

Biomechanics of Musculoskeletal Pain: Dynamics of the Neuromatrix

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Abstract

Pain, due to mechanical stimuli, is a normal, indeed healthy, response of animals to potential or actual damage to tissues. Mammals in general, and humans in particular, have evolved a highly sophisticated system of pain perception, which is characterized in humans by complementary but distinct neural processing of the intensity and location of a noxious stimulus, and a motivational/emotional or affective response to the stimulus. The peripheral and central neurons that comprise this system, which has been called the “neuromatrix”, dynamically (temporally) respond and adapt to noxious biomechanical stimuli. However, phenotypic variability of the neuromatrix can be large, which can result in a host of musculoskeletal conditions that are characterized by altered pain perception, which can and often does unto itself alter the course of the condition. This neural plasticity has been well recognized in the central nervous system, but it has only more recently become known that peripheral nociceptors also adapt to their altered extracellular matrix environment. This work reviews the biomechanics of pain focusing on the relevant stimulus that initiates responses by nociceptors to the cognitive perception of pain.

Introduction

Pain, due to mechanical stimuli, is a normal, indeed healthy, response of animals to potential or actual damage to tissues [96]. Mammals in general, and humans in particular, have evolved a highly sophisticated system of pain perception [84,111,148], which in humans is characterized by complementary but distinct neural processing of the intensity and location of a noxious stimulus [59], and the motivational/emotional or affective response to the stimulus [110]. The peripheral and central neurons that comprise this system, which Melzack has termed the “neuromatrix” [82,83,85], dynamically (temporally) respond and adapt to noxious biomechanical stimuli [22] (Figure 1). The importance of these divisions within pain perception is illuminated by considering how humans with congenital *insensitivity* to pain respond to noxious stimuli (reviewed in [100]). During their lifetimes, these individuals, with one of five types of hereditary sensory radicular neuropathy (HSAN I – V), accumulate a plethora of “painless injuries”. HSAN causes a loss of unmyelinated (or ‘fine’) peripheral afferents, specifically C-nociceptors, due to aberrations of the gene that encodes for receptors for nerve growth factor (NGF), esp. *trkA* for HSAN IV [52] (Table 1). In contrast, individuals with congenital *indifference* to pain have normal sensation, including responses to noxious stimuli, but do not have the affective response to noxious stimuli [14,49,70]. Individuals with lesions affecting the limbic system may develop loss of the affective-motivational component of pain, but still retain recognition of the intensity and location of pain [8,114]. The reverse of this has also been seen in patients with lesions of the somatosensory cortex, who can only vaguely report where the noxious stimulus is occurring, but know that it’s unpleasant or painful [109].

The dynamic and adaptive response of the neuromatrix to noxious mechanical

stimuli is well exemplified by individuals with fibromyalgia syndrome (FMS), for whom there is a growing consensus that this is primarily a disorder of the central nervous system (reviewed in [42,137]). Patients with FMS demonstrate many characteristics of central sensitization [27], which is characterized by increased neural responses of the second-order nociceptive neurons (with their cell bodies in the dorsal horn of the spinal cord) to primary nociceptor inputs from skin and especially muscle [152]. FMS patients have greatly enhanced pain responses during temporal summation or “wind-up” [112,138,139], which is characterized by increasing pain to constant mechanical stimuli repeated at short intervals (on the order of 3 s). Further, they also demonstrate sensitization to the initial pain [139]. The mechanism by which wind-up occurs is due to a relative depolarization of the second-order neurons that have N-methyl-D-aspartate (NMDA) receptors [24,30,101]. The repeated stimulation removes a magnesium ion block on membrane channels allowing a calcium ion influx. Using a NMDA antagonist, for example ketamine, blocks the wind-up in FMS patients but not their initial pain [139].

The transmission by second-order nociceptive neurons (with their cell-bodies principally in laminae I and II of the dorsal horn) to the thalamus (and from there to the higher level brain centers, including the somatosensory cortex) is dynamically modulated by neurons descending from the midbrain (esp. ventrolateral periaqueductal gray), which synapse in the rostral medulla (e.g., nucleus raphe magnus), which in turn synapse on the second-order nociceptive neurons [6,7] (and reviewed in [11]) (Figure 2). The neurons in this antinociceptive or negative feedback system utilize a variety of neurotransmitters (reviewed in [36]) for synaptic transmission of their signals including non-peptides (serotonin [119], norepinephrine [157], gamma-aminobutyric acid (GABA –

an inhibitory amino acid [44,116,156]), and opioid peptides (endorphins [149], enkephalins [135], and dynorphins [76]). The presence of this descending antinociceptive system raises the epistemological question of why is it there in the first place. Bolles and Fanselow [12] published the first model that hypothesized that it was an evolutionary development in mammals that enabled them to respond to real danger (i.e., life-threatening situations) without activating the recuperative processes involved with dealing with noxious stimuli. Their seminal work has subsequently been further augmented and elaborated by others, which essentially validated their hypothesis (reviewed in [44,130]).

