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Review

Co-players in Chronic Pain: Neuroinflammation and the Tryptophan-Kynurenine Metabolic Pathway

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Abstract: Chronic pain is an unpleasant sensory and emotional experience that persists or recurs more than three months and may extend beyond the expected time of healing. Recently nociplastic pain has been introduced as a descriptor of mechanism of pain, which is due to disturbance of neural processing without actual or potential tissue damage, appearing to replace a concept of psychogenic pain. An interdisciplinary task force of the International Association for the Study of Pain (IASP) compiled a systematic classification of clinical conditions associated with chronic pain, which was published in 2018 and will officially come into effect in 2022 in the 11th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-11) by the World Health Organization. ICD-11 offers the option for recording the presence of psychological or social factors in chronic pain; however, cognitive, emotional, and social dimensions in the pathogenesis of chronic pain are missing. Earlier pain disorder was defined as a condition with chronic pain associated with psychological factors, but it was replaced with somatic symptom disorder with predominant pain in Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) in 2013. Recently clinical nosology is trending toward highlighting neurological pathology of chronic pain, discounting psychological or social factors in the pathogenesis of pain. This review article discusses components of the pain pathway, the component-based mechanisms of pain, central and peripheral sensitization, roles of chronic inflammation, and the involvement of tryptophan-kynurenine pathway metabolites, exploring participations of psychosocial and behavioral factors in central sensitization of diseases progressing into development of chronic pain, comorbid diseases that commonly present a symptom of chronic pain, and psychiatric disorders that manifest chronic pain without obvious actual or potential tissue damage.

Keywords: chronic pain; nociceptive pain; neuropathic pain; nociplastic pain; psychogenic pain; neuroinflammation; kynurenine

1. Introduction

Chronic pain is an unpleasant sensory and emotional experience that persists or recurs more than three months and may extend beyond the expected time of healing [1,2]. Chronic pain occurs as a part of symptoms due to an underlying medical condition or remains despite successful treatment of the condition that originally caused it [3]. Chronic pain frequently becomes the sole or predominant clinical complaint [4]. The prevalence of chronic pain estimates as much as 20% and the incidence reaches about 10% every year of the world adult population [5]. Nearly 10% of individuals with chronic pain was found to suffer from moderate to severe debilitating pain [6]. Furthermore, individuals with severe chronic pain are twice more likely to die of respiratory disease or heart disease than those with mild pain or without pain [5]. The Global Burden of Disease Research ranked low back pain and migraine first and second place of Years Lived with Disability (YLD), respectively and thus, chronic pain imposes substantial socioeconomic burden directly and indirectly on society [7].

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The International Classification of Diseases, Eleventh Revision (ICD-11) classifies chronic pain into primary and secondary. The primary chronic pain is fibromyalgia or low-back pain; the secondary chronic pain occurs secondary to an underlying medical condition subcategorizing into cancer-related, post-trauma, neuropathic, headache and orofacial, visceral, and musculoskeletal pain. ICD-11 offers minimal options for recording psychological or social factors in chronic pain [8]. Meanwhile, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) recognizes chronic pain in the diagnosis of somatic symptom disorder (SSD), having replaced pain disorder, a condition with chronic pain due to psychological factors [9]. SSD is caused by somatosensory amplification which is associated with fibromyalgia [10]. The trend toward a neurological explanation obviously discounts cognitive, emotional, and social dimensions in the pathomechanism of chronic pain. Hyperalgesia is a condition of abnormally increased sensitivity to pain caused by injury to tissues or nerves, or by opioid medication for pain treatment. Hyperalgesia is a challenging issue for pain specialists who treat patients at terminal care [11]. Chronic pain is often elicited by stimuli that previously did not provoke discomfort sensation. It is called allodynia. Allodynia is commonly observed in patients with neuropathies, fibromyalgia, migraine, complex regional pain syndrome, and postherpetic neuralgia [12]. Chronic pain may proceed to clinical conditions accompanied often by mood alterations such as depression, anxiety, anger, cognitive disturbance including memory impairment, sleep disturbances, fatigue, loss of libido, and/or disability, called chronic pain syndrome (CPS). CPS appears to be linked to dysfunction of the hypothalamic–pituitary–adrenal axis and the central nervous system (CNS), but exact mechanisms remain unknown [13].

Neuroinflammation has been intricately linked to the pathogenesis of chronic pain. Chronic pain was proposed to be caused by disturbance of peripheral nociception, neuropathy in the somatosensory system, motor system, central and peripheral nociplasticity, and/or psychosocial system [14]. Increasing evidence suggests that chronic inflammation is strongly tied to aberration in each mechanism of chronic pain. Furthermore, the tryptophan (TRP)-kynurenine (KYN) pathway and its metabolites were observed to play an important role in neuroinflammation and chronic pain [15]. This review article presents components of pain pathway, mechanisms of chronic pain based on the components, development of chronic pain through peripheral and central sensitization, evidence in presence of chronic neuroinflammation in each pain mechanisms, involvements of the TRP-KYN metabolic pathway, and need of a psychogenic component in the pathogenesis of chronic pain.

2. Pain pathway, Mechanisms, Neuroinflammation, and the Tryptophan Metabolism

Pain perception is signaling through the pain pathway whose components consist of transduction, conduction, transmission, modulation, and perception. Transduction is the process by which noxious or potentially damaging stimuli activate the nociceptors to convert to neural signals. Transmission refers to the signal transfer from the peripheral neurons to the second order neurons in the spinal cord, which wire the signals to the thalamus and brain stem in the brain. Pain modulation takes place by inhibition of pain signaling in the spinal cord and the activation of the descending inhibitory fibers. The third order neurons project to the somatosensory cortex, enabling perception on pain. Perception is the subjective awareness in connection with arousal, physiological, and behavioral brain centers, involving the integration of psychological processes such as attention, expectation, and interpretation [16-18] (Figure 1).

