Anatomy and Physiology

I. Peripheral mechanisms

A. Be aware of the existence of two kinds of nociceptors: lightly myelinated A-delta and unmyelinated C fibers. Know the structure and anatomical organization of peripheral and central endings of cutaneous and deep primary afferents (Willis and Coggeshall 1991; Byers and Bonica 2001; Kruger et al. 2003).

B. Know the cytoarchitectural organization of the dorsal horn and how the different laminae are related to the terminal location of primary afferents. Know that large, A-beta afferents terminate mainly in laminae III through V, whereas cutaneous A-delta and C fibers terminate in a highly topographic fashion, mainly within laminae I and II (Willis and Coggeshall 1991; Sugiura 1996; Byers and Bonica 2001). Be aware that primary afferents from the viscera terminate in a more diffuse fashion in laminae I, V, and X (Ness and Gebhart 1990; Byers and Bonica 2001).

C. Know the capabilities of nociceptors to detect different kinds of noxious stimuli and the difficulties of defining a nociceptor only by its threshold or by the fact that its activation elicits pain (Besson and Chaouch 1987; Handwerker and Kobal 1993, Raja et al. 1999). Know the molecular and biophysical mechanisms underlying mechanical, heat, cold, and chemical nociceptive transduction. Be aware that most nociceptors have the ability to detect a wide range of physical or chemical noxious stimuli. Know that the sensation of pain results from the integration of the signals traveling in different types of primary afferents, which, when stimulated alone, act as labeled lines (Waldmann and Lazdunski 1998; Hill 2001; Julius and Basbaum 2001; Belmonte et al. 2004; Wood et al. 2004).

D. Be aware that, compared to the nociceptors in skin, the primary afferents in corneal (Belmonte et al. 2004), dental (Byers and Närdh 1999), visceral (Ness and Gebhart 1990; Cervero and Laird 1999), and other deep tissues (Byers and Bonica 2001) have distinct protective functions that may account for their particular functional features and anatomical distribution.

E. Know that, in addition to signaling damaging stimuli, subpopulations of small-diameter afferent fibers convey inputs that elicit pleasant sensations of touch (Wessberg et al. 2003) and innocuous thermal (Green 2004), and itchy sensations (Ikoma et al. 2003). Be aware that nociceptors convey other inputs important for homeostatic functions including local metabolism, neuroendocrine, vascular, and trophic functions (Byers and Bonica 2001; Craig 2003).

F. Be aware that fine primary afferents, including “silent nociceptors,” can be activated or become sensitized by substances released during inflammation, and actually participate in neurogenic inflammation. Know the mechanisms by which A-beta fibers and the nociceptors participate in neuropathic and inflammatory forms of hyperalgesia and allodynia. Be aware of the involvement of nociceptors in primary and secondary hyperalgesia (Levine and Reichling 1999; Handwerker and Schmelz 2004).

G. Know that sensitization is mediated by a number of substances, including inflammatory mediators, proteinases (Vergnolle et al. 2003), and neurotrophic factors released following tissue damage or by inflammatory cells (McMahon and Jones 2004), and that these in turn may regulate gene expression and affect sensory neuronal function (Woolf and Salter 2000). Be aware that several molecular mechanisms participate in sensitization phenomena, including G-protein-coupled receptors, ligand-gated ion channels, and Trk receptors (Hill 2001; Julius and Basbaum 2001; Wood et al. 2004).
H. Know of the existence of subpopulations of C fibers based on their neurochemical features. Know what peptides and excitatory amino acids are found in primary afferent nociceptors and understand their role in nociception and in neurogenic inflammation (Carlton 2001; Hill 2001).

I. Be aware of the interactions between the immune system and nociceptors. Know the substances that are synthesized in immune cells and the circumstances that elicit their release (Machelska and Stein 2002; Cunha and Ferreira 2003). Know the mechanisms by which the sympathetic nervous system alters nociceptor function (Baron and Jänig 2004).

J. Know that antidromic activation of nociceptors may occur following presynaptic interactions between primary afferents at the level of the dorsal horn (Wall 1995; Cervero et al. 2003).

II. Central mechanisms of nociceptive transmission: the spinal and medullary dorsal horns

A. Know Rexed’s lamination scheme for the spinal and medullary dorsal horns, how it relates to the terminals of different types of primary afferents, and the location of superficial, noxious-specific and deep, wide-dynamic-range neurons (Willis and Coggeshall 1991; Byers and Bonica 2001).