Segmental levels of the spinal cord themselves possess some antinociceptive functions using GABAergic interneurons [77,146]. In cat and monkey laminae I and II of the lumbar dorsal horn, interneurons immunoreactive to GABA were found to have presynaptic and postsynaptic influences on primary high threshold mechanoreceptor (HTM) A δ terminal endings [2]. GABAergic interneurons also synapse on A δ and C terminal endings that express metabotropic glutamate receptors [145]. However, using the spinally-mediated tail-flick test in rats combined with selective cord transection, antinociception to paw shock in the forelimb was shown to be controlled by supraspinal descending control, whereas in the hindlimb it was controlled by lumbar intraspinal mechanisms [154]. In addition to GABAergic interneurons themselves, intraspinal antinociception is also strongly mediated by neurons expressing opioid receptors (e.g., mu and kappa or mu and delta opioid receptors) [155]. The intensity of the noxious stimulus also appears to play a role in whether antinociception is dominated by intraspinal or supraspinal mechanisms. More intense electric (3.0 mA vs. 1.0 mA) tail-

shock to rats produced intraspinal antinociception [80,81].

The time frames, in which neurons change in response to noxious stimuli, range from milliseconds to weeks (& even months). Longer term, and more persistent, changes in neural responsiveness all require changes in gene expression, transcription, and protein expression. The magnitude of these changes has recently been illuminated using a combination of DNA microarray, quantitative real-time PCR, and immunohistochemistry to examine differential gene expression in a rat, chronic neuropathic pain model [153]. Using sciatic nerve ligation (SNL), gene expression in neural soma of the ipsilateral dorsal root ganglia (DRG) was differentially compared to the contralateral DRG. Wang et al. [153] found that 88 genes were up-regulated (i.e., increased) more than two-fold, with three neuropeptide encoding genes (NPY, Galanin, and VIP) having increases of 45-, 18-, and 14-fold, respectively. Up-regulation of genes occurred in the following broad categories (with the number of specific genes in parenthesis): cell cycle- and cell death-related (7), neuroinflammatory and immune activation (22), ion channel (10), transcription (3), and tissue maintenance/remodeling/plasticity (23). Notably, these DRG up-regulation changes were not found in the dorsal spinal cord [144]. Focusing on several immediate early genes (IEG), Delander et al. [25] also used a SNL model and found that c-fos, NGFI-A, and jun B were transiently up-regulated within hours, though c-jun mRNA expression was increased during the entire 4 week period of the study. Not only were there profound changes in gene expression of DRG soma of injured neurons, SNL also produced profound changes in the expression and distribution of voltage-gated sodium channels in uninjured unmyelinated axons (i.e., C fibers) [41]. This suggests that

aberrant responses in uninjured C fibers appear to be necessary for persistence of neuropathic pain.

The mechanosensitive terminal endings of nociceptors that directly transduce noxious mechanical stimuli are affected by, and also secrete, a variety of neuropeptides (reviewed in [33,43,117]). The basal lamina of “free” nerve endings of nociceptors (Group IV or C afferents in muscle and skin, respectively) are exposed to the interstitial fluid only at certain regions and otherwise are covered by Schwann cell cytoplasm [97,150]. Near these exposed areas are vesicles containing neuropeptides, including substance P (SP), somatostatin (SOM), and calcitonin-gene related peptide (CGRP), which are secreted when the nociceptor is stimulated [4,99]. These areas are the putative locations for a variety membrane receptors and ion channels [46,47,97], though these receptors and channels also appear elsewhere in the neurons.

Background of Primary Muscle Nociceptors

Historically, there are two important conceptual developments that began the scientific, neurophysiological examination of pain. First, in 1900, Sherrington [127] formally defined the difference between the perception of pain and the neurons which transduce noxious stimuli:

“... the skin is provided with a set of nerve-endings whose specific office it is to be amenable to stimuli that do the skin injury, stimuli that in continuing to act would injure it still further. These nerve-endings when still connected with the sensorium (using that term simply to mean the neural machinery to which consciousness is adjunct) on excitation evoke skin pain. ... For physiological reference, therefore, they are, it seems to me, both on this ground and on others which need not be entered upon here, preferably termed *nocicipient*, a name which has the advantage of greater objectivity.”

A few years later, he described a relationship between noxious stimuli and behavioral reflexes (e.g., withdrawing a limb) to reduce further tissue damage and to avoid further pain [128]. Second, in 1906, he formalized the concept of the “adequate stimulus”

whereby specific types of neurons preferentially respond to specific types of stimuli [129]. Thus, our current concept of muscle pain developing from the activation of primary nociceptive afferents innervating muscle came from his insights almost a century ago.

Another major historical development was the development almost 40 years ago of the gate control theory of pain by Melzack and Wall [86]. Arguably, the main contribution of their theory was the inclusion of the brain as an influence on the transmission of nociceptive signals from the spinal cord [83], rather than the more well known concept of gating in the dorsal horn of transmission of small diameter afferents (i.e., nociceptive afferents) by large diameter afferents (i.e., mechanoreceptive afferents), which had been proposed earlier by Noordenbos [105]. Their “revolutionary” idea was that the central nervous profoundly influenced the perception of pain, and this theory contravened much of the previous three centuries of scientific thought and investigation, which originated with the philosopher, physicist, and mathematician Descartes (Figure 3) [83].

The majority of modern basic science studies investigating pain and primary nociceptors have focused on cutaneous nociceptors because the skin and its innervation are easily accessed. These studies have been helpful in understanding the neurophysiology of nociceptors, but are not necessarily as clinically relevant as investigations of muscle nociceptors. Further, the structural components and their organization are profoundly different in muscle than skin [35], and hence the mechanical states encoded by muscle nociceptors may be quite different from those encoded by cutaneous nociceptors.