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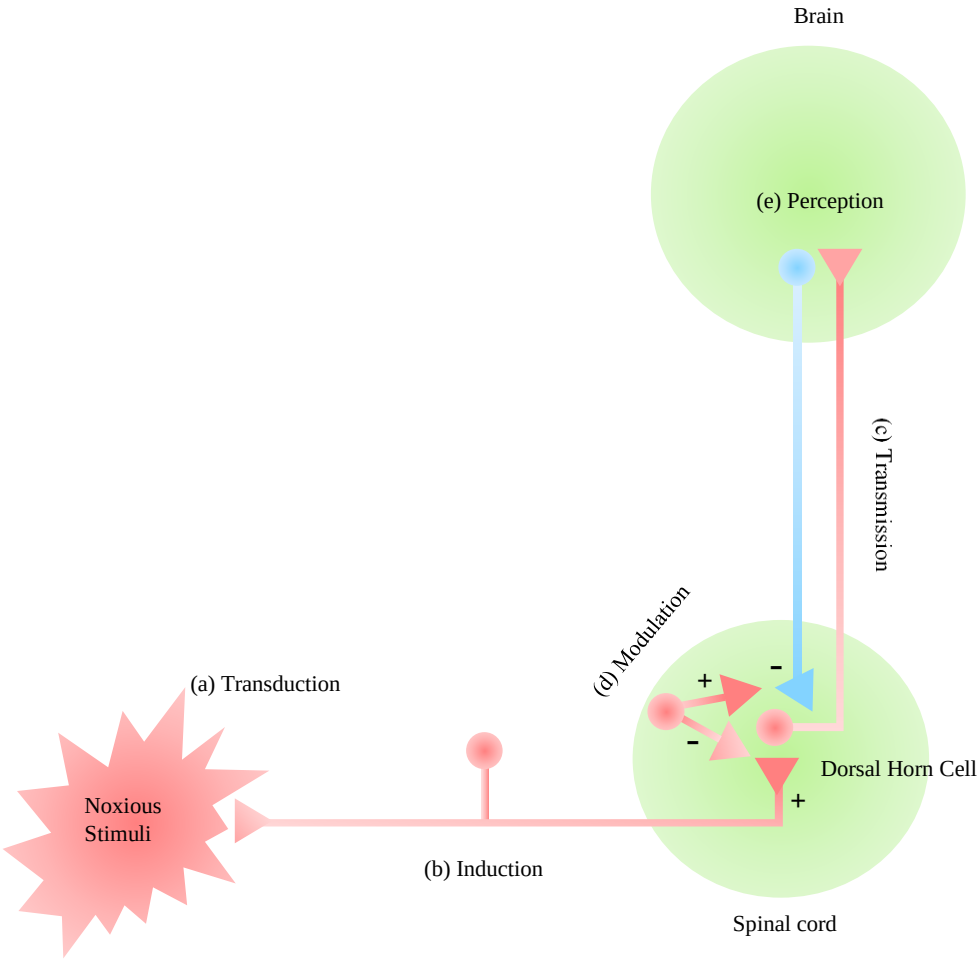

Figure 1. Main components in pain pathway. (a) Transduction, (b) Induction, (c) Transmission, (d) Modulation, and (e) Perception.

Pain is a complex and intricate process attributable to nociceptic, neuropathic, and/or neuroplastic mechanisms. The most common type of pain is nociceptive pain caused by damage or potentially harmful to peripheral tissues involving nociceptors responsible for transduction. Neuropathic pain is caused by lesions or diseases affecting the somatosensory nervous system responsible for transmission of peripheral to central pain signals. Nociplastic pain refers to the condition caused by altered nociceptive processing without actual or potentially harmful tissue damage activating peripheral nociceptors (nociceptive pain) or without lesions or diseases of the somatosensory nervous system (neuropathic pain). Cortical perception is one of the main components in pain pathway, however, the ICD-11 excludes psychogenic pain [19] (Figure 2). Thus, participation of cortical perception in chronic pain mechanisms remains ambiguous.

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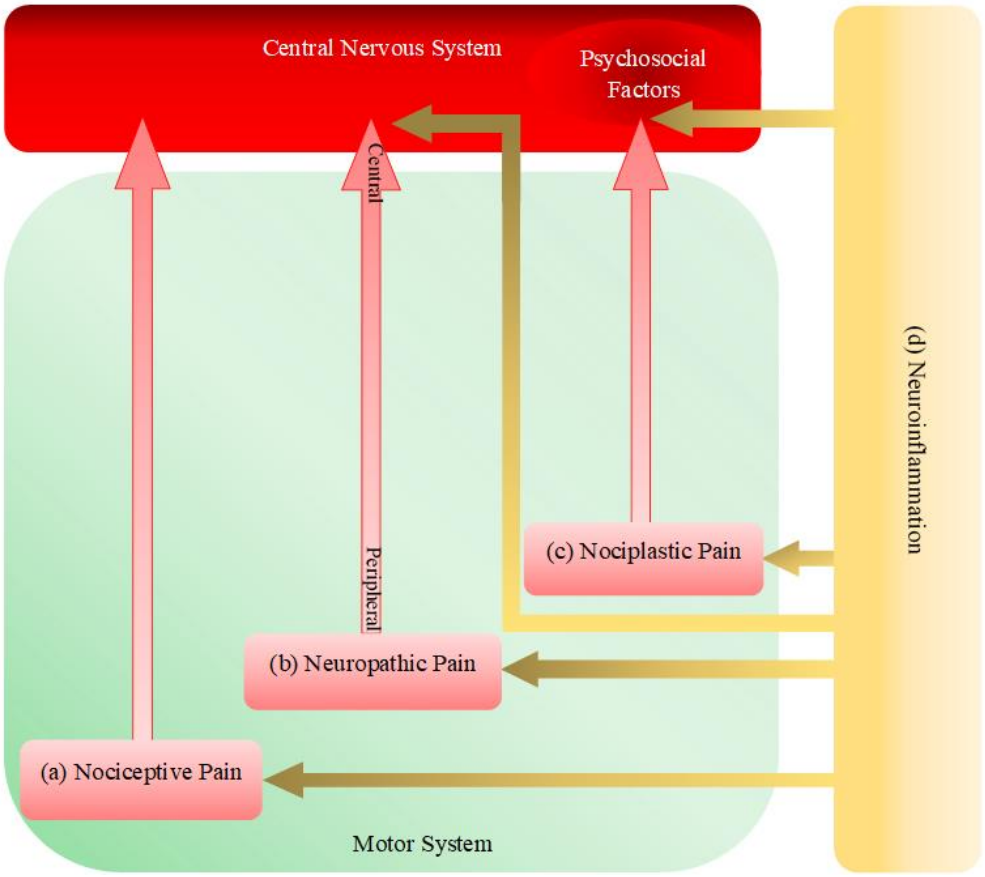

Figure 2. Main components in pain pathway. (a) Transduction, (b) Induction, (c) Transmission, (d) Modulation, and (e) Perception.

