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An Overview of Pathways Encoding Nociception

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Abstract

The nervous system detects and interprets a variety of chemical, mechanical, and thermal stimuli. In the face of tissue injury, local inflammatory products perpetuate ongoing activity and sensitization of the peripheral nerve termini. This ongoing activity evokes a state of robust spinal facilitation mediated by a number of local circuits, the net effect yielding an enhanced message of nociception to higher centers. This messaging typically wanes with the resolution of inflammation or wound healing. However, there are situations in which peripheral and central components of the pain transmission pathway extend and enhance the pain state, leading to a persistent hypersensitivity, e.g. an acute to chronic pain transition. Current work points to the contribution of innate and adaptive immunity in creating these enduring conditions. We briefly describe the underlying biological components of the above both physiological pain processing and pathological pain processing, as well as the acute to chronic pain transition and the role of innate and adaptive immunity in this transition.

Introduction

Detection of noxious stimuli is essential for survival. Acute, high intensity stimuli are alerting, and warn the organism of impending tissue damage. This acute pain sensation often subsides with the resolution of inflammation. However, there are instances in which pain may extended beyond the period of initial inflammation and tissue repair (1–5). Indeed, individuals with chronic inflammatory conditions can experience intense pain that persists even with remission of the inflammatory signs (6). In these cases, the pain state is pathologic, maladaptive, and debilitating. This uncoupling of pain from other signs of injury and inflammation represents a transition from an “acute to a chronic pain state”. In this review, we will briefly outline mechanisms of acute and persistent or chronic pain. In addition, we will consider current thinking regarding the transition from an acute to a chronic pain state, which is thought to involve innate and adaptive immune signaling. A schematic summary of the mechanisms to be discussed are presented in Figure 1. Abbreviations used in the text are presented in the figure legend.

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Physiological Pain Processing Initiated by Acute Stimulation

Under normal conditions, activity in all classes of sensory afferents is largely absent. However, application of a noxious (potentially tissue injuring) stimulus (e.g. thermal, mechanical, chemical) will activate ion channels on the peripheral terminal causing depolarization of the small, first order primary afferent neurons expressing these channels. The action potentials, with a frequency proportional to stimulus intensity, are propagated along the axons of nociceptive Aδ and C fibers, through the dorsal root ganglion (DRG) to the axon terminals in the spinal cord dorsal horn. In response to an intense stimulus, the medium diameter, rapidly conducting Aδ fibers relay well-localized “first” or fast pain, while the small diameter, unmyelinated, slow conducting C fibers convey poorly localized “second” or slow pain. High threshold afferents project into the superficial dorsal horn (referred to as Rexed Laminae I and II), while large, low threshold, mechanically sensitive afferents (Aβ) project into the dorsal horn to terminate in deeper lamina (Lamina III-V). For a detailed review, see (7).

The second order dorsal horn neurons involved in pain circuitry exist in two broadly characterized populations. Lamina I (marginal) neurons lie in the superficial spinal cord, primarily receive high threshold input, and are “nociceptive specific”. Other populations of second order neurons lie more deeply (Lamina V) and send their dendrites dorsally to receive input from low threshold (A fibers) and then high threshold (A∂/C fiber) input, either mono- or poly-synaptically on their distal (superficial) dendrites. This population, referred to as convergent or wide dynamic range (WDR) neurons, shows a graded response over a wide range of A and C fiber mediated inputs. Second order neurons, activated by the acute release of glutamate, acting though glutamate ionophores, such as the AMPA receptor, project to supraspinal sites through crossed ventrolateral tracts. Within the brain, there is not one region responsible for processing all sensory inputs. Rather, projections from the ventrolateral quadrants of the spinal cord ascend following two principal trajectories: i) to the somatosensory thalamus and thence to the somatosensory cortex, and ii) to the medial and ventromedial thalamus, to the limbic forebrain (e.g. anterior cingulate and the inferior insula) (8). The first trajectory appears to encode both location and intensity of the stimulus, while the second provides information to systems associated with emotionality and affect. Hence, acute pain processing is mediated by signals from the periphery through the dorsal horn, relayed through the thalamus to specific central regions for processing, giving rise to the somatosensory and cognitive aspects of pain. For a detailed review, see (9,10). Typically, these signals cease when the peripheral inciting stimulus subsides.

Persistent Pain Processing Secondary to Local Injury and Inflammation

While acute pain is adaptive, local inflammation and injury frequently result in a pain state initiated by otherwise innocuous or moderately aversive stimuli (allodynia and hyperalgesia, respectively). This change in the input-output function reflects two related events: peripheral and central sensitization.