Anatomy and Physiology of Muscle Nociceptors

Sensory information from muscles is carried by afferent neurons that are typically categorized as belonging to groups I – IV based upon their conduction velocities (CVs). Lloyd [75] originated this nomenclature specifically for afferent neurons from muscles (and their tendons and fascia). Groups I and II afferents are thickly myelinated and, respectively, have large diameter axons (12-20 μm and 2 –16 μm) and conduct impulses at fast rates (79 –114 m/s and 30 – 80 m/s). Group I afferents mostly, but not exclusively [5], innervate muscle spindles and tendon organs, while Group II afferents innervate spindle secondary endings and spray (Ruffini) endings [98]. Noxious stimuli in muscle are transduced by small diameter afferents with thinly myelinated axons (group III: CV ranging from 2 – 30 m/s) or unmyelinated axons (group IV: CV < 2 m/s) [51,106]. However, groups III and IV afferents are not exclusively nociceptive, and some of these afferents transduce non-noxious mechanical and thermal stimuli. Using early histological methods [48], light and electron microscopy [136], as well as three-dimensional reconstruction of series of semi- and ultrathin sections [46], both groups III and IV afferents have been found to terminate as ‘free’ or ‘non-corporcular’ receptive endings. In other connective tissues (e.g., skin, ligament, or joint capsule), afferents with these same CVs and also terminating as ‘free endings’ are termed A δ and C fibers, respectively. Despite their small diameter axons and slow CVs, group IV afferents supply 40 – 60% of the total sensory innervation to muscle [71].

The receptive endings of muscle nociceptors, imaged by light and electron microscopy, are found in all types of tissues within muscles: connective tissue, extra- and intra-fusal muscle fibers, adventitia of arterioles and venules, tendon, and fat cells [136]. However, the majority of nociceptors, expressing SP &/or CGRP, appear to be

associated with capillaries and arterioles [118]. A single axon will typically branch, forming 2 – 4 separate receptive endings that can often innervate different histological structures within the muscle [13,97]. Messlinger [97] has termed this multiple innervation of different histological structures as *polytopographical innervation* and speculates that it may be related to the well-documented phenomena of polymodality of nociceptors (cf. [89]). The term “polymodal nociceptor” was first introduced by Bessou and Perl [10] to describe feline, cutaneous nociceptors that had high thresholds to mechanical stimuli and were also activated by noxious heat ($> 45^{\circ}\text{C}$) as well as irritant chemicals. The same type of afferents were subsequently found in human, cutaneous neurons using percutaneous microneurography [147], and were also found to be present in canine muscle [69].

Activation of a peripheral nociceptor by an adequate stimulus depends upon the presence of specific ion channels and receptors in the plasma membrane of the receptive ending [37] (Figure 4). Ion channels are formed by proteins that span the lipid bi-layer that forms the cell plasma membrane. Conformational changes in the proteins result in opening and closing of these channels (also called ‘gating’), and when the channels are open, ions can pass into or out of the cell through diffusion. Change in ionic concentration at the membrane level produces a change in the electric ‘potential’ (or voltage), which is also termed the ‘receptor potential’. If sufficiently large, the receptor potential will depolarize the axon to threshold and evoke an ‘action potential’ that is actively propagated along the length of the axon.

Some nociceptors have cationic channels that are gated by mechanical loads [20,32], but the probability (or sensitivity to) gating can be influenced by various ligands

(Figure 4). Bradykinin (BK) binds to either a B1 or a B2 membrane-bound receptor, which then initiates an intracellular cascade that ends in increased protein kinase C (PKC) concentration that increases the sensitivity of sodium (Na^+) channels [31]. Prostaglandin E_2 (PGE_2) binds to an EP1 or EP2 receptor, and via the cyclic adenosine monophosphate (cAMP) pathway, increases non-specific cation channel opening [65]. Similarly, serotonin (5-HT) and adenosine utilize the cAMP pathway to affect protein kinase A (PKA), which sensitizes a Na^+ channel that is tetrodotoxin (TTX)-resistant. A mechanical stimulus sufficient to injure muscle cells (disrupt their cell membranes) will cause them to release their stores of adenosine tri-phosphate (ATP), which can bind to a purinergic receptor P2X and directly gate a Na^+ channel [15]. Acid sensing ion channels (ASIC) are cation channels (Na^+) that are gated by protons (H^+) or increased pH of the extra-cellular matrix [151], and can be sensitized by neuropeptide SF [28]. Similarly, the now well-known vanilloid receptor, which responds to capsaicin and heat [16,17] can be sensitized by BK, NGF, and ATP [29]. Finally, the terminal ending of a nociceptor can be de-sensitized (antinociception) by the binding of endogenous opioids released by lymphocytes, which have migrated to the inflamed tissue [142,143]. Hence, there are a wide range of influences on the terminal endings of nociceptors that can directly activate and/or sensitize its neural response, and may cause primary nociceptors to function as pattern generators (i.e., more than just relaying the intensity of a noxious stimulus) [117].

Muscle Nociceptor response to stimuli

To examine the types of stimuli to which in-vivo muscle nociceptors respond, electrophysiological recordings have been made from single peripheral afferents from cat and rat muscles. Nociceptors were found to respond to single and/or combinations

of natural stimuli including: noxious (tissue damaging) mechanical stimuli [56,57,92], temperature [92], BK [93], PGE₂ [123], 5-HT [87], thromboxane A₂ [58], ATP [23], and leukotrienes [90]. In human psychophysics experiments, combinations, but not isolated peptides, of CGRP and either SP or neurokinin A injected into skeletal muscle produced pain [108]. In skin, nociceptors have been shown to respond to protons (H⁺ ions, low pH) [140,141] as well as SP [91]. Further, Heppelmann et al. [46] have found that group III afferents with receptive endings terminating in dense connective tissue were more likely to have high mechanical thresholds while those that terminated in soft, more vascularized, connective tissue tended to have lower mechanical thresholds. Thus, single nociceptors with multiple terminal branches may be influenced solely or predominantly by one type of noxious stimulus (e.g., mechanical or endogenous chemical) because of their location within a muscle.