Inflammation is generally involved in the pathogenesis of various diseases and plays a key role in diseases which cause chronic pain [20]. Resident and recruited immune cells release inflammatory mediators at peripheral nerve innervating damaged or inflammatory tissue to trigger action potentials in sensor neurons or sensitize neurons by increasing transduction and excitability. Inflammatory mediators also act directly on peripheral nerves to damage peripheral transmission [21]. Immune cells infiltrate the spinal cord and the dorsal root ganglia to damage central transmission and/or modulate pain sensitivity (Ji et al., 2016). Activated immune cells release inflammatory cytokines, chemokines, and other factors influence cognition, mood, and behaviors through immune-to-CNS signaling [16,22]. Accumulating evidence suggests that chronic dysregulation of the immune response is involved in pathogenesis of psychiatric disorders such as mood disorders, substance abuse disorders, psychotic disorders, attention-deficit disorders, and autism spectrum disorders [23-25] (Figure 2).

Inflammation is invariably linked to the disturbance of TRP metabolism [26]. The essential amino acid TRP is a precursor to serotonin, melatonin, and nicotinamide adenine dinucleotide (NAD^+), among others. More than 95% of TRP is metabolized through the TRP-KYN pathway, synthesizing various bioactive metabolites such as neuroprotective antioxidants and neuroprotectants, toxic oxidants and neurotoxins as well as immunomodulators. Disturbance of KYN metabolites has been linked to immune disorders, cancers, neurodegenerative diseases, and psychiatric disorders [27]. Furthermore, TRP-KYN metabolites are under extensive research in search of peripheral biomarkers as well as novel drug prototypes for a wide range of diseases [28-34]. Inflammation activates the TRP-KYN pathway, elevating the levels of oxidative compounds or neurotoxic ligands to receptors of the excitatory glutamatergic nervous system, which damage the peripheral nervous system or CNS through the broken blood-nerve or blood-brain-barrier, respectively [16]. Furthermore, the immunomodulators are known to trigger the shift of acute

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inflammatory status toward tolerogenic and chronic inflammation, perpetuating low-grade inflammation [35]. KYN is synthesized from TRP by the tryptophan 2,3-dioxygenase (TDO) in the liver and the indoleamine 2, 3-oxygenase (IDO) in the brain and the immune system, which are induced by cortisol, and IFN-α, IFN-γ, and TNF-α, respectively [36]. Anthranilic acid (AA), 3-hydroxykynurenine (3-HK), or kynurenic acid (KYNA) are produced from KYN by the kynureninase, the KYN-3-monooxygenase (KMO), the KYN aminotransferases (KATs), respectively. The KATs also converts 3-HK to xanthurenic acid (XA). XA converts into cinnabarinic acid (CA) by autoxidation. AA and 3-HK converts into 3-hydroxyanthranillic acid (3-HAA) and then into picolinic acid (PA) and quinolinic acid (QA). QA converts into NAD^+, which is a feedback inhibitor of TDO [29] (Figure 3). Generally, 3-HK and QA are described as neurotoxic, while KYNA is considered to be neuroprotective. The 3-HK/KYNA ratio is often applied for an indicator of neurotoxicity. However, emerging evidence suggests that some metabolites of the TRP-KYN pathway possess Janus-face properties, depending on the dose or the situation. For example, KYNA is excitatory in lower concentrations, but inhibitory in higher concentrations at AMPA receptors. 3-HK is known to be oxidant but observed to be antioxidant in a certain condition [26].