Peripheral Sensitization: In the periphery, tissue injury results in a peripheral sensitization that induces a hyperexcitability of afferent nociceptive neurons (11–14). In the face of tissue injury, there is cell damage, plasma extravasation, activation of local primary

afferent terminals, and the movement of inflammatory cells into the injury site all leading to the release of a myriad of active products including amines, lipids, cytokines, and peptide transmitters (15–33). Importantly, the sensory afferent terminal expresses receptors for virtually all of these products. Activation of the terminal receptors leads to depolarization and increased intracellular calcium. The net effect is terminal depolarization and the activation of a variety of protein (e.g. protein kinase C) and mitogen activated protein kinases (MAPKs). These kinases phosphorylate transducer proteins (e.g. TRPV1) and ion channels, such as the voltage sensitive sodium channels, leading to their enhanced activation (34–36).

Not all peripheral afferents share the same threshold for transmitting signals. Many C-fibers have little or no spontaneous activity and are activated only by intense physical stimuli and are referred to as “silent nociceptors”. In the presence of injury products, these terminals are sensitized such that they become spontaneously active and their activity can be elicited by moderate physical stimuli, analogous to an allodynic state. This functional motif is common to virtually all innervated tissues, (consider diagnoses that end in “-itis”).

Central Sensitization: In the dorsal horn, WDR (Lamina V) neurons display a stimulus dependent response to the discrete activation of afferent C-fibers. Repetitive stimulation of C, but not A, fibers at a moderately fast rate results in a progressively facilitated discharge. The exaggerated discharge of WDR neurons evoked by repetitive small afferent stimulation was dubbed “wind up” by Mendell and Wall (37,38). Intracellular recording in the WDR neuron has indicated that the facilitated state is represented by a progressive and long sustained partial depolarization of the cell, rendering the membrane increasingly susceptible to subsequent afferent input. This central facilitation represents a complex cascade, including: i) phosphorylation of NMDA (N-methyl-D-aspartate) receptor and removal of the magnesium block, which otherwise prevents the functioning of the NMDA ionophore (39–44); ii) activation of metabotrophic receptors for glutamate and substance P (sP, the NK1 receptor), leading to increased intracellular calcium (45–55); iii) activation of voltage gated calcium channels (Cav 2.2, 3.1, 3.2, 3.3 channels) (56,57); iv) activation of a variety of kinases leading to the phosphorylation of membrane channels and receptors enhancing their excitability (33,58–63); v) activation of non-neuronal cells (astrocytes, microglia, T cells) (64–69) leading to the release of a variety of pro-excitatory lipids (prostaglandins) (70,71), cytokines (Interleukin (IL), IL-8, IL-1β, IL-6, tumor necrosis factor (TNF)) (23,72–75) , chemokines (76–80), matrix metalloproteinases (81–86), and endogenous damage/danger associated membrane signals (DAMPS) (87–90); vi) afferent activation of spinobulbospinal excitatory feedback onto dorsal horn nociceptive neurons (8,91–94); and vii) reduced activation and efficacy of intrinsic GABA and glycinergic inhibitory regulation of large (Aβ) excitatory input and second order WDR neuron excitability (e.g. by disinhibition) leading to an enhanced response to large afferent input (95). Together, these cascades contribute to the ongoing hyperalgesic and allodynic states initiated by tissue injury and inflammation. Blockade or inhibition of components of the cascade can reduce the hyperpathic phenotype in models of peripheral inflammation and tissue injury. Usually, these states initiated by inflammation and tissue injury abate with resolution of the inflammatory state and wound healing.