The sensitivity of muscle nociceptors to noxious mechanical stimuli can be increased by the presence of different endogenous substances [55] (and reviewed comprehensively by Mense [89]). This mechanism is presumed to be the cause of muscle tenderness and hyperalgesia [89]. Following the administration of BK, muscle nociceptors will respond to non-noxious mechanical stimuli, which is termed allodynia (i.e., their mechanical thresholds have been lowered) [34,93]. Intriguingly, Mense and Meyer [93] did not find that nociceptors were sensitized equally to all types of mechanical stimuli; rather, some afferents could be sensitized to stretch but not to contraction and others to other combinations of mechanical stimuli. Administration of PGE₂ and 5-HT further sensitized the nociceptors to effects of BK [87].

Ischemic contraction of muscle activates nociceptors that would not otherwise

respond to muscle contractions of similar magnitude [56,88,94]. However, ischemia alone is not an effective stimulus for muscle nociceptors [94], and in humans does not produce pain unless it persists for long duration [74]. Muscle mechano-nociceptors that do respond to contraction do not show an increase in discharge rate during ischemic contraction [94]. Thus, nociceptor activation during ischemic contraction appears to affect a subpopulation of nociceptors that may be responding to changes in pO₂, pH, BK, and/or PGE₂ [89].

Following an acute mechanical trauma to a muscle (e.g., blunt blow or over-stretch), the resultant pain can be attributed to two different, though related, mechanisms. First, the initial pain would undoubtedly be due to the direct activation of mechanically sensitive groups III and IV afferents with mechanically gated channels in their receptive endings [38]. While the neural responses of low threshold mechanoreceptors (predominantly group II, but some group III afferents) would tend to quickly saturate during such a noxious mechanical stimulus, they would certainly contribute to a perceptual localization. Conjointly, the nociceptors innervating the injured tissue would vigorously respond during the time that their mechanically gated channels were open. In skin, spatial populations of mechano-nociceptors have been shown to encode the location and intensity of a noxious indentation, as well as provide some information about the geometry of the indenter [63]. Second, mechanical stimulation of the nociceptors would cause them to secrete, via the axon reflex, SP, CGRP, and SOM into the extracellular matrix, which would produce a neurogenic inflammation. SP causes an increased permeability of local blood vessels, which may be assisted by damage to the vessels from the noxious mechanical stimulus. Extravasation of blood plasma

results in increased concentration of BK (from kallidin in the blood), PGE₂ (& other prostaglandins) from endothelial cells, and 5-HT from platelets. The net effect would be a reduction in threshold and increase in sensitivity of mechano-nociceptors (producing allodynia and hyperalgesia, respectively), as well as activating previously “silent” or insensitive mechano-nociceptors [115,124,125,126].

Sympathetic efferents are known to influence the development of some types of pain (for review see [113]). However, the interaction between sympathetic efferents and muscle nociceptors is not certain for a number of reasons. First, most studies reported in the literature have examined the interaction between sympathetic efferents and cutaneous nociceptors [113] rather than muscle nociceptors, and it is not known if results from the cutaneous nociceptors can be appropriately extrapolated to muscle nociceptors. Second, increases in neural response by cutaneous nociceptors during sympathetic efferent stimulation have been produced by electrical stimulation of the sympathetic trunk, but this is not a physiological mechanism (cf. [120]). Third, injection of inflammatory substances have produced increased nociceptive responses (cf. [50,67]), but again these are not necessarily physiological stimuli. Fourth, it seems unlikely that sympathetic efferents would play any significant role in *acute* muscle pain. Rather, their role would be plausible in persistent or chronic muscle pain since they have potent roles as inflammatory mediators [66,73] and tissue compliance mediators via vasomotor control [95] among others.

Delayed onset muscle pain is most commonly associated with the performance of muscle contractions where the external force is greater than that generated by the muscle itself [54]. This results in muscle lengthening during the contraction and is

commonly termed an “eccentric contraction”. Clinical trials have clearly demonstrated that greater pain is developed from eccentric than concentric or isometric contractions [103]. Eccentric exercise in humans increases inorganic phosphate [1] and creatine kinase [104] concentrations in muscle. Preventive administration of L-carnitine before eccentric exercise results in significantly decreased pain levels [40] compared to controls. L-carnitine has vasodilatory effects and presumably flushes endogenously released nociceptor ligands from the muscle. Contrary to popular opinion, muscle lactate (or lactic acid) does not appear to be directly involved in muscle soreness following rigorous exercise [68]. Lactate concentrations rapidly decrease to resting levels in less than one hour [122] following exercise, and unless they are activating a secondary agent, are unlikely to be involved in development of pain that commonly occurs 12 to 24 hrs later. Similarly, decreases in muscle pH following exercise are relatively transient and return to resting levels generally in less than 30 mins [3,18,122]. However, a recent rat model of long-lasting hyperalgesia has been developed that created hyperalgesia by injections, separated by two or five days apart, of low pH saline (4.0 – 6.0 pH) into the gastrocnemius muscle [133]. The lowered pH was transient, lasting less than 20 min, but the subsequent hyperalgesia lasted for four weeks. There are no published reports of direct neurophysiological tests of nociceptor responses to either phosphate or creatine kinase. Thus, these substances may or may not be causally related to delayed onset muscle pain. Finally, the role of muscle inflammation due to eccentric contractions as a cause of delayed onset muscle pain is unclear [134]. There is no doubt that inflammatory mediators can activate muscle nociceptors and produce pain (as described earlier in this article). However, the administration of anti-

inflammatory medication is ineffective in relieving delayed onset muscle pain [102]. Hence, the hypothesis that delayed onset muscle pain is a result of inflammation is yet unproven.