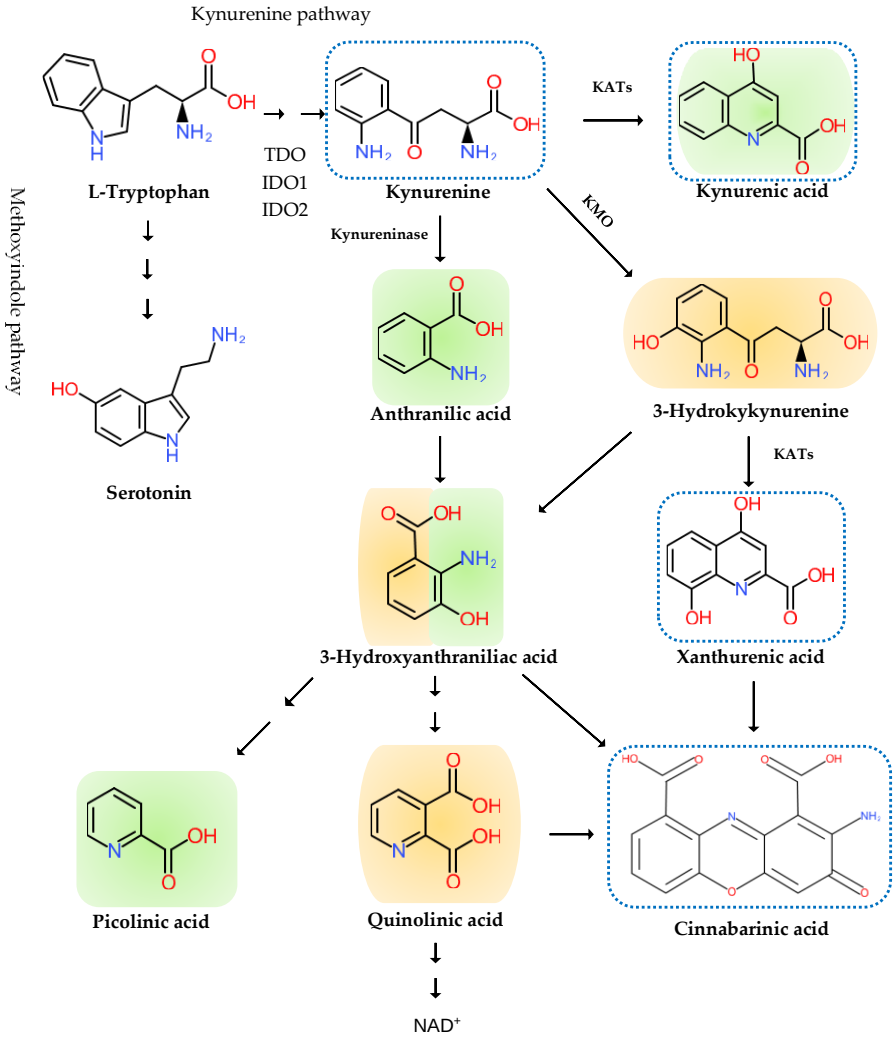

Figure 3. The tryptophan (TRP)-kynurenine (KYN) metabolic pathway and its metabolites. The TRP-KYN metabolic pathway synthesizes various metabolites including oxidants (orange color), antioxidants (green color), and immunomodulators (blue dotted line). Furthermore, 3-hydroxykynurenine and quinolinic acid are neurotoxic, whereas

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kynurenic acid is neuroprotective. TDO: tryptophan 2,3-dioxygenase; IDO: indoleamine 2, 3-oxygenase; KMO: KYN-3-monooxygenase; KATs: KYN aminotransferases.

3. Transduction and Nociceptive Pain

The transduction of pain sensation takes place when noxious stimuli depolarize the afferent terminal of nociceptive myelinated A-beta (Aß) and A-delta (Aδ) fibers and unmyelinated C fibers, through the terminal membrane proteins and voltage-gated ion channels converting them into electric signals in the neurons (Figure 1 (a)).

Nociceptive pain is the most common pain that originates from a tissue injury or inflammation in which the nociceptor of peripheral sensory nerves detects noxious or potentially harmful stimuli [37]. In chronic pain the peripheral nociceptors continue to transmit painful stimuli even after the original injury has healed [38]. Osteoarthritis is a classical nociceptive pain condition when abnormal loading of a damaged joint opens mechanogated ion channels on nociceptive nerve endings [39]. Overextending or tearing a ligament sensitizes nociceptors causing acute nociceptive pain as in the case of ankle sprain. In addition to mechanical irritation or physical injury, the primary cells of the epidermis, keratinocytes induce pain by releasing endogenous mediators such as adenosine triphosphate, IL-1β, prostaglandin E2, endothelin, and nerve growth factor. But keratinocytes act in dual matter in pain sensation: they release β–endorphin that help pleasurable feeling during modest sun-bathing but activate transient receptor potential cation channel subfamily V member 4 (TRPV4) and release pro-inflammatory cytokines, eliciting pain sensation in sunburn [40,41] (Figure 2 (a)) (Table 1).

Table 1. Pain pathway components, pain mechanisms, and representative diseases.

Pain Pathway Components	Pain mechanisms	Diseases
Transduction	Nociceptive pain	Ankle sprain, Osteoarthritis
Conduction Transmission	Neuropathic Pain	Diabetic neuropathy, Singles, Nutritional deficiencies, Toxins, Cancer, Guillain-Barre syndrome, Amyloidosis, Fabry's disease, Nerve trunk injuries
Modulation	Nociplastic Pain	Fibromyalgia Temporomandibular disorders, Nonspecific back pain
Perception	Psychogenic Pain	Depression, Anxiety, Cognitive impairment

Inflammation also activates nociceptors in the nerve endings. Inflammatory mediators bind to their receptors on nociceptive sensory neurons in the peripheral nervous system, resulting in pain [20]. Pro-inflammatory factors including tumor necrosis factor gamma (TNF$-\gamma$) and Interleukin-1 beta (IL-1β) secreted by monocytes and macrophages at the site of a peripheral injury facilitate pain transduction and conduction by modifying ion channels including transient receptor potential cation channel subfamily A member 1 (TRPA1), transient receptor potential cation channel subfamily V member 1 (TRPV1), and Nav1.7-1.9. But those cells secret anti-inflammatory factors such as IL-10 and/or pro-resolution mediators including resolvins, protectins, and maresins to reduce nociception in the resolution phase of acute inflammation. Different phenotypes macrophages such as pro-inflammatory M1 and anti-inflammatory M2 contribute to the induction and resolution of pain, respectively [42]. Schwann cells of the peripheral nervous system also secret TNF-γ and IL-1β to sensitize nociceptors at axons in neuronal injury. Activated Schwann

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cell secrete matrix metalloprotease (MMP) 9 that help open the blood-nerve barrier, resulting in the recruitment of immune cell that release inflammatory cytokines [43,44]. Furthermore, nociceptive afferent sensory neurons directly modulate inflammation by releasing inflammatory mediators such as substance P, calcitonin gene-related peptide (CGRP), neurokinin A (NKA), and endothelin-3 (ET-3). The process is called neurogenic inflammation (Figure 2 (d)).

The disturbance of TRP metabolism is observed in neurogenic inflammation. The increased levels of stress hormone cortisol and inflammatory cytokines such as IFN-α, IFN-γ, and TNF-α activate the TRP-KYN pathway producing higher levels of oxidant KYN metabolites which leak into the peripheral nervous system through the damaged gap junction following the immune reaction. The oxidative KYN metabolites 3-HK, 3-HA and QA are harmful compounds to nerve endings of the afferent sensory neurons (Figure 3).

4. Conduction, Transmission, and Neuropathic pain

In conduction the electrical signals are conducted from the peripheral neurons to the central neurons where a network of interneurons facilitates or inhibits transmission to second order neurons in the dorsal horn [45]. The presynaptic terminals of C fibers release glutamate, substance P, and CGRP, which activate postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, NK1 receptors, and CGRP receptors, respectively [46] (Figure 1 (b)). In transmission activation of the postsynaptic receptors generate an action potential of the second order neurons and interneurons which relay signals through the contralateral spinothalamic tract (STT) to the thalamus, or the spinoreticular (SRT) and spinomesencephalic (SMT) tracts to the medulla and brain stem, or the spinohypothalamic tract (SHT) to the hypothalamus [47] (Figure 1 (c)).

