the maintenance of the behavioural manifestations of neuropathic pain.

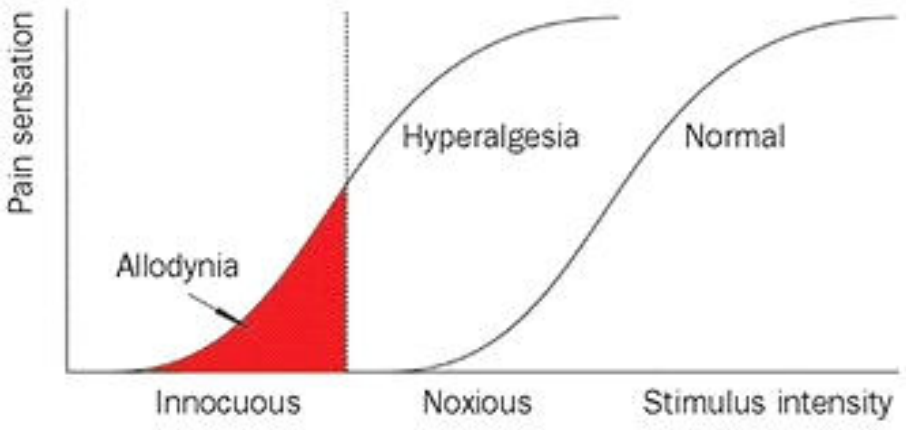

Fig. 3: Abnormal Pain Transmission and Pain Perception: Hyperaesthesia
Source: **Sandkuhler, 2009.**

Opioids act on the pre-synaptic terminal (nociceptor) of primary neurone *via* the μ-opioid receptor by indirectly blocking voltage-gated N-type Ca^{2+} channels while opening K^+ channels (Vanderah, 2007). The inhibition of Ca^{2+} conductance into the pre-synaptic nerve terminal and the efflux of K^+ (with the influx of Cl^- into the nerve cell) creates a state of intracellular negativity, and

consequently, the hyperpolarisation of the neuronal cell membrane, and thus rendering the cell incapable of firing action potential. This inhibits nociceptive (pain) neurotransmitter release from the primary afferent fibres, and ultimately leads to analgesia. Opioid medicines also act at the spinal level, where they activate the post synaptic nerve cell (second-order neurone), and thus hyperpolarise the neurone.

Clinical Correlates

Studies have shown that analgesic medicines facilitate the effects of the DCPP, especially the inhibitory inputs (anti-nociceptive pathway). Antidepressants (e.g., imipramine, amitriptyline) block the re-uptake of monoamine neurotransmitters (e.g., serotonin and noradrenaline) at the synaptic clefts into the pre-synaptic nerve terminal. This action increases the concentration of these transmitter substances in the synapse, thereby promoting the activity of the descending inhibitory system.

4. *Perception*

The conscious appreciation of peripheral nerve impulses arriving in the higher brain centres as pain is termed perception, and is the last step (stage IV) in the neuro-physiology of pain. The third order neurones project from the thalamus to somatosensory areas I and II in the post-central gyrus and superior wall of the Sylvian fissure. Perception and discrete localisation of pain occur in these cortical areas. Some fibres project to the anterior cingular gyrus and are likely to mediate the suffering and emotional components of pain (Swamy, 2005). Pain experience is generally modulated by interactions between the ascending and descending neural circuitry. The supraspinal structures, cerebral cortex and the limbic system (also known as paleomammalian cortex) are involved in the cascading and processing of pain signals, and the eventual perception of pain, and therefore, lends credence to the fact that supraspinal mechanisms play a key role in the modulation of pain experience (Apkarian *et al*., 2005). Nociceptive input from some dorsal horn projection neurones travels *via* the thalamus to the opposite somatosensory cortex, where input is somatotopically mapped (i.e., pain signals initiated in the hand will terminate in the area of the cortex dedicated to represent sensations of the hand) to preserve information about the site, intensity, and quality of the pain. The thalamus relays other nociceptive input to the limbic system. The dorsal horn input then joins other inputs from the spinoreticular and spinomes-encephalic tracts to mediate the affective (emotional) aspects of pain.

These neural mechanisms may contribute to inter-individual variations and disabilities associated with chronic pain conditions (Apkarian *et al*., 2005). Social and environmental factors also affect the perception of pain, just as previous experience and culture. As a consequence, any major causes of pain, for instance, surgical procedures like caesarean section can generate humongous differences in the perception of pain in human subjects. It, therefore, demonstrates that there is perhaps a discrepancy in the neural circuitry of the brain for the perception of acute pain and that of chronic pain in normal humans, and that chronic pain engages brain sites that are crucial for cognitive and emotional assessments, which indicates that this component of pain may be a distinctive feature between chronic and acute pain (Apkarian *et al*., 2005). Recall that nociceptive signals from primary afferents are transduced at peripheral sites to the CNS. The A-β fibers, some large A-δ fibers and small C-fibers, which convey these impulses terminate in the laminae of the dorsal horn and in the SG. The laminae (layers of neurones within the spinal cord that perform specific functions) then transmit specific nociceptive information to a second (order) afferent neurone. Second order neurone transmits the impulse from the SG and laminae through the ventral and lateral horns, crossing in the same or adjacent spinal segment, to the opposite (contralateral) side of the spinal cord. The impulse is then carried *via* the spinothalamic tracts and other ascending tracts to the higher brain centres. There are two divisions of the spinothalamic tract:

i. The neo-spinothalamic tract - this conveys nociceptive signals to the midbrain, thalamus and the post central gyrus, where pain perception takes place. The neo-spinothalamic tract is also known as the lateral spinothalamic tract.
ii. The paleo-spinothalamic tract - this conveys nociceptive signals to the reticular formation, pons, limbic system, and the midbrain, producing a multiplicity of synapses to diverse anatomical structures in the brain. The paleo-spinothalamic tract is otherwise known as the medial spinothalamic tract.

