Chapter 3
Pathophysiology of Chronic Pain

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Abbreviations

BDNF	Brain-derived neurotrophic factor
Caspase-6	Cysteine-aspartic acid protease-6
CNS	Central nervous system

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CSF-1	Colony-stimulating factor-1
CX	Connexin
DAMPs	Damage-associated molecular patterns
GABA	Gamma-aminobutyric acid
JAK-STAT	Janus kinase/signal transducer and activator of the transcription
lncRNA	Long non-coding RNAs
MMPs	Matrix metalloproteinases
NMDA	*N*-methyl-D-aspartate
PRR	Pattern-recognition receptors
RAGE	Advanced glycation end products
TNF	Tumor necrosis factors
TRP	Transient receptor potential channels

Introduction

Chronic pain is a clinical status characterized by persistent symptoms of pain e.g., hyperalgesia, allodynia which may persist for longer than 3–6 months. The pathogenesis of chronic pain is not fully understood, and its treatment still represents a significant health problem; 19% of adult European suffer chronic pain and a third of children experienced it in their life [1–3]. The Global Burden of Disease Study estimated pain and its related diseases as the leading cause of disability worldwide [4]. Understanding the underlying pathophysiology of chronic pain is crucial for all healthcare workers involved in pain management. Advancing in age, being female, living in low socioeconomic status, being illiterate, unemployed, obese, drinking too much alcoholic, living a sedentary life, following an unhealthy diet are associated with higher prevalence and intensity of pain according to Mills et al. in their epidemiological review [5].

Normal Physiology

Normal physiology of pain signaling includes transduction (intracellular changes upon ligand activation), transmission (movement of pain signals), modulation (alteration in pain signals), and perception (unpleasant sensory and emotional experience). Any tissue damage or inflammatory reactions affecting the receptors or peripheral fibers will affect the normal physiology, also pain processing in the CNS may be dysregulated. Chronic pain is classified as nociceptor pain and neuropathic according to the type of the noxious agent, they may coexist, and pain sensitization is classified to peripheral or central according to the site of dysregulation [6].

Pathway of the Chronic Pain

Receptors
Nociceptors
Afferent
Small-diameter myelinated A and unmyelinated C nerve fibers.
First-order neurons
Dorsal horn of the spinal cord.
Spinothalamic tract
The major ascending pathway for pain and temperature.
Second-order neurons
Rexed layers I, II, and V.
Third-order neurons
Ventral posterolateral (VPL) nucleus of the thalamus.
Cortex
Signal projected to the primary somatosensory cortex.

Information in the dorsal root ganglion is subjected to modulation by descending signals from the brain stem nuclei [7].

Nociceptors (Pain Receptors)

Nociceptors localize at the somatic body parts (bone, muscle, joints) or visceral body organs. Location of receptors classifies nociceptors pain as somatic; well localized and intense, and visceral pain; poorly localized and diffuse. Nociceptor pain is the body's reaction to a painful stimulus like a muscle sprain or tissue damage [8]. Nociceptors and their related afferent nerves differ according to their function and size in myelination, electrophysiological pattern, surface markers, and gene expression [9].

Neuropathic Pain

Noxious agents to the peripheral nociceptor may be caused by inflammation trauma, cancer, arthritis, and others. Those noxious agents promote an increase in the release of the pain mediators' substances and neurotransmitters such as substance P, prostaglandins, and bradykinins. Depolarization starts at the level of the nociceptors and travels up to the second-order neurons in the spinal cord, and midbrain then to the higher centers and limbic system. Neuropathic pain is chronic pain associated with lesions or dysregulation in the pain pathways. Neuropathic pain may be in the form of dysesthesia, abnormal sensation, allodynia, or pain from non-painful stimuli. Neuropathic pains are more severe and more difficult to treat [6, 10, 11].

Possible Mechanisms and Pathogenesis

Peripheral Sensitization

The presence of peripheral nerve injury increases the sensitivity of the nerve to pain through local release of inflammatory substances, recruiting immune cells, and release of cytokines e.g., TNF and interleukins which potentiate the action of both Na and Ca channels [6, 12, 13]. Activation of receptors on the nociceptor neurons proceeds post-transduction modification on the regulation of ion channels, transient receptor potential channels (TRP), pattern-recognition receptors (PRR), toll-like receptors (TLRs), and receptors for advanced glycation end products (RAGE) [14].