Muscle cramps are defined as painful, involuntary contractions of muscle [26]. While muscle cramps are extremely common [72], the mechanisms for the resultant pain due to the cramp are still largely unknown [89]. Presumably, groups III and IV nociceptors sensitive to muscle contraction are activated as has been observed in single unit recordings from electrically stimulated cat muscle [51,56,57,68,92,94,106,107]. However, the relevant mechanical stimulus for causing nociceptor activation during cramp is unknown. Mense [89] has speculated that shearing forces may directly activate muscle nociceptors during a cramp where only part of the muscle is contracting at a high frequency.

Adequate mechanical stimulus to activate muscle nociceptors

Natural, mechanical stimuli (other than muscle cramp) that provoke the neural responses of muscle nociceptors are compression and/or stretch. Using hindlimb muscles in the cat, Bessou and Laporte [9] were the first to systematically examine the responses of group III and IV afferents to these stimuli. They were followed by Paintal [106] who stimulated group III muscle afferents by also squeezing, stretching, and prodding the cat hindlimb muscles. These investigations showed that some, but not all, group III and IV afferents respond to 'natural' mechanical stimuli. They also established that some group III afferents responded to innocuous (i.e., non-noxious) mechanical loads, and, hence, functioned as mechanoreceptors rather than nociceptors.

Compression and/or stretch of muscles has also been used to examine the role of group III and IV afferents as 'ergoreceptors' (i.e., neural receptors that reflexively affect

respiration and cardiovascular output) [56,57,68]. Group III afferents were found to be more responsive to static contraction than to rhythmic contraction in the cat hindlimb, and group III afferents that were associated with cardiovascular response to hindlimb muscle stimulation acted more as mechanoreceptors than as nociceptors. Group III afferents are also sensitized by muscle fatigue, though they probably function only in a secondary fashion to mediate the initial decline in motoneuron rate observed during fatiguing maximum voluntary muscular contraction [45]. Group III and IV afferents mediate the clasp-knife reflex whereby vigorous mechanical stimulation (i.e., stretch) of a muscle inhibits nearby extensor muscles and excites nearby flexor muscles [21,121].

The techniques of microneurography and intraneural microstimulation have been employed to examine in humans how muscle nociceptors encode deep pain [79,131]. Briefly, the technique involved inserting a thin diameter recording electrode through the skin of an alert, human volunteer, and advancing the electrode until its tip penetrated a nerve. The electrode was manipulated incrementally until the neural responses of single afferents could be discriminated. Putative nociceptors were identified on the basis of their conduction velocities. Discriminated, single, groups III or IV afferents were electrically stimulated and the reported painful area in the muscle was superficially mapped on the skin. Then, the same area was compressed with a cylinder at intensities reported as being 'painful' by the human volunteers, and the neural responses of the identified afferents were recorded. These studies showed that painful (and noxious) mechanical stimuli in human muscles are carried by group III and IV afferents in the same fashion as noxious mechanical stimuli in animal models.

Relevant Mechanical Stimulus

An important question to determine is what is the "relevant" mechanical stimulus

that activates muscle nociceptors [78,89,132]. During compression or stretch, mechanically sensitive neurons (e.g., nociceptors) do not experience the global load or deformation, which we can relatively easily measure. Rather, they experience the change in the local, internally developed *stresses* (related to force) and/or *strains* (related to deformation) in their immediate environs in the muscle [61]. The mechanical state developed at a receptive ending during compression is further influenced by the substrate beneath the tissue [62]. If the substrate is hard (e.g., bone), then *compressive* stresses and strains will primarily influence the nociceptor. However, if the substrate is compliant (e.g., muscle or fat), then both *compressive* and *tensile* stresses and strains will develop and can influence the nociceptor. In rat hairy skin, it was found that cutaneous nociceptors were more sensitive to tensile than to compressive stress [62]. Hence, during noxious compression of skin overlying soft tissues, the response of the cutaneous nociceptors would be expected to be substantially driven by the tensile loading developed by the compression [63]. Using an isolated rat gracilis muscle – nerve preparation to examine putative group III & IV mechano-nociceptors, the neural response to noxious indentation was significantly and substantially more correlated with compressive stress than force, strain, or displacement [38]. However, during uniaxial stretch, group III & IV afferents equally encoded stress and strain [39], suggesting that different mechanisms may be involved for compression versus stretch.