C. The Gate Control Hypothesis

The gate control hypothesis of pain states that non-noxious input closes the nerve 'gates' to painful input, which prevents the sensation of pain from being propagated to the CNS (Deardorff, 2017; Cherry, 2020). The synaptic junctions between the first order neurones and the dorsal horn cells in the spinal cord are sites of considerable plasticity (i.e., the synaptic connections demonstrate the ability to alter the strength of their relationship). As a result, the dorsal horn has been referred to as a gate, where pain impulses can be modified (or 'gated') (Swamy, 2005).

The stimulation of larger nerve fibres (A-alpha and A-beta) causes the cells in the SG to 'close the gate' for the transmission of noxious signals to the CNS. A closed gate leads to decreases in stimulation of T-cells (the second order neurone or second afferent neurone), which decreases the transmission of impulses, and diminishes pain perception. Stimulation of small fibers (C- and Aδ-fibres) input inhibits cells in the SG and 'open the gate'. An open gate increases the stimulation of T-cells, leading to increased transmission of impulses, and enhances pain perception. Endogenous opioids act by binding to

opiate receptors on the plasma membrane of the afferent neurone. This causes the inhibition of neurotransmitter release, thereby blocking the transmission of the noxious information.

D. Peripheral and Central Sensitisation

Terminal nerve endings at the site of tissue injury exhibit an enhanced neuronal response (Dostrovsky, 2014). This local increase in nerve membrane excitability is referred to as peripheral sensitisation (Latremoliere. and Woolf, 2009). The exaggerated response to stimuli in the region of tissue damage is called primary hyperalgesia (Kaufman *et al.,* 2005). In peripheral sensitisation (nociceptor sensitisation), there is an increased, repetitive, and elongated painful stimulation of the nociceptors consequent upon tissue injury (inflammation). Peripheral sensitisation is a receptor-based activity. When sensitisation occurs in the primary afferent nerve fibre, it decreases the threshold for activation and increases the rate of firing of action potential (i.e., elicits nerve impulse more frequently and at a very fast rate). This phenomenon is critical in central sensitisation, and is responsible for the abnormal transmission of pain impulses that occurs in certain clinical conditions (e.g., hyperalgesia and allodynia).

Central sensitisation refers to heightened functional status of the pain circuitry and pain processing in the CNS (Latremoliere. and Woolf, 2009; Brennan, 2011; Woolf, 2011). Secondary hyperalgesia (an increase in pain intensity to noxious stimuli outside the location of tissue damage) and allodynia (pain perception arising from innocuous stimuli such as light touch), are characteristic features of central sensitisation (Brennan, 2011). Therefore, central sensitisation is the excessive activation (hyperexcitability) of the spinal neurone, and may be due to either inflammation or nerve injury. Central sensitisation requires an existing peripheral nociceptive input (nerve injury) for its sustenance. The 'wind-up' phenomenon is a specialised form of sensitisation, in which repetitive electrical stimulation of the nociceptors in the C-fibres progressively increases the frequency of neuronal firing of action potential in the dorsal horn. Therefore, 'wind-up' phenomenon is nociceptive specific. The activation of the glutamate receptor, N-Methyl D-Aspartate (NMDA) is crucial in the 'wind-up' phenomenon. The wind-up event could be likened clinically to a gradual increase in pain perception due to a repetitive application of a noxious stimulus. Studies have shown that repetitive and prolonged painful stimulation of the nociceptors in the C-fibres or damage to the nerves causes hyper-excitability and hyper-responsiveness in the dorsal horn, which tends to outlast the stimulus. Central sensitisation is associated with decreased central inhibition, spontaneous activity in the dorsal horn neurone, and the recruitment of responses from neurones that normally respond only to low intensity stimuli (i.e., altered neural circuitry), and expansion of dorsal horn neurone receptive fields. These alterations in neural circuitry and enlargement of the receptive fields in the dorsal horn neurone can clinically manifest thus:

- Hyperalgesia
- Allodynia
- Persistent pain
- Referred pain

Clinical Correlates

Lingering pain and hyperalgesia have been fingered to be a consequence of peripheral sensitisation. These clinical conditions may be secondary to nociceptive inputs and inflammation, as well as injury to the nerves and the ganglia. Hyperalgesia and allodynia both represent an adaptive response that protects an injury during healing (Sandkuhler, 2009). The sustenance of this response could progress to chronic pain. Neuropathic pain is a consequence of central sensitisation, and arises due to nerve injury or functional deficit. It is this phenomenon of central sensitisation that prolongs the period of neuropathic pain long after the stimulus has disappeared.

CONCLUSION

Clinical pain is a serious public health concern. The causes of pain are manifold, and people respond to it in diverse ways. The neuronal processes that generate noxious impulses that are transmitted to the CNS which culminate in pain perception are multi-stage and complex biological events. An understanding of the complex bio-chemical and physiological mechanisms underlying the processing of nociceptive signals provides an important pathway towards the discovery and development of effective, novel and robust therapeutic drugs. Research has provided some in-depth knowledge and insight into the neural basis of pain, but despite the plethora of information on pain and its modulatory molecular mechanisms, workers have continued to explore for better therapeutic options with a view to improving the quality of life and living in individuals with clinical pain conditions.

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Conflicts of Interest

The author has no interests to declare.

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