Neuropathic pain originates from lesion or diseases of the somatosensory nervous system made up of peripheral and central components. Peripheral neuropathic pain is commonly caused by diabetic neuropathy, metabolic disorders, shingles, HIV-related distal symmetrical neuropathies, nutritional deficiencies, toxins such as arsenic and thallium, paraneoplastic manifestation of cancer, immune-mediated inflammatory diseases such as Guillain-Barre syndrome, amyloidosis, Fabry's disease, and nerve trunk injuries [48]. Presumably burning and poorly localized pain is transmitted by C fibers, while sharp and lancinating pain is relayed by Aδ fibers [49]. Diabetic neuropathy is the most common neuropathies associated with severe pain, which presents a distal symmetrical polyneuropathy with numbness and loss of sensation in the distal extremities, often accompanied with peripheral vascular diseases, leading to infection and ultimately amputation [50]. Neuropathic pain is also caused by direct invasion to peripheral nerves by tumor, side effect of chemotherapy, radiation injury, or surgery [51] (Figure 2 (b)) (Table 1). Central neuropathic pain is a common sequela to injury to the CNS such as vascular accidents including ischemic and hemorrhagic stroke, infection including abscess, encephalitis, and myelitis, demyelinating disease including multiple sclerosis, tumors, and brain or spinal cord [52-54] (Figure 2 (b)) (Table 1). Mixed pain is a term never formally defined, but it indicates pain caused by combination of nociceptive and neuropathic mechanisms, observed in patients who suffer from osteoarthritis, sciatica, and cancer.

Neuropathic pain is often manifested as a part of symptoms of psychological disorders. Lifetime and current prevalence of psychiatric disorders in patients with chronic peripheral pain were 39% and 20%, respectively. Diseases that cause neuropathic pain include diabetes, herpes zoster infection, nerve compression, nerve trauma, channelopathies, and autoimmune diseases. The most common psychiatric disorders were generalized anxiety disorders and mood disorders [55]. Furthermore, antidepressants showed efficacy for neuropathic pain in patients with depression, suggesting neuropathic pain and depression have a bidirectional relationship [56]. Individuals with chronic neuropathic pain were associated with substance abuse or suicide ideation [57] (Figure 2 (b)) (Table 1).

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Inflammation plays an important role in neuropathic pain. Around afferent peripheral nerves monocytes and macrophages release pro-inflammatory factors including TNF-γ and IL-1β, while they secrete anti-inflammatory factor IL-10 and pro-resolving lipid mediators (SPMs) at the resolution of acute inflammation. T lymphocytes (T-cells) play an important role in neuropathic pain. T-cells secret a pro-inflammatory cytokine IL-17 and accumulate in the dorsal root ganglion (DRG) to release pro-analgesic leukocyte elastase (LE), inducing mechanical allodynia. In the resolution phase T-cells secrete anti-inflammatory cytokines IL-4 and IL-10. In response to noxious stimuli the satellite glial cells (SGCs) are activated and proliferated at DRG to release pro-inflammatory cytokines TNF and IL-1β and a nociceptive neurotransmitter ATP signaling through P2 receptors (P2Rs) [58]. SGCs also release MMPs that open the blood-nerve barriers, allowing entry of immune cells [59]. Bone marrow stem cells (BMSCs) trigger analgesic actions by secreting anti-inflammatory cytokine transforming growth factor-beta1 (TGF-β1), by suppressing glial activation induced by nerve injury, and migrating to DRG via a CXCL12 chemotactic signal after intrathecal injection.

Spinal cord microglia play major roles in pathological pain. Following peripheral injury, ATP, colony-stimulating factor-1 (CSF1), chemokines including (C-C motif) chemokine ligand 2 (CCL2) and fractalkine **(**CX3CL1), and proteases activate spinal microglia. Meanwhile, expression of the receptors for ATP and CX3CL1 increases, converging an intracellular signaling cascade leading to phosphorylation of p38 mitogen-activated protein (MAP) kinase, which in turn elevates production and release of TNF- γ, IL-1β, IL-18, brain-derived growth factor (BDNF), and prostaglandin E2. TNF-γ and Il-1β increase synaptic transmission and decrease inhibitory synaptic transmission lamina II spinal cord neurons. BDNF suppressed gamma-aminobutyric acid (GABA)-ergic inhibitory synaptic transmission in projection to lamina I spinal cord neurons. Microglia release anti-inflammatory cytokine IL-10 in the resolution phase of inflammation.

An astrocyte is in contact with more than one million synapses and thus, chronic pain in astrocyte activation is more persistent [60]. Astrocytes communicate with neurons through gap junction mediated by connexin-43 (Cx43). Cx43 is upregulated in astrocytes after nerve injury, serving as a paracrine modulator. The paracrine modulation results in elevating the release of glutamate, ATP, MMP2 and chemokines including CCL2 and (C-X-C motif) chemokine ligand 1 (CXCL1). The chemokines function as neuromodulators that potentiate excitatory synaptic transmission. Meanwhile, following nerve injury spinal cord neurons upregulate (C-X-C motif) chemokine ligand 13 (CXCL13) that activate astrocytes via C-C chemokine receptor type 5 (CCR5) to sustain neuropathic pain [61]. Spinal cord and cortical astrocytes upregulate thrombospondin-4 (TSP4) that leads to new synapsis formation and subsequent somatosensory cortical circuit rewiring, causing neuropathic pain [62]. Astrocytes cause neuronal hyperexcitability resulting from disturbance of homeostasis of extracellular potassium and glutamate. IFN-α produced by astrocytes inhibits nociceptive transmission in spinal cord [60].

