UNIT NO. 1

PATHOPHYSIOLOGY OF PAIN

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ABSTRACT

Pain, which is an unpleasant sensory and emotional experience generally associated with actual or potential tissue damage, can be persistent or chronic. Persistent pain can be nociceptive or neuropathic. Nociceptive pain arises due to activation of nociceptors in response to tissue injury and usually arises from accompanying inflammation. On the other hand, neuropathic pain results from direct injury to nerves or the central nervous system. This article examines some aspect of pathophysiology of pain with focus on inflammatory pain, especially arising from damage to skin.

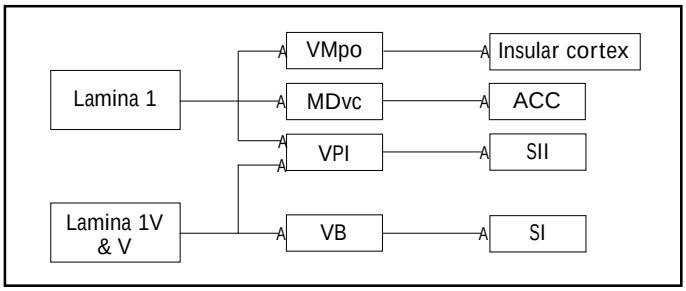
Definition and pain pathways

According to the official IASP definition, pain is an 'unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. The unpleasantness of pain is a subjective negative expression (feeling-emotion). This unpleasant emotional feeling may also be associated with somatic, autonomic and endocrine changes, e.g. changes in heart rate, vocalization, secretion of glucocorticoids, variations in pattern of musculature and postural changes. In addition, unpleasantness compels changes in activity (or behavior) that reflect motivation (e.g. escape, avoidance, seeking help).

In human experiments, unpleasantness and perceived pain intensity is coupled to intensity of acute noxious stimuli applied to the subjects indicating that these are stimulus-bound qualities (cf Fields, Pain Suppl. 6: S61-S69, 1999; Rainville et al., Pain 82: 159-171, 1999). However, unpleasantness is not invariantly coupled to pain intensity suggesting neural circuits that mediate unpleasantness are at least partially separate from those mediating pain intensity. Furthermore, unpleasantness may also be modified by internal state and cognition-evaluation separately from pain intensity. In this context, hypnosis can reduce the pain unpleasantness ratings without altering pain intensity ratings (Rainville et al., Pain 82: 159-171, 1999). On the other hand, hypnosis-induced changes in perceived pain intensity also altered in parallel pain unpleasantness ratings (Rainville et al., Pain 82: 159-171, 1999).

Psychophysical studies indicate that the primary sensory neurons that signal for pain include the C- and Ad-fiber type. The C- and Ad-fibers are further classified based on their response to noxious, mechanical, and chemical stimuli. Of the various type at least two type, namely CMH (C-fiber responding to noxious mechanical, heat; and also chemicals stimuli) and AMH (Ad-fiber responding to noxious mechanical and heat stimuli) from the skin have been most well studied. The various classes of nociceptors signal to spinal dorsal horn neurons that are either wide-dynamic range type (responding to both innocuous and noxious stimuli; however, response to noxious stimuli is intense) and nociceptive specific neurons.

Based on experimental evidence in rodent, cat, and monkey number of parallel pathways are suggested that convey nociceptive information from dorsal horn to the cortex via thalamus. These pathways are outlined as follows:



Output from nociceptive dorsal horn neurons in laminae I, IV or V reaches cortex by at least 4 parallel thalamo-cortical relays. One, from ventrobasal complex (VB; includes ventroposterolateral and ventroposteromedial nucleus) to somatosensory cortex I (SI). Two, from ventroposterior inferior nucleus (VPI) to somatosensory cortex II (SII). Three, from caudoventral mediodorsal nucleus (MDvc) to anterior cingulated cortex (ACC). Four, from posterior part of ventromedial nucleus (VMpo) to insular cortex. The figure is adapted from Fields, Pain Suppl. 6: S61-S69, 1999, and Craig, Nature Reviews 3: 655-666, 2002.

The contribution(s) of the above pathways to unpleasantness and perceived pain intensity is not clearly defined.

Pathophysiological features of cutaneous inflammatory pain

Features that are observed with inflammatory (and neuropathic) pain include allodynia and hyperalgesia. Allodynia is defined by the IASP as 'pain due to a stimulus that does not normally provoke pain' (http://www.iasp-pain.org/dict.html#RTFToC3). Thus, there is thus a loss of specificity of a sensory modality. On the other hand, hyperalgesia is defined as 'an increased response to a stimulus which is normally painful' (http://www.iasp-pain.org/terms-p.html#Hyperalgesia).

