Medical Neuroscience | Tutorial Notes

Pain Systems

Map to Neuroscience Core Concepts[1]

NCC1. The brain is the body's most complex organ.

NCC3. Genetically determined circuits are the foundation of the nervous system.

NCC7. The human brain endows us with a natural curiosity to understand how the world works.

NCC8. Fundamental discoveries promote healthy living and treatment of disease.

Learning Objectives

After study of today's learning, the student will:

1. Discuss the complex phenomenology of pain.
2. Describe two categories of pain sensation (first and second pain) and explain the neural basis of each.
3. Characterize the peripheral and central mechanisms underlying hyperalgesia.
4. Characterize the neural mechanisms for the feedback modulation of nociceptive processing.
5. Characterize the neural mechanisms for the feedforward modulation of nociceptive processing.
6. Discuss the affective dimensions of pain and identify the neural systems that are involved in pain affect (suffering).

Tutorial Outline

I. Introduction: complex phenomenology of pain
   - A. both sensory (nociception) and affective (emotional unpleasantness) dimensions
   - B. pain usually engages the emotional systems, both in the short-term and the long-term
   - C. emotional feelings about the long-term consequences of pain, termed **secondary affect**, contribute to the psychosocial aspects of pain management

II. Central processing of pain
   - A. parallel pathways for nociception
     1. first order neurons are ganglion cells (DRGs & V-Gs) with peripheral processes that terminate as free nerve endings (refer back to **Figure 9.5**[2] and **Table 9.1**)
        - a. primary axons conduct relatively slowly, with most fibers being small and many 'unmyelinated' or only lightly myelinated

[1] Visit **BrainFacts.org** for *Neuroscience Core Concepts* (©2012 Society for Neuroscience) that offer fundamental principles about the brain and nervous system, the most complex living structure known in the universe.

[2] Figure references to Purves et al., *Neuroscience, 5th Ed.*, Sinauer Assoc., Inc., 2012. [click here]

b. axons are broadly classified into three groups, which respond to somewhat different types of painful and/or thermal stimuli

(i) **Aδ mechanosensitive nociceptors**

- respond to intense or damaging mechanical stimuli
- lightly myelinated; slowly conducting

(ii) **Aδ mechanothermal nociceptors**

- respond to intense or damaging thermal stimuli
- lightly myelinated; slowly conducting

(iii) **C polymodal nociceptors**

- respond to thermal, mechanical or chemical stimuli
- unmyelinated; conduct very slowly

c. generally, the receptive fields of nociceptors are relatively large (compared to innocuous mechanosensory receptors)

d. sensory transduction

i. receptors for nociceptive transduction are members of a large family of Transient Receptor Potential (TRP) channels

ii. channels are gated by thermal changes, protons (acid), and some natural compounds (e.g., capsaicin) (see **Box 10A**)

iii. sensory thresholds can be modified directly and indirectly by interactions of sensory endings with inflammatory mediators (see below: peripheral sensitization)

e. central processes of first order neurons enter the dorsal roots and synapse on local circuit neurons and projection neurons in the superficial dorsal horn (marginal zone and substantia gelatinosa) and near the base of the dorsal horn (see **Figure 10.3B**)

i. as considered below, this local circuitry is important for feedforward and feedback modulation of nociceptive communication in the CNS

2. there are distinct qualities of pain that are conveyed via parallel central pathways that originate with these different classes of first order neurons

a. **first** (sharp) **pain**

i. early perception of “sharp” pain conveyed by Aδ afferent fibers (see **Figure 10.2**)

ii. relayed via the ventral posterior complex of the thalamus to S1, both of which are somatotopically organized

iii. provides information about acute onset of pain and location of injury

- provides input to segmental spinal reflexes that withdraw limb from painful stimuli
- provides warning of tissue damage and encourages escape from source of injury

b. **second pain**

i. later, longer-lasting perception of a "dull", burning type of pain conveyed by C fibers (see **Figure 10.2**)

ii. relayed to widespread cortical areas via other thalamic and brainstem projections, with little somatotopic organization

iii. provides information about ongoing presence of trauma, with little specification of the location of injured tissues

- may encourage 'guarding' or disuse of injured region (e.g., promote modified gait to avoid weight-bearing)
- provides input to 'limbic' structures in the medial and ventral forebrain that process the affective dimensions of pain

B. affective dimensions of pain (see **Figure 10.5**)

1. nociceptive signals reach 'limbic' structures in the forebrain, including the **anterior cingulate gyrus**, **insular cortex**, **amygdala** and **orbital-medial prefrontal cortex**

a. subcortical inputs arise from brainstem centers and several thalamic nuclei (outside of the ventral posterior complex)

b. cortico-cortical inputs arise from higher-order somatic sensory areas in the parietal lobe