Oligodendrocytes form myelin sheath insulating axons in the CNS [63]. Little is known about their roles in pain. IL-33 produced from oligodendrocytes contributes to pain sensitivity via MAP kinases and nuclear factor kappa-light-chain-enhancer of activated B cells in chronic constriction injury model of nerve injury-induced neuropathic pain [64]. Diphtheria toxin ablation of oligodendrocytes neuropathic pain, suggesting analgesic roles of the cells. Following nerve injury T-cells infiltrate in spinal cord, contributing development of mechanical sensitivity. T-cells release pro-inflammatory cytokine TNF-γ, they secrete anti-inflammatory cytokines IL-4 and IL-10 in the resolution phase of inflammation [65]. Following chemotherapy, intrathecal injection of cytotoxic T-cells enhanced neuropathic pain, while injection of regulatory T-cells diminished neuropathic pain [66] (Figure 2 (d)).

The involvement of the TRP-KYN pathway was reported in inflammation-induced neuropathic pain. The enzyme activities of the TRP-KYN pathway were studied in a lipopolysaccharide-stimulated chronic constriction injury at the spinal cord and DRG levels of rats. The intrathecal administration of L-KYN and the intraperitoneal injection of L-

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KYN and an organic anion transport inhibitor probenecid significantly reversed tactile allodynia in L5-L6 spinal nerve root-ligated rats, suggesting that N-methyl-D-aspartate (NMDA) receptor an organic anion transport inhibitor agonist KYNA mediates relieving the allodynia [67]. The increase ratio of QA/KYN and the mRNA expression of KMO, KYNU, and HAOO was elevated in neuronal nuclear antigen-positive neurons of the contralateral hippocampal dentate gyrus in a neuropathic mouse model [68]. Tryptophan 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenase (IDO) 1 and 2, kynurenine 3-monooxygenase (KMO), kynureninase (KYNU), and 3-hydroxyanthranilate dioxygenase (HAOO) were found to be de derived from cerebral microglial cells and mRNA expression of IDO-2, KMO, and HAOO were upregulated at the spinal cord after one week. Microglia inhibitor, minocycline decreased the levels of IDO-2 and KMO enzymes and tactile and thermal hypersensitivity, furthermore, IDO-2 inhibitor 1-methyl-d-tryptophan and KMO inhibitor UPF 648 significantly decreased mechanical and thermal hypersensitivity [69]. This suggests the participation of IDO-2 and KMO enzymes in the pathogenesis of neuropathic pain. The intracerebroventricular administration of KMO inhibitor Ro 61-8048 alleviated spared nerve injury-induced depressive-like behavior and the intrathecal injection of Ro 61-8048 attenuated both the depressive-like behavior and mechanical allodynia in rats [70]. The NMDA receptor seems to play a major role in neuropathic pain and in the development of opioid tolerance. Dextromethorphan is an NMDA antagonist at high doses. Both animal and human studies showed that NMDA antagonist ketamine was beneficial for analgesic [71] (Figure 3).

5. Modulation and Nociplastic Pain

Modulation of pain transmission occurs at all levels of pain pathway from peripheral to the brain as well as from upward to downward pain regulations, involving both excitatory and inhibitory mechanisms which facilitate or suppress the responses of second order neurons, respectively [46]. Peripheral pain modulation is achieved through local growth factor, hormonal, and peptide release which alters signaling through neurotransmitter, ion, or receptor-based mechanisms. The pain modulation takes place neuronal signaling though corticospinal, corticoperiheral, and intraspinal pathway and neuroplasticity regulation [72] (Figure 1 (d) and Figure 4).

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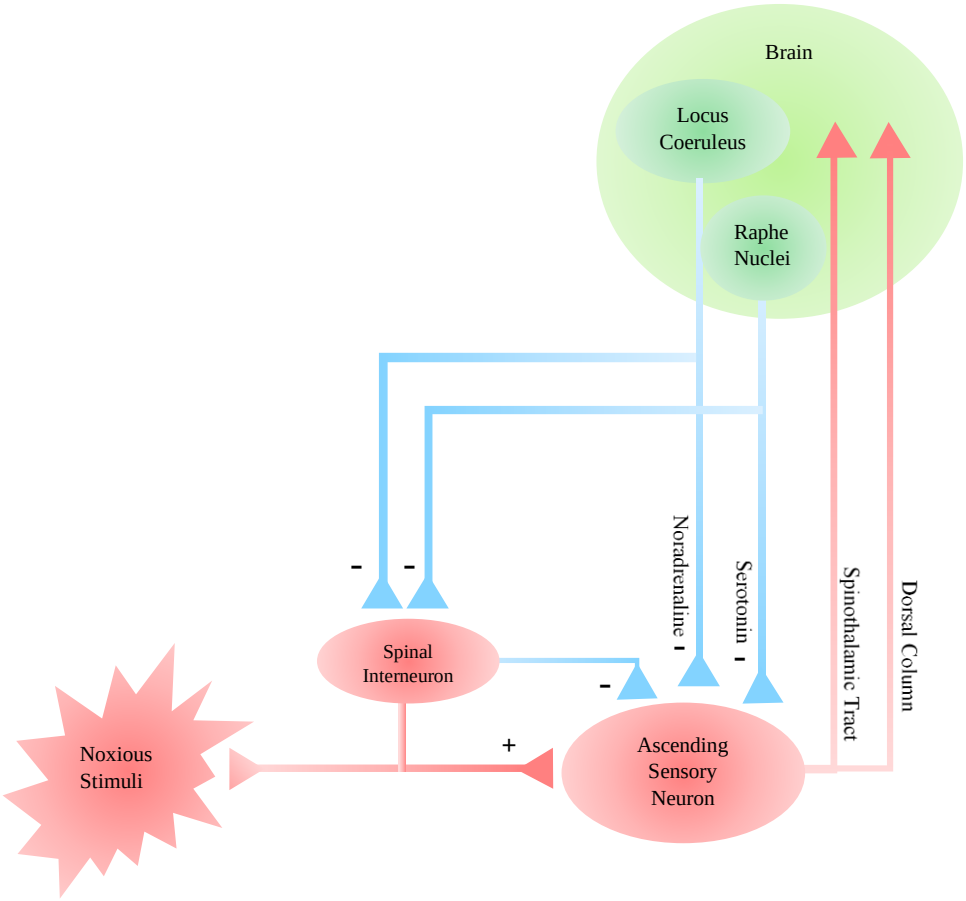

Figure 3. Pain pathway and pain modulation.