Acute to Chronic Pain Transition

As discussed previously, the pain state associated with and originating from prolonged inflammation may persist even when the inflammatory state resolves. This has been demonstrated in a variety of clinical conditions associated with tissue trauma (post-surgical) and chronic inflammation (rheumatoid disease). This phenomenon has been experimentally demonstrated in antibody generated murine models of joint inflammation, such as the K/BxN (96–98) and collagen antibody induced arthritis (CAIA) models (99,100). In these models, mice develop long lasting, but reversible clinical signs which peak by several days following initiation. At the onset of paw swelling, mice show a decrease in paw withdrawal threshold, indicating development of tactile allodynia. Unexpectedly, this tactile allodynia persists long after resolution of visible swelling and inflammation. Several observations suggest that the pain-like behavior occurring during active inflammation (inflammatory phase tactile allodynia) is phenotypically distinct from pain-like behaviors persisting after the resolution of inflammation (post-inflammatory phase tactile allodynia). First, tactile allodynia in the inflammatory phase is transiently reversed by anti-inflammatory agents (e.g. non-steroidal anti-inflammatory drugs) and centrally active anti-hyperalgesic agents (e.g. gabapentin) used for the treatment of neuropathic pain, while the post-inflammatory phase tactile allodynia is only affected by the centrally active anti-hyperalgesics (96). Second, mice in the post-inflammatory phase show increased activating transcription factor 3 (ATF3) positive neurons in the DRG, a marker associated with nerve injury and neuropathic pain (96). Finally, in chronic inflammatory models, there is a sprouting of peptidergic and non-peptidergic primary afferents as well as post-ganglionic sympathetic (tyrosine hydroxylase positive) fibers into the inflamed joint and the appearance of growth associated protein (GAP 43), a marker of axonal neurite formation and regeneration (101–104). Together, these observations indicate that there is a transition from an acute inflammation to a post-inflammatory *neuropathic* pain phenotype in these models of arthritis, leading to a persistent pain condition. Additional studies have implicated both the innate and adaptive immune systems as playing distinct roles in governing this transition to chronic pain state.

Innate immunity.—There is a growing appreciation that components of the evolving pain may reflect a role for innate and adaptive immunity (64,87,105–108). The role of microglia (brain resident macrophages) and astrocytes in pain pathophysiology is well appreciated. Recent work has shown that several Toll-like receptors (TLRs), such as TLR4, are robustly expressed on glia and primary afferent neurons (109–111). These receptors are activated by a variety of exogenous pathogen-associated molecular patterns (PAMPs) and endogenous ligands commonly referred to as damage associated molecular patterns (DAMPS) (112,113). For example, TLR4 may be activated by agents such as high mobility group box 1 (HMGB1), Tenacin C and various lipids to activate downstream signaling, leading to the production of a variety of proalgesic cytokines (64,87,88). A specific role of TLR4 in mediating the acute to chronic pain transition in the K/BxN model of arthritis has been described (114). In those studies, TLR4 mutant mice (C3H/HeJ) developed an inflammation commensurate to the wild type control. In contrast, the TLR4 mutants showed a resolution in their pain state with the resolution of inflammation. This work has been confirmed using a TLR4 knockout mouse. Additional work has shown that spinal TLR4 signaling can mediate the acute to chronic pain transition. The intrathecal administration of a TLR4 antagonist

(LPS-RS) during the inflammatory phase has no effect on inflammation, but prevents the development of the persistent pain state in a wild type mouse (114). It is important to note, however, that this same treatment in the post-inflammatory phase did *not* affect thresholds, indicating that spinal TLR4 signaling here is specifically mediating the transition from acute to chronic pain.

Adaptive immunity.—Current work is beginning to show that elements associated with adaptive or acquired immunity also play a role in persistent pain states. Anomalous chronic pain states have been linked to T-cell activation and the release of cytokines from spinal microglia that enhance neuronal activity (115). Interestingly, recent evidence indicates that microglia are not required for pain hypersensitivity in female mice. Rather, female mice develop hypersensitivity through the activation of T-lymphocytes (116). This sexual dimorphism is only beginning to be investigated, but is a very important subject of current work (117–119). It appears likely that a variety of chronic pain states as diverse as fibromyalgia (120), paraneoplastic syndrome (121), and complex regional pain syndrome (122) may involve autoantibody mediated mechanisms. The role of autoantibodies in the induction of chronic pain states are of significance and may contribute to a pain state by several mechanisms. First, it has been shown that IgG immune complexex may initiate a pain state in the rat through an interaction with Fcγ receptors, which have been identified to have stimulatory effects on DRG neurons (123,124). Alternatively, autoantibodies may be formed against self-epitopes leading to antibody binding to nerves and DRG, complement fixation, and pain. In fact, autoantibodies against paranodal proteins leading to complement binding have been associated with painful inflammatory demyelinating polyneuropathies (125). Additionally, nerve injury may lead to the generation of autoantibodies to nerve injury products such as myelin basic protein leading to hyperpathia in females (126). Further, plasma taken from human rheumatoid arthritis patients containing autoantibodies against anti-citrullinated protein antibodies (ACPA) can induce pain states independent of inflammation in mice (99,127). In that study, it was observed that, rather than a direct effect on sensory neurons, ACPA binds CD68+ osteoclasts in the bone marrow and induces CXC-chemokine ligand (CXCL) 1 and 2 expression and release from the joints, which then activates pro-nociceptive receptors on local primary afferents. Importantly, these autoantibodies often appear long before signs of inflammation in rheumatoid arthritis, and this ACPA – osteoclast interaction may contribute to the early arthralgia reported by patients. In other conditions, the targeting of autoantibodies directed at voltage-gated potassium channel complexes leads to neuronal hyperexcitability (128). Overall, there is an emerging and very exciting literature on the role of autoantibodies in generating pain states with chronic inflammatory conditions and after nerve injury indicating, again, a possible mechanistic convergence for the chronic inflammatory with the neuropathic pain phenotype.