Another unexplored area in mechanical activation of nociceptors is the physical process whereby the load is transferred from the extracellular matrix (specifically collagen fibrils) to the plasma membrane and/or the ion channels responsible for producing the receptor potential. Ingber [53] has proposed that the cytoskeleton of cells

acts like a 'tensegrity' model. In this model, deformation of a cell results in mechanical stresses that would distribute nearly uniformly over the entire plasma membrane. It is also known that transmembrane proteins called integrins can connect the cell cytoskeleton with the extracellular matrix [19], and rat cutaneous mechanoreceptors and nociceptors express integrin $\alpha 2\beta 1$, the receptor for collagen [64]. Further, diffusion of a function-blocking monoclonal antibody to integrin $\alpha 2\beta 1$ into the receptive fields of all types of cutaneous mechanoreceptors and nociceptors significantly and substantially reduced their neural responses to compression [60]. Finally, in high threshold, but not low threshold, mechanosensitive ion channels in cultured rat DRG neurons, their response to pressure was significantly reduced in the presence of cytoskeleton-disrupting agents, colchicine and cytochalasin D [20]. Taken together, these studies all suggest that the in-vivo response of individual mechano-nociceptors is strongly dependent on their physical connection to the extracellular matrix [64].

Conclusion

Pain perception in humans is a highly complex system that integrates noxious stimuli from the tissue with the overall status (physical, emotional, and mental) of the individual. Unlike the five primary senses, pain is strongly influenced by positive and negative feedback systems within the brain, spinal cord, and the primary nociceptor. Nonetheless, within the pain perceptive system, there is a sensory/discriminant component for which the intensity of an acute noxious stimulus is essentially proportional to the perceived pain. As we continue to better understand the complexity of this system, we will be better able to create treatments to prevent and treat patients suffering from pain.

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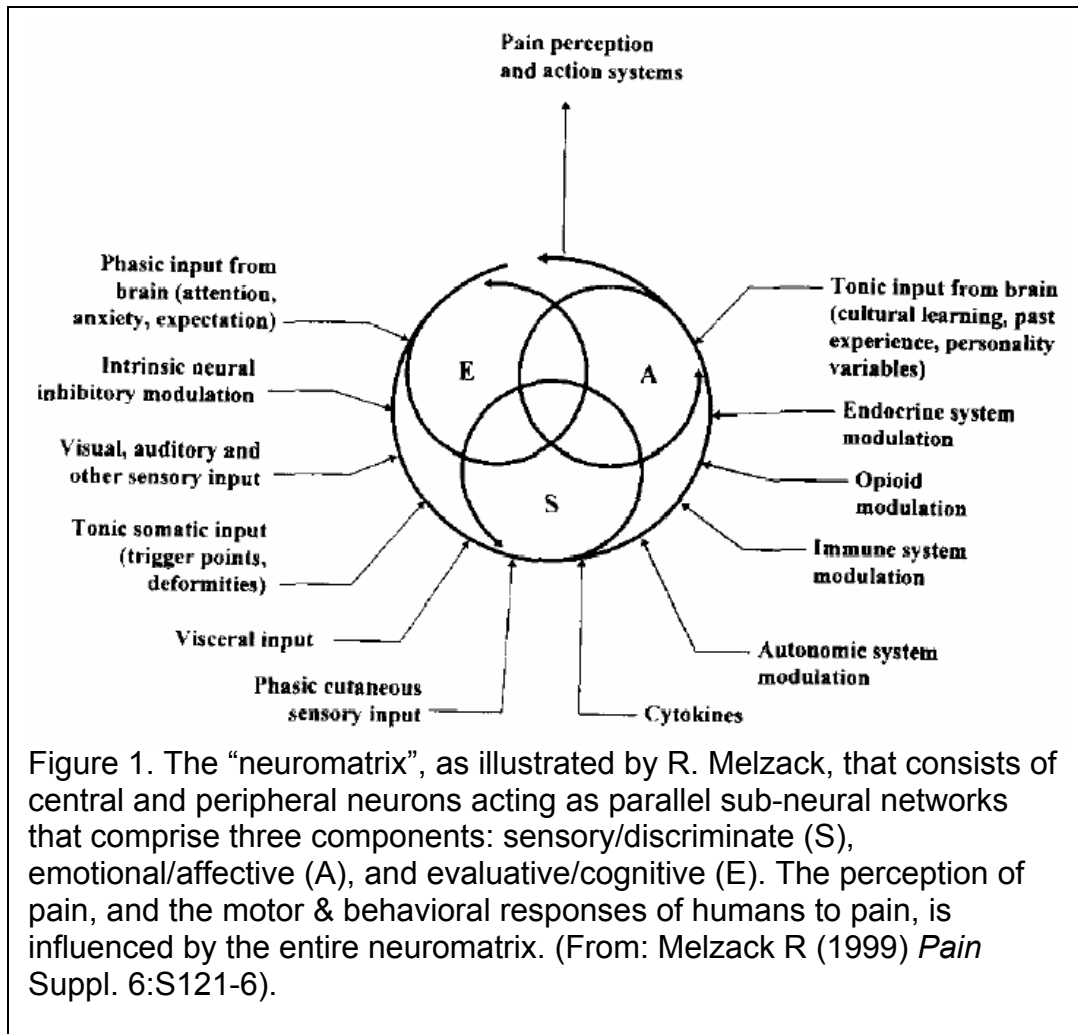
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Figures