Nociplastic pain is defined as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage or causing the activation of peripheral nociceptors or evidence disease of lesion of the somatosensory causing the pain [73,74]. Nociplastic pain is generally chronic and widespread and is caused by disturbance of central pain processing mechanisms such as elevated excitability of ascending and descending pain facilitatory pathways and/or reduced inhibition of descending anti-nociceptive pathway [14,75,76]. The condition refers to central sensitization in which pain is elicited by innocuous stimuli or different kind of stimuli, resulting in causing central hyperalgesia or allodynia, respectively [77]. The process involves increased activity of the insula, anterior cingulate cortex, and the prefrontal cortex, which becomes active during acute pain sensation as well as of the brain stem nuclei, dorsolateral frontal cortex, and parietal cortex, which do not participate during acute pain sensation [78]. Fatigue, negative affect, unrefreshing sleep, and cognitive dysfunction are common accompanying findings in centralized nociplastic pain [79]. This typical pattern of nociplastic pain is observed in fibromyalgia, a medical condition of unknown cause but known to be involved in genetic and environmental factors [80] (Figure 5). Temporomandibular disorder and nonspecific back pain are also characterized by central sensitization (Figure 2 (c)) (Table 1).

The inflammatory response is remarkable in nociplastic pain. The levels of proinflammatory cytokines including IL-1RA, IL-6, and IL-8 were observed to be higher, while anti-inflammatory cytokine Il-4 was found to be lower in patients with fibromyalgia. Several chemokine levels were elevated in fibromyalgia patients. They were monocyte recruiting such as protein eotaxin (CCL11), TARC (CCL17), and MDC (CCL22) and neutrophil chemoattractant MIG (CXCL9) and I-TAC (CXCL11) [81]. Furthermore, the disruption of proinflammatory and anti-inflammatory cytokine network was considered to play a key role in pathogenesis of central sensitization in fibromyalgia. Chronic inflammation

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has been considered to induce central pain in rheumatoid arthritis [82]. Thus, inflammation certainly contributes to the development of nociplastic pain as in fibromyalgia (Figure 2 (d)).

The alteration of TRP metabolism has been linked to nociplastic pain such as temporomandibular disorders myalgia and fibromyalgia. The levels of TRP were observed to be significantly lower in plasma of fibromyalgia compared to control and the KYN/TRP ratio was negatively correlated with anxiety levels. The plasma levels of TRP were negatively correlated with the wrist pain intensity, whereas the KYN/TRP ratio was positive correlated with the average and wrist pain intensity in temporomandibular disorders [83]. TRP depletion appears to be involved in pathogenesis of fibromyalgia and temporomandibular disorders; however, little is known about roles of NMDA receptor agonists 3-HK and QA and NMDA receptor antagonist KYNA. Furthermore, the direct link between KYNs and nociplastic pain has not been reported (Figure 3).

6. Cortical Perception and Psychogenic Pain

Perception of pain is processed in the brain and the spinal cord. The thalamus, sensorimotor cortex, insular cortex, and anterior cingulate decode signals of unpleasant sensation carried through ascending STT, whereas the amygdala and hypothalamus decode signals of urgency and intensity brought through ascending the spinobulbar tract. The third order neurons transfer signals and communicate with the cortex centers. Overall, integration of sensations, emotions, and cognition in the brain lead to perception of pain [84] (Figure 1 (e)). Psychogenic pain is pain without relevant anatomic tissue injury or inconsistent with functional causes in distribution and considered to be caused by psychological factors such as depression, anxiety, and emotion [85]. Individuals with depression, and anxiety often experience psychogenic pain all over their body without any relevant physical cause [86]. Other psychiatric disorders frequently observed in individuals with chronic pain include substance abuse, somatoform disorder, and panic disorders [87]. Furthermore, chronic pain is associated with cognitive impairments such as attention, working memory, reasoning ability, and information processing [88].

Inflammation is obviously involved in psychiatric disorders such as depression and anxiety. Meta-analyses reported strong evidence of significantly increased levels of c-reactive protein (CRP), IL-1, IL-6, TNF-α and sIL-2R in serum of major depressive disorder (MDD) patients [89-93]. Higher concentration of CCL2/MCP-1 was also reported in patients with MDD. CRP of blood, serum or plasma samples was significantly raised in generalized anxiety disorder (GAD) by meta-analysis, and IFN-γ and TNF-α levels were significantly increased in GAD in at least two or more studies [94]. Lower levels of IL-10 and higher ratios of TNF-α /IL10, TNF-α /IL4, IFN-γ /IL10, and IFN-γ/IL4 were observed in the serum of GAD patients, showing significantly increased pro- to anti-inflammatory cytokine ratios, which suggests a distinct cytokine imbalance [95] (Figure 2 (d)).

Similarly, activation of the TRP-KYN pathway has been reported in depression and anxiety. Meta-analyses reported decreased levels of plasma TRP and decreased levels of KYN and KYNA in MDD, while antidepressant-free patients showed increased level of QUIN. The postmortem brain tissues from patients with MDD showed the increased QUIN immunoreactivity in the prefrontal cortex and hippocampus [96,97]. Magnetic resonance spectroscopy suggested a higher turnover of cells with KYN and the 3-HAA/KYN ratio in adolescent depression. Those findings are in accordance with the KP activation toward 3-HK and QUIN branches by pro-inflammatory cytokines activating IDO, and KMO, resulting in higher neurotoxic 3-HK and QUIN levels [98]. Decreased plasma KYN levels were observed in endogenous anxiety and normalized after treatment [99]. KP imbalance by stress or inflammation may cause serotonin and melatonin deficiency, making more susceptible to anxiety (Figure 3).