Conclusions

Traffic in small afferents leads to a stimulus dependent central processing that is highly aversive. In the face of tissue injury and inflammation, there is the generation of a robust effect on the peripheral terminal that leads to a sensitization of the peripheral terminal and the generation of ongoing afferent traffic. At the level of the dorsal horn, this input activates

second order dorsal horn neurons that encodes the intensity and modality of the stimulus and relays input to higher order centers that give rise to the perceptual experience of pain and drive systems that are associated with complex responses. In the face of injury and inflammation, the persistent afferent input leads to a robust increase in the input / output function and results in modest stimuli being encoded more intensely. Under many circumstances, this input and the attendant pain states will resolve as the injury and inflammation are resolved. Under other circumstances, the chronic inflammatory state leads to major changes in the pain phenotype to resemble that produced by nerve injury. While the mechanisms underlying this transition are not clear, current work points to the importance of resident inflammatory cells in the spinal cord and the pivotal role played by systems commonly associated with innate and adaptive immunity. This immune signaling appears to play a common role in the evolution of a variety of persistent pain phenotypes. Further understanding of neuroimmune interactions will allow for the better treatment or prevention of persistent pain states.

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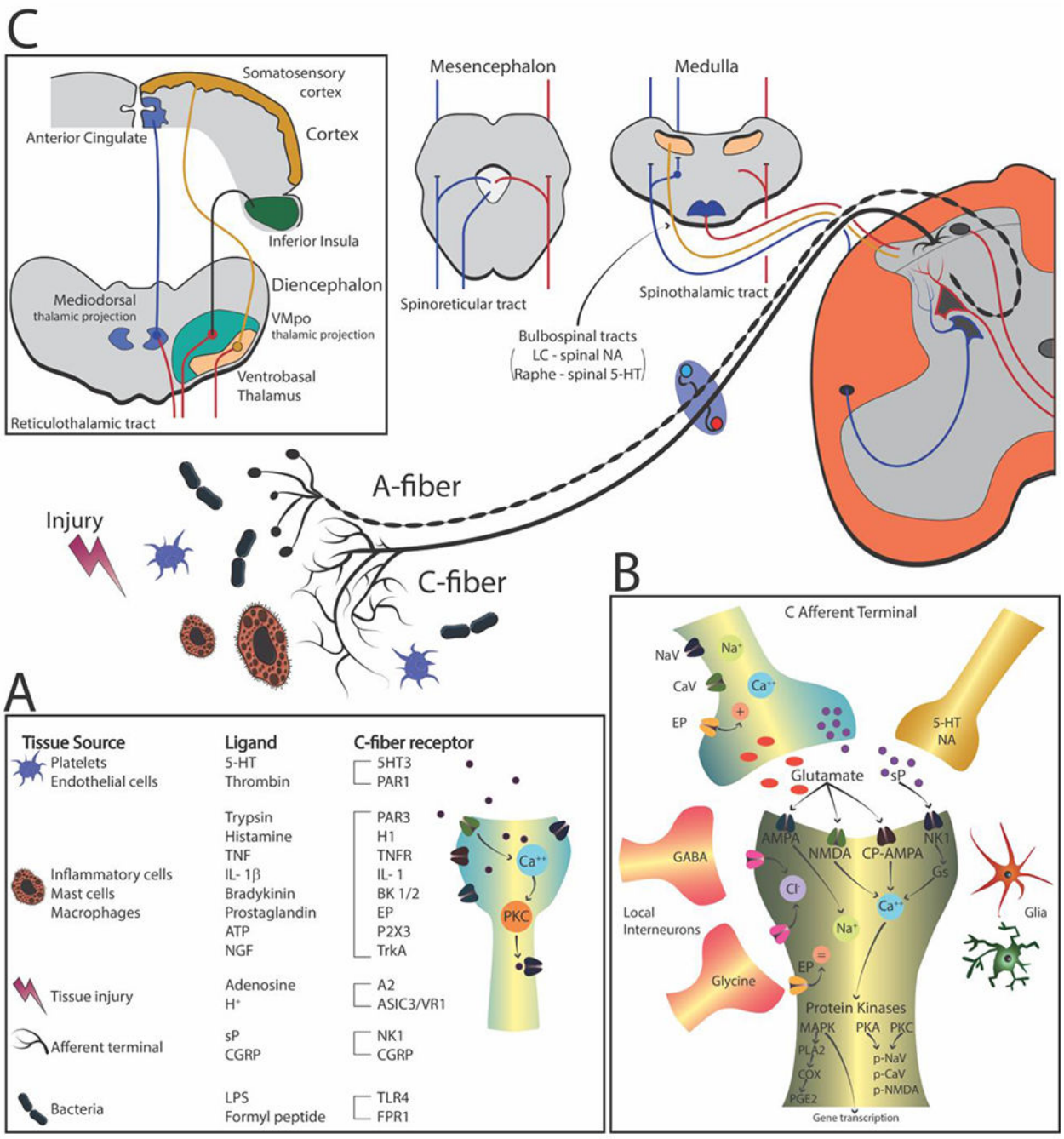