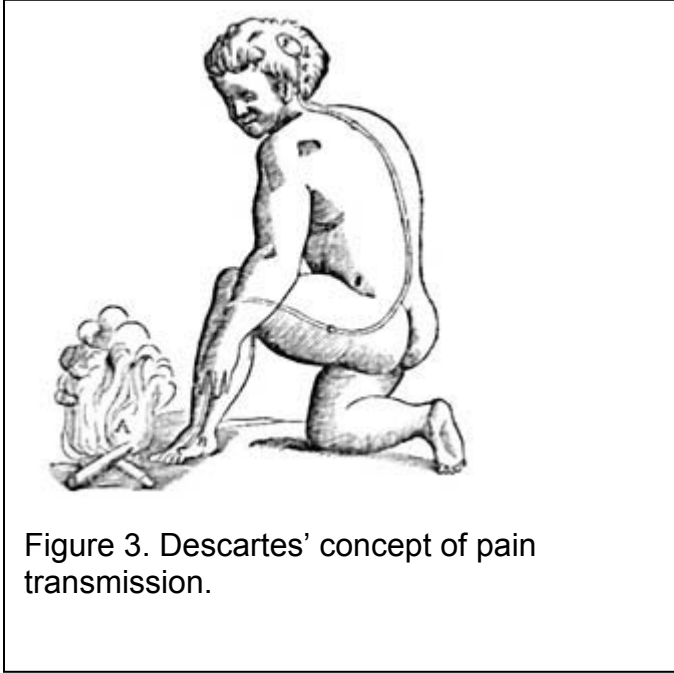


Figure 3. Descartes' concept of pain transmission.