B. Know the response properties, coding mechanisms, convergence of peripheral inputs, and differential projections to supraspinal centers of superficial and deep dorsal horn nociceptive neurons (Willis and Coggeshall 1991; Sessle 2000; Villanueva and Nathan 2000; Craig 2003; Price et al. 2003). Be aware that lamina I neurons modulate the excitability of deep spinal and medullary dorsal horn neurons through both local intraspinal pathways and pathways descending from the brainstem (Dallel et al. 1998; Dickenson et al. 2004).

C. Know that modulatory inputs subserved by inhibitory and excitatory cotransmission may change the intrinsic firing properties of dorsal horn neurons to several functional states (Jo and Schlichter 1999; Derjean et al. 2003). Be aware of the contribution of short-term (wind-up) and long-term (LTP) amplification mechanisms to synaptic plasticity in the dorsal horn following noxious stimulation (Herrero et al. 2000; Sandkühler 2000; Ji et al. 2003). Know that dorsal horn sensitization by noxious stimuli is mediated by several molecular signaling mechanisms including glutamate, neuropeptides, the expression of immediate early genes, and neurotrophic factors (Hill 2001; Hunt and Mantyh 2001; McMahon and Jones 2004).

D. Know that the anterolateral quadrant of the spinal cord contains the axons of both superficial and deep dorsal horn nociceptive neurons and the main ascending pathways giving rise to both cutaneous and visceral pain in animals and humans (Vierck et al. 1986; Gybels and Sweet 1989; Villanueva and Nathan 2000). Be aware that in addition to spinothalamic axons, the anterolateral quadrant contains two main nociceptive pathways that relay within the brainstem reticular formation and parabrachial nucleus (Craig and Dostrovsky 1999; Villanueva and Nathan 2000; Gauriau and Bernard 2002).

III. Central mechanisms of nociceptive transmission: segmental and brainstem pain modulation

A. Know that segmental inhibitions can be elicited by activity in large-diameter cutaneous afferent fibers and innocuous mechanical stimuli (Wall 1996). Be aware that stronger, longer-lasting segmental and extrasegmental analgesic effects can be obtained following percutaneous activation of fine-diameter fibers (Chung et al. 1984; Bouhassira et al. 1987; Sandkühler 2000).

B. Know that sympathetically maintained spontaneous and evoked activity may generate a state of central sensitization (Baron and Jänig 2004). Be aware that dorsal column stimulation, which is usually termed spinal cord stimulation in human beings, may relieve ischemic pain and probably does so through central inhibitory mechanisms influencing sympathetic neurons (Linderoth and Meyerson 1995).

C. Know that several spino-brainstem-spinal pathways are activated simultaneously when a noxious stimulus occurs, providing widespread negative and positive feedback loops by which nociceptive signals may attenuate or increase their own magnitudes (Villanueva and Le Bars 1995; Porreca et al. 2002; Dickenson et al. 2004; Fields et al. 2005).
IV. Central mechanisms of nociceptive transmission: thalamocortical mechanisms

A. Know that medial and lateral thalamic regions distribute nociceptive signals to a number of cortical areas. Be aware that these thalamic areas receive nociceptive inputs either indirectly via the brainstem (Craig and Dostrovsky 1999; Villanueva and Nathan 2000; Gauriau and Bernard 2002) or directly from superficially or deeply located parts of the dorsal horn (Willis and Coggeshall 1991; Apkarian and Shi 1994; Lenz and Dougherty 1997; Craig 2003). Know that thalamic activity is highly dependent on reciprocal interactions with its cortical targets (Villanueva and Fields 2004).

B. Know that a noxious stimulus activates not only several cortical areas, but also an increasing number of subcortical and cortical regions as the intensity of the stimulus increases (Derbyshire et al. 1997; Porro 2003). Be aware that powerful top-down, endogenous mechanisms of pain modulation originate in the cortex because almost all nociceptive relays within the central nervous system are under corticofugal modulation (Jasmin et al. 2003; Villanueva and Fields 2004). Know that a painful stimulus activates not only cortical and subcortical structures but also the endogenous mu-opioid system (Zubieta et al. 2001). Know that corticofugal modulation selectively alters pain perception following manipulation of a number of factors including attention, expectation, placebo and hypnotic manipulations, and the pain that can occur in the absence of detectable organic lesions (Ramachandran 1998; Harris 1999; Casey and Bushnell 2000; Peyron et al. 2000; Rainville 2002; Plögau et al. 2003).

REFERENCES