Central Sensitization

Continuous peripheral sensitization leads to changes at the level of CNS named "central sensitization". Central sensitization is associated with reduced pain threshold and modulation in pain pathways at the level of CNS. These modulations in CNS are possible explanations for depression and anxiety attacks associated with chronic pain. It also explains the high prevalence of chronic pain among patients with depression as depression is itself characterized by inflammatory activity [5, 15–17]. Central sensitization is thought to be the reason for neuropathic pain symptoms such as allodynia, hyperalgesia, secondary hyperalgesia, temporal summation, expansion of referred pain region, and defective descending inhibitory control [17–19].

Glial Cells

CNS glial cells play an important role in the pain pathways; reactive changes are seen in astrocytes, microglia, and oligodendrocytes as a sequela of pathological conditions evoking pain [20–22]. Proinflammatory mediators derived from neurons themselves are responsible for microglial cell activation e.g. colony-stimulating factor 1 (CSF1) caspase-6, interleukin-1β, and extracellular proteases damage-associated molecular patterns (DAMPs) [20, 23–26]. Those mediators activate glial cells by binding to pattern-recognition receptors (PRR) [20]. The role of microglial cells in pain can be noticed by the effect of drugs inhibiting their activation [27, 28]. minocycline, propentofylline, and ibudilast [29–31]. Microglia release IL-1β a cytokine seen to be upregulated in chronic pain which enhances NMDA receptors and inhibits GABA transmission [32–35]. Drugs antagonizing its action showed good results in attenuating pain intensity [35–38]. Transmission of ions dramatically increases between glial cells through connexin-43 (CX43) gap junction. This increase is associated with high expression of connexin-43 (CX43) protein [39]. Carbenoxolone as a gap junction inhibitor showed positive results [40]. Matrix

metalloproteinases (MMPs) also play a role in the regulation of inflammatory cytokines associated with nerve injury; using tissue inhibitors of MMP showed positive results in attenuating chronic pain [41, 42]. Other mediators like catecholamines and oligodendrocytes precursor cells are seen to be upregulated in chronic pain pathways [22, 43].

Pattern Recognition Receptors (PRP)

Pattern recognition receptors (PRP)) such as TLRs and RAGEs play their role in chronic pain through both peripheral and central sensitization [14]. TLRs are responsible for the induction of proinflammatory mediators and generating biologically active IL-1β. RAGEs are membranous proteins with cytoplasmic domain upon activation they increase transduction and upregulation of cytokines and proinflammatory material [14].

JAK-STAT Pathway

A new therapeutic target is Janus kinase/signal transducer and activator of the transcription (JAK-STAT) pathway. This pathway is very crucial in immune cell activation and cytokine production. Once cytokines bind to JAK receptors they become phosphorylated and translocate to the nucleus where they enhance gene transcription. Those genes are related to numerous cytokines and proinflammatory materials [44, 45].

Cysteinyl-Aspartate-Specific Proteases (CASPs)

They are proteases responsible for initiating cell apoptosis. They are highly expressed in dorsal root ganglions, peripheral nerves, and the brain. In chronic pain, their activation leads to the neuroinflammatory response, cell apoptosis, and microglial cell activation. Injection of CASPs inhibitors showed positive results in alleviating neuropathic pain [46, 47].

Long Non-coding RNAs (lncRNA)

They are transcripts not coding for protein synthesis and found to be highly expressed in the spinal cord and dorsal ganglia in chronic neuropathic pain. Researchers supposed they are involved in cytokine production, activation, and interaction with TLRs to be an important part of neuropathic chronic pain pathways [48, 49].

GABAergic Plasticity

After nerve injuries, changes occur in peripheral nerves and nociceptors leading to pain hypersensitivity. Decrease in GABA inhibition though to be one of the causes and named "neuropathy-induced decrease of GABA synaptic inhibition". Injury through to causes cell apoptosis decreasing GABAergic nerves [50, 51].

Purinergic Signaling in Microglia

Stimulation of P2X4 receptors on the surface of microglia release brain-derived neurotrophic factor (BDNF), this substance dysregulates ion exchanges inverting cell polarity and converting GABA and glycine to the polarizing agent rather than hyperpolarizing agents [52–54].

Mitochondrial Role in the Pathogenesis of Chronic Pain

Recently, mitochondria were found to be involved in the pathogenesis of chronic pain. Increase production of reactive oxygen species (ROS) and superoxide associated with hyperalgesia even without nerve injury. Blocking of ATP-dependent mechanism in mitochondria gave positive results in reducing some types of neuropathic pain [55–57].

Conclusion

Despite the pathogenies of chronic pain is not yet well understood, numerous theories have been proposed and new therapeutic agents have been tried and are anticipated to reach an effective agent in decreasing the burden of chronic pain.

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