Figure 1:

A. Tissue injury, inflammation, or infection lead to local release of pro-inflammatory mediators (inflammatory soup) from resident cells (mast cells, Schwann cells), in migrating cells (macrophages, neutrophils), damaged cells, and blood vessels. These products act on receptors expressed on the afferent C fiber terminal to mediate an ongoing terminal depolarization and increased intracellular Ca^{++}, which, in turn, activates terminal kinases. Phosphorylation of terminal receptors and channels enhances their responsiveness and results in “terminal sensitization”. **B.** Nociceptive afferents synapse onto superficial (Lamina

1) and deep (Lamina V) neurons, and, though activation of afferent terminal CaVs, release glutamate and peptides (substance P) which act on eponymous post-synaptic receptors. In the face of ongoing C fiber input, the second order neuron displays marked increases in excitability resulting from increased intracellular Ca^{++} that activates a myriad of protein kinases which i) phosphorylate receptors and channels, and ii) activate a variety of excitatory enzyme systems and iii) enhancing gene transcription. Other facilitatory components of dorsal horn function activated by ongoing C fiber input are: i) activation of glia (microglia and astrocytes) which release a constellation of pro-inflammatory molecules, ii) reduced effects of local GABA and glycinergic inhibition and iii) bulbospinal facilitatory input. **C.** These events initiate and maintain a hyperexcitable state, sending the processed nociceptive signals to higher brain centers though the contralateral spinothalamic tract to the thalamus, and collateral projections into brainstem nuclei. Supraspinal projections largely follow two major trajectories: those projecting into the lateral (somatosensory) thalamus and thence to the somatosensory cortex and those projecting to more medial regions that then project to areas such as the inferior insula and the anterior cingulate. Other details considered in this figure are presented in the text. Abbreviations: 5-HT, serotonin; A2, adenosine receptor; AMPA, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; BK 1/2, bradykinin receptor; CaV, voltage-gated calcium channel; CGRP, calcitonin gene related peptide; CGRP, calcitonin gene related peptide; COX, cyclooxygenase ; CP-AMPA, calcium permeable AMPA receptor; EP, prostaglandin receptor; FPR1, formyl peptide receptor 1; GABA, gamma-aminobutyric acid; Gs, stimulatory signaling protein.; H1, histamine receptor; IL-1, Interleukin-1; IL-1b, Interleukin-1; LC, locus coeruleus; LPS, lipopolysaccharide; MAPK, mitogen activated protein kinase; NA, noradrenalin; NaV, voltage-gated sodium channel; NGF, nerve growth factor; NK1, neurokinin 1 receptor; NMDA, N-methyl-D-aspartate receptor; P2X3, purinoreceptor 3; PAR, proteinase activated receptor; PGE2, prostaglandin E2; PKA, protein kinase A; PKC, protein kinase C ; PLA2, phospholipase A2; sP, substance P; TLR4, Tropomyosin receptor kinase A; VMPO, ventromedial pars oralis; VR1, vanilloid receptor type 1.