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7. Conclusion

Pain pathway, pain mechanisms, inflammation, KYN metabolites and enzymes of the TRP-KYN pathway, and representative diseases of pain are overviewed in this review article. Pain sensation can attribute to damage and/or potential harm in various components of pain pathway and corresponding pain mechanisms, involving inflammation and alteration of the TRP-KYN pathway [100]. Chronic inflammation triggers not only nociceptive pain but induces other mechanisms including psychogenic pain. Thus, a search for unique inflammatory signatures and various interventional targets in chronic inflammation is currently under extensive research [101-104]. Intervention through the TRP-KYN pathway is under extensive research to alleviate oxidative stress and excitotoxicity in various illness [105-112]. Chronic pain arises through complex pathogenic process involving more components and developing into the pain continuum. Central sensitization, peripheral sensitization, and somatization are pathogenic processes of pain development in the pain continuum spanning components of the pain pathway and the pain mechanism, which is hardly understood without the presence of the cortical perception (Figure 5). The nociplastic mechanism of pain attempts to delineate pain without relevant cause or lesions of the somatosensory nervous system as altered perception of nociception. Chronic pain presented in fibromyalgia syndrome, chronic back pain, and complex regional pain syndrome are best understood in the framework of pain perception including cognitive, emotional, and social components. Chronic pain experienced in psychiatric condition in particular, is not fully explainable in the view of nociplastic pain mechanism. Pain sensation is developed through complex interactions with higher cortical centers governing mood, emotion, and cognition. More and more emerging findings shed light on relationship of psychiatric symptoms and networks of the brain centers in neuropsychiatric disorders [113-115]. Neuroimaging techniques such as functional magnetic resonance imaging and positron emission tomography may open the gate to understanding underlying mechanisms in signaling to the third order neurons to the cortex in chronic pain sensation [116-118]. Relief of pain can be achieved through accompanying symptoms such as cognition, mood, and sleep by pharmacotherapy and/or psychotherapy [116,119]. Therefore, psychogenic components of pain play an essential role to understand pathomechanism of chronic pain, unless nociplastic pain mechanism can sufficiently elucidate the reciprocal interaction with third order neurons in pathogenesis of chronic pain.

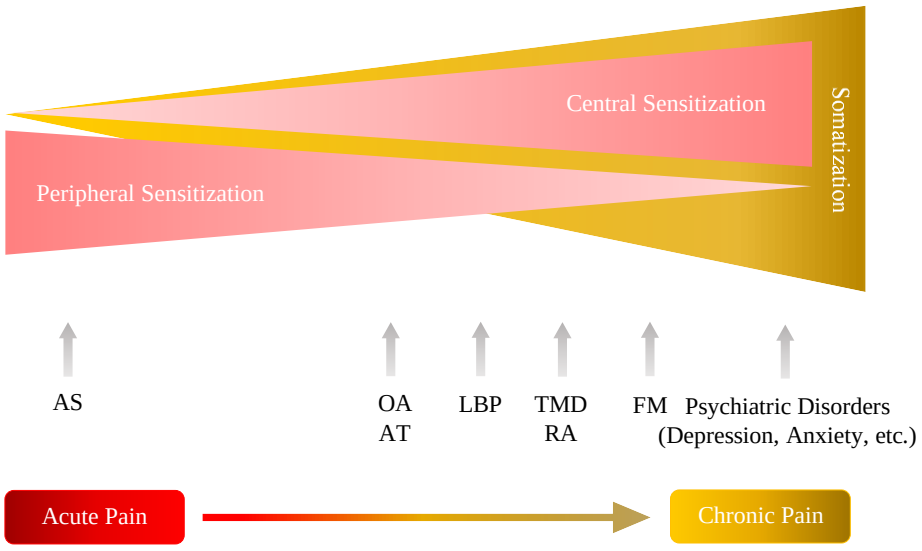

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Figure 4. Continuum of pain sensitization and somatization. AS: ankle sprain, OA: osteo-arthritis, AT; Achilles tendinopathy; LBT: low back pain, TMD: temporomandibular joint disorder, FM: fibromyalgia.

Abbreviations

AA anthranilic acid
Aß fiber A-beta fiber
Aδ fiber A-delta fiber
AMPA receptor α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor
BDNF brain-derived growth factor
BMSCs bone marrow stem cells
CCL2 (C-C motif) chemokine ligand 2
CCR5 C-C chemokine receptor type 5
CGRP calcitonin gene-related peptide
CNS central nervous system
CPS chronic pain syndrome
CRP c-reactive protein
CSF1 colony-stimulating factor-1
CX3CL1 fractalkine
Cx43 connexin-43
CXCL1 (C-X-C motif) chemokine ligand 1
CXCL13 (C-X-C motif) chemokine ligand 13
DRG dorsal root ganglion
DSM-5 Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ET-3 endothelin-3
GABA gamma-aminobutyric acid
GAD generalized anxiety disorder
3-HAA 3-hydroxyanthranic acid
3-HK 3-hydrokykynurenine
IASP International Association for the Study of Pain
ICD-11 11th revision of the International Statistical Classification of Diseases and Related Health Problems
IDO indolamine 2,3-dioxygenase
IL-1β interleukin-1 beta
KAT kynurenine aminotransderase
KMO kynurenine 3-monooxygenase
KYN kynurenine
KYNA kynurenic acid
LE leukocyte elastase
MAPK p38 mitogen-activated protein kinase
MMP-9 matrix metalloprotease 9
NAD^+ nicotinamide adenine dinucleotide
NKA neurokinin A
NMDA N-methyl-D-aspartate
PA picolinic acid
P2R P2 receptor
QA quinolinic acid
SGCs satellite glial cells
SHT spinohypothalamic tract
SMT spinomesencephalic tract
SPMs pro-resolving lipid mediators
SRT spinoreticular tract
SSD somatic symptom disorder
STT spinothalamic tract
T-cells T lymphocytes
TDO tryptophan 2,3-dioxygenase
TGF-β1 transforming growth factor-beta 1
TNF-γ tumor necrosis factor gamma

TRP tryptophan
TRPA1 transient receptor potential cation channel, subfamily A member 1
TRPV1 transient receptor potential cation channel subfamily V member 1
TRPV4 transient receptor potential cation channel subfamily V member 4
XA xanthurenic acid
YLD Years Lived with Disability

Supplementary Materials: None

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