Current evidence suggests that hyperalgesia observed to thermal stimuli has a basis in peripheral sensitization of nociceptors. For example, psychophysical studies indicate that primary thermal hyperalgesia following experimental injury is observed in correlation with increased activation of nociceptors to a given intensity of noxious heat stimulus (sensitization; Handwerker and Kobal, Physiological Reviews 73: 639-671, 1993; also see Atlas of Anesthesia volume VI, ed. SE Abram).

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Both CMH and AMH nociceptors are suggested to be involved. The threshold of CMH nociceptor activation may also drop that may partially account for thermal allodynia.

Animal studies suggest that thermal hyperalgesia is linked, at least in part, to VR1 receptors expressed by the nociceptors. In this regards, compared to wild type mice, $VR1^{-/-}$ mice show significantly less increase in responsiveness in hot plate test following inflammatory injury to the paw (Caterina et al., Science 288: 306-313, 2000). However, VR1 deletion did not affect thermal hyperalgesia to nerve injury. Here it is notable that chemicals released at the inflamed site, such as bradykinin, may facilitate the function of heat channel (Cesare and McNaughton, Proc. Natl. Acad. Sci. USA 93: 15435-15439, 1996) via activation of an isoform protein kinase C (Cesare et al., Neuron 23: 617-624, 1999). The threshold of activation of heat channel is also shifted to lower temperatures. Such facilitation or sensitization and shift in threshold may act to promote thermal hyperalgesia and allodynia. Bradykinin per se also increases the activity of CMH and AMH that leads to pain (see Atlas of Anesthesia volume VI, ed. SE Abram).

In addition to bradykinin, experimental evidence suggests that agents such as prostaglandin E_2 (PGE_2) may also affect VR1 receptor and, in addition, sensitizes the sensory-neuron specific voltage-gated sodium channel. These effects are suggested to involve activation of protein kinase A (Gold et al., Journal of Neuroscience 18: 10345-10355). Both these effects may underlie the pro-nociceptive effect of PGE_2. Indeed, administration of an inhibitor of protein kinase A attenuates the mechanical hyperalgesia due to administration of PGE_2 (Aley and Levy, Journal of Neuroscience 19: 2181-2186, 1999).

In contrast to changes in heat responsiveness, mechanical sensitization of both CMH and AMH cutaneous nociceptor is not observed after experimental injury of the skin (Handwerker and Kobal, Physiological Reviews 73: 639-671, 1993); although animal studies indicate that at least Ad-nociceptors from joints and viscera may become sensitized to mechanical stimuli after experimental arthritis and inflammation of bladder. Interestingly, one psychophysical study suggests that augmented pain response to repeated tonic mechanical pressure applied to skin is accompanied by sensitization (enhanced response) of a class of cutaneous C-fibers that are initially unresponsive to even very high pressures (silent C-fibers; Schmidt et al., Neuroscience 98: 793-800, 2000). In contrast to these 'silent' units, CMH exhibit adaptation of activity. Collectively, the above suggests a possibility that the nociceptor basis of mechanical hyperalgesia may differ depending upon site of injury and may involve recruitment of silent nociceptors in some cases.

It is very interesting to note that allodynia to touch in the surrounding of the trauma in human subjects is accompanied by perception of pain to micro-stimulation of Ab-fibers (Torebjork et al., Journal of Physiology 448: 765-780, 1992). On the other hand, such micro-stimulation in uninjured skin evokes sensation of touch or tapping but not pain (Torebjork et al., Journal of Physiology 448: 765-780, 1992). In animal studies, injury evokes a phenotypic switch in a subpopulation of Ab-fibers so that they, like C-fibers, now express substance P (Neumann et al., Nature 384: 360-364, 1996). This is accompanied by decrease in nociceptive threshold. At the same time the ability of these fibers to excite nociceptive wide-dynamic range neurons of the spinal cord is dramatically enhanced. The foregoing points to the possibility that phenotypic switch in touch sensitive Ab-fibers might be involved, at least partly, in generation of mechanical allodynia.