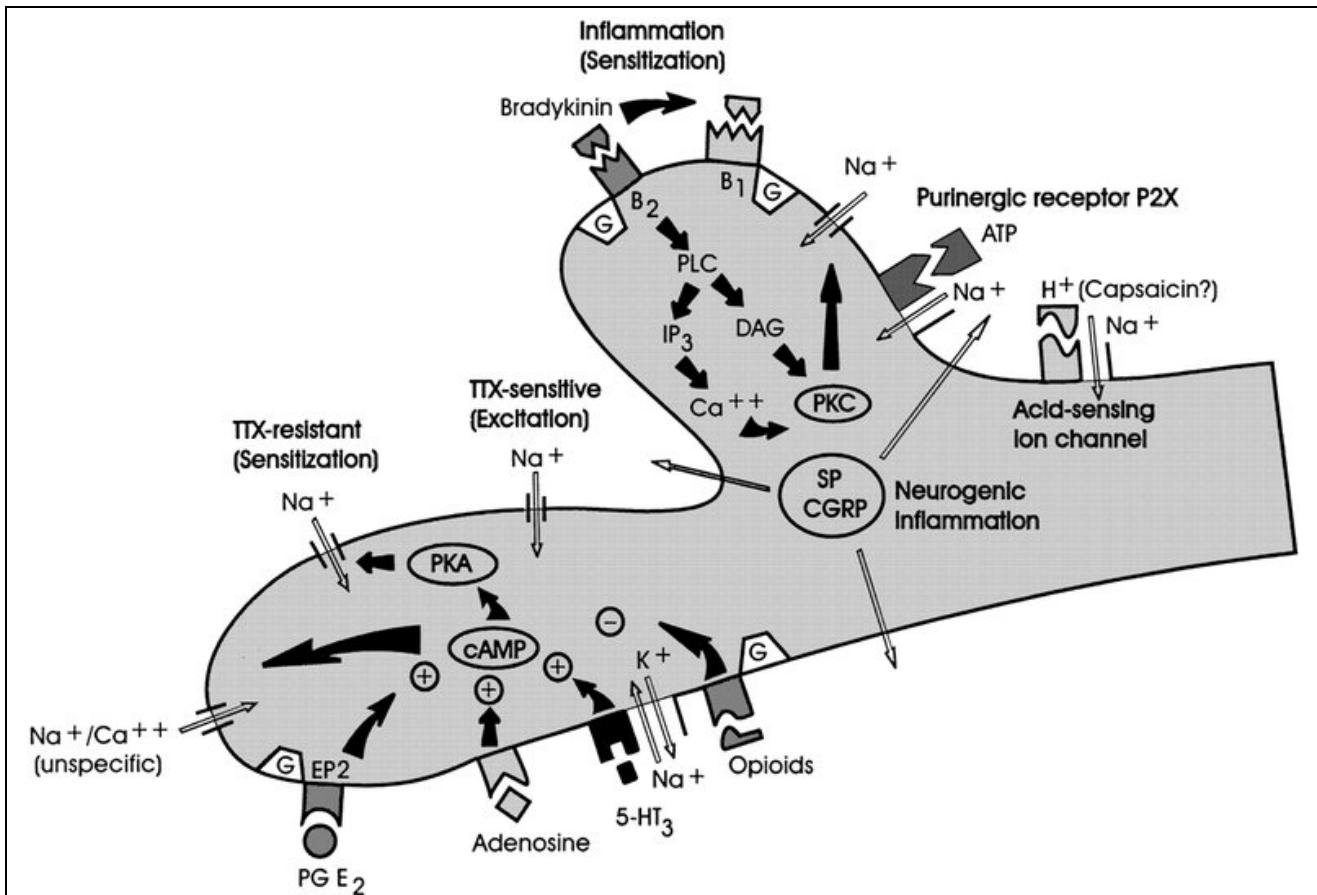


FIG. 4. Schematic overview of the receptor molecules in the membrane of a nociceptive ending. For reasons of brevity, only four points will be addressed: (1) Nociceptive nerve endings possess a special type of Na^+ channel that is tetrodotoxin-resistant, meaning that it cannot be blocked by the neurotoxin tetrodotoxin. Sensitization of the ending is accompanied by the synthesis of larger amounts of the membrane protein that forms the tetrodotoxin-resistant channel. This increases the excitability of the nociceptor. (2) In intact tissue, bradykinin (BK) excites nociceptors by binding to the B2 receptor molecule; the sensitized ending, however is activated by the BK through B1 receptors. Binding of BK to the specific receptor molecules is followed by the activation of an intracellular cascade that leads to the synthesis of increased amounts of protein kinase C (PKC), which enhances the sensitivity of Na^+ channels to stimulus-induced depolarization. (3) Sensitization of the nociceptor also is caused by the binding of other endogenous algescic substances (such as PGE_2 , adenosine, and serotonin) to specific membrane receptors whose activation leads via cyclic adenosine monophosphate (cAMP) to the formation of protein kinase A (PKA), which increases the sensitivity of the tetrodotoxin (TTX)-resistant Na^+ channels. Binding of opioids to peripheral opioid receptors inhibits the cyclic adenosine monophosphate cascade, thereby counteracting the sensitization. (4) Other types of Na^+ channels are open after binding of adenosine triphosphate (ATP) to purinergic membrane receptors or after binding of protons (H^+). The latter type is important for pain from inflamed tissue because inflammation is associated with a lowered pH. This channel is probably also opened by capsaicin, the active ingredient of the red pepper. G, G protein. After binding of the ligand to the membrane receptor, the G protein changes the intracellular metabolism. PLC, phospholipase C; DAG, diacyl glycerin; IP_3 , inositol triphosphate (after Kidd et al.⁵⁰ and Cesare and McNaughton⁵¹).

From: Graven-Nielsen & Mense (2001) Clin. J. Pain 17(1):1-10.

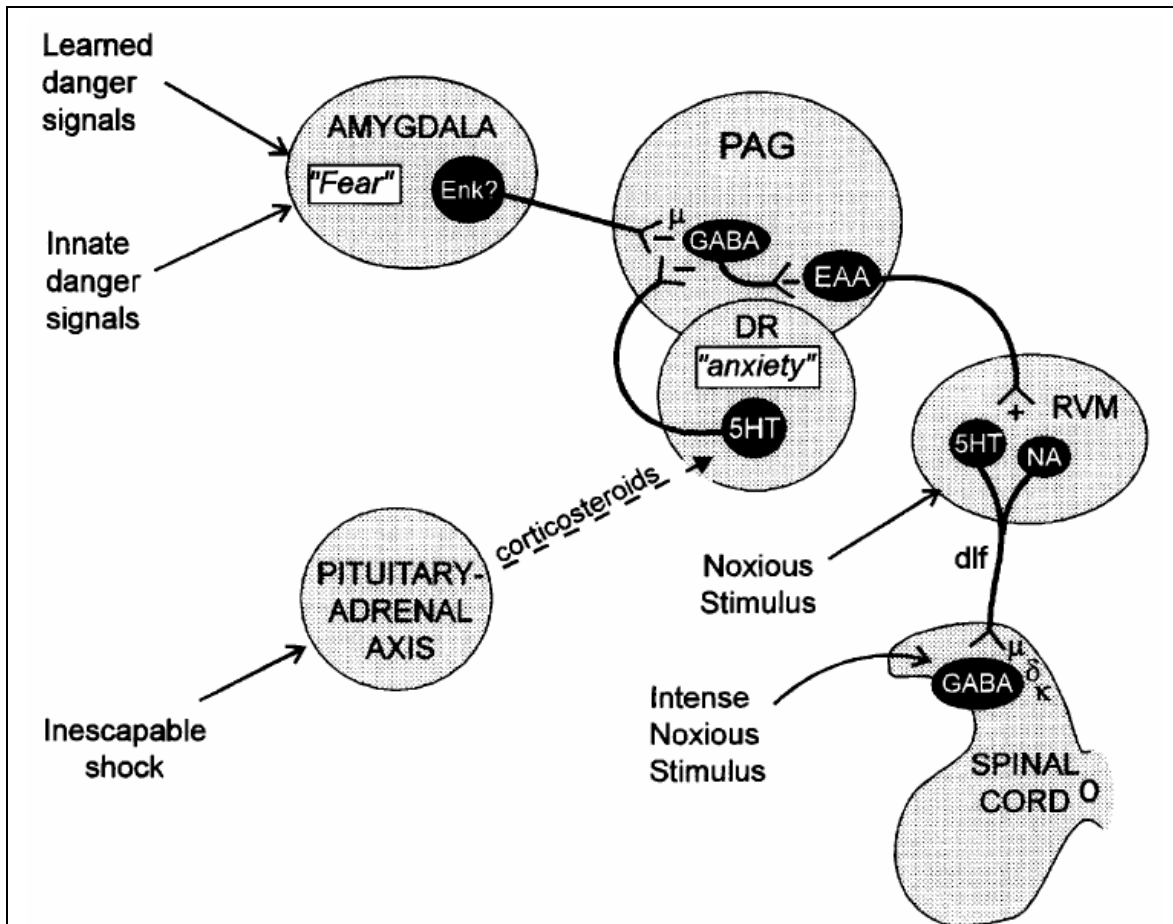


Figure 2. Descending antinociceptive mechanisms and their activation by environmental sources of danger. 5HT – serotonergic, NA – noradrenergic, RVM – rostral ventro-medial medulla, PAG – periaqueductal grey, DR – dorsal raphe nucleus. From Harris JA (1996) *J Physiology (Paris)* 90:15-25.