Besides changes in the primary sensory neurons, alterations in the central nervous system, especially at the spinal cord level, are also suggested to play a role hyperalgesia and allodynia. It has been suggested based on experimental work in animals that the injury-induced intense discharge of nociceptive primary afferent sensitizes dorsal horn nociceptive neurons which is characterized by reductions in threshold and increases in the responsiveness of dorsal horn neurons, as well as by enlargement of their receptive fields. In a model of spinal sensitization Woolf and Salter (Science 288: 1765-1768, 2000) have proposed that sensitization involves, at least partly, action of glutamate at N-methyl-d-aspartate (NMDA) receptors-channel complex. In this model a barrage of input from nociceptors may (a) depolarize the postsynaptic dorsal horn nociceptive neurons to remove the pre-existing suppression of NMDA channel and/or (b) evoke release of neuromodulators such as substance P and brain-derived neurotrophic factor (BDNF) which acts on NK1 receptor and tyrosine kinase receptor, respectively, to activate signaling cascades that enhances the gating of the NMDA channel. Both of these changes will facilitate the action of glutamate on NMDA receptors leading to increased calcium influx. Increased influx of calcium will activate a variety of enzyme (protein kinases) that further enhances the kinetics of glutamate receptors and facilitating synaptic transmission. New glutamate receptors may also be inserted into the neural membrane that again will enhance synaptic transmission. The central role for NMDA receptors is indicated by the evidence that deletion of a subunit of the receptor in the spinal cord drastically reduced the injury-induced pain behavior in mice (South et al., Journal of Neuroscience 23: 5031-5040, 2003) while in humans intrathecal administration of a NMDA receptor antagonist significantly attenuate allodynia (cf Atlas of Anesthesia volume VI, ed. SE Abram).

Physiology of pain control

Endogenous circuits and receptors in the central nervous system exercise a significant modulation of pain. In a review, Dubner and Ren (Pain Supplement 6: S45-S53, 1999) have pointed out that factors such as attention, motivation and cognition that influence human pain experience also affect activity of nociceptive spinal neurons. A proposed mechanism of such modulation is suggested to involve endogenous pathways that originate from higher centers and descend to spinal cord (descending modulation; also see Sandkuhler, Progress in Neurobiology 50: 49-81, 1996). Animal studies indicate that disruption of descending modulation exacerbates hyperalgesia and sensitization of spinal neurons in animals (Ren and Dubner,

Journal of Neurophysiology 76: 3025-3037, 1996; Dubner and Ren, Pain Supplement 6: S45-S53, 1999). Brainstem sites have been identified that may be involved in such descending modulation, including noradrenergic neurons of nucleus locus coeruleus and serotonergic neurons of raphe magnus that may influence sensitization of neurons in lamina I-II and V, respectively (Dubner and Ren, Pain Supplement 6: S45-S53, 1999).

More recent work suggests that forebrain sites such as amygdala also modulate pain. Interestingly, in a functional imaging study performed on humans, regression analyses indicated that sensory rating was inversely correlated with opioid system activation in the amygdala (Zubieta et al., Science, 293: 311-315).

Implications

The findings described above provide evidence that the problem of pain can be addressed in the periphery at site of injury and at central nervous system sites. Such pain control may involve anaesthetizing or blocking nociceptors, antagonizing the action of peripheral inflammatory mediator at receptor sites, and using agents to modulate central sensitization to attenuate the pathophysiological aspects of pain.

LEARNING POINTS

The following are the major learning points of this article:

- Pain, which is defined as unpleasant sensory and emotional experience, has a basis in nociceptor activation. The nociceptors signal through a number of ascending pathways
- Human experience and experimentation suggests that the neural basis of sensory-discrimination and unpleasant emotions may partly diverge
- Current evidence suggests that hyperalgesia observed to thermal stimuli has a basis in peripheral sensitization of nociceptors
- Chemicals released at the inflamed site, such as bradykinin and prostaglandin E_2, promote hyperalgesia including thermal hyperalgesia. The latter effect is linked to the facilitatory action on the function of heat receptor-channel VR1 on nociceptors
- The nociceptor basis of mechanical hyperalgesia may differ depending upon site of injury and may involve recruitment of silent nociceptors in some cases
- Phenotypic switch in touch sensitive Ab-fibers might be involved, at least partly, in generation of mechanical allodynia
- In addition to peripheral changes, central sensitization, especially of spinal nociceptive neurons is linked to hyperalgesia and allodynia. Central sensitization is linked to activation of N-methyl-d-aspartate type of glutamate receptor
- Inflammatory pain states can be modulated by noradrenergic and serotonergic neurons of the brainstem. In addition, forebrain sites, including amygdala is also linked to pain modulation.