2. nociceptive sensations become integrated together with the other somatic and visceral sensations arising from changes in body state (related to alterations in autonomic and somatic motor activity) and cognitive processes, all of which gives rise to the subjective feelings associated with pain

3. ongoing appraisals of these complex somatic and visceral sensations and their long-term consequences gives rise to secondary affect

III. Visceral Pain

A. visceral pain pathways: conveyed up the neuraxis via a newly discovered pathway in the dorsal columns of the spinal cord (see **Table** above)

B. referred pain (see **Box 10B**)

1. some primary afferents from the viscera synapse on second order neurons in the dorsal horn that also receive input from more superficial (non-visceral) nociceptors

2. consequently, activation of visceral nociceptors may lead to visceral pain percepts and percepts associated with peripheral cutaneous fields, a phenomenon known as "**referred pain**"

3. convergence may also occur at other gray matter centers along the somatic sensory pathways (e.g., dorsal column nuclei)

IV. Hyperalgesia (inflammatory pain)

A. enhanced sensitivity to mechanosensory stimulation in a local region surrounding an area of tissue damage

B. due to peripheral sensitization of nociceptors by paracrine mediators of inflammation (see **Figure 10.7**)

1. mediate immune response to injury and increase in local perfusion of damaged tissues
2. increase the sensitivity of nearby nociceptors by directly altering sensory transduction at the TRP receptors
3. activate second messenger systems within the terminal endings of the nociceptors
4. release of neuropeptides by the nociceptor ending itself, which in turn, facilitate the local inflammatory response
5. these diverse mechanisms are potential targets for pharmaceutical intervention (e.g., aspirin inhibits synthesis of prostaglandins)

C. central sensitization may also contribute to hyperalgesia

1. activity-dependent increase in the excitability of second-order neurons (dorsal horn) following high levels of nociceptor activity
2. may generalize to other sources of input to second-order neurons
    a. some primary nociceptive afferents synapse on second order neurons in the dorsal horn that also receive input from mechanosensory afferents
    b. should such second-order neurons become sensitized, an innocuous input may become painful (= **allodynia**)
3. two mechanisms of central sensitization (a form of LTP):
    a. transcription independent ("wind-up")
        i. repeated activation of nociceptors leads to a sustained depolarization of the second–order neuron
        ii. postsynaptic conductances gated by glutamate become more effective in depolarizing neurons
    b. transcription dependent
        i. activation of second messenger systems may lead to changes in gene transcription that increase the excitability of the second-order neuron

V. Central Regulation of Nociception and Pain

A. **analgesia**: the absence of pain in the presence of a nociceptive stimulus

B. the perception of pain is subject to a broad range of modulatory influences

1. contextual influences
    a. emotional context of trauma (e.g., stress) can heighten or diminish sensations of pain
    b. cognitive understanding ("expectation") can similarly shape the experience of pain (e.g., the placebo effect, exercise)
    c. cultural differences in a person's response to painful stimuli
    d. at least some of these influences may be explained by "descending" neural pathways that modulate the central transmission of nociceptive information
2. feedback (descending) modulation of nociception

a. higher centers, including the somatic sensory cortex, the limbic forebrain and hypothalamus, project to groups of neurons in the brainstem that modulate that primary transmission of nociceptive signals (see **Figure 10.8A**)

i. descending projections from the telencephalon target (among many sites) the **periaqueductal gray** of the midbrain

ii. these midbrain structures in turn project to serotonergic neurons in the pontine Raphe nuclei, noradrenergic neurons in the locus coeruleus (pons), and portions of the **reticular formation** in the ventral lateral medulla

iii. neurons in these brainstem regions project to the dorsal horn of the spinal cord and the spinal trigeminal nucleus

iv. some of these neurons release a wide variety of excitatory and inhibitory neurotransmitters, including biogenic amines (serotonin, norepinephrine), that can activate local circuit neurons in the dorsal horn that release opioids (endorphins, enkephalins, dynorphins)

v. the analgesic effects of opioids in the dorsal horn are due to the interruption of nociception at the first synapse in the pathway

vi. opioids also have more widespread analgesic actions by modulating descending systems, as well as cortical neurons that generate painful perceptions (opioid receptors are widespread in the CNS)

vii. perhaps the placebo effect (an other related phenomena that manipulate "expectation") is mediated by endogenous opioids acting upon this descending modulatory system

3. feedforward modulation of nociception: "gate theory" of pain

a. central idea: pain results from the balance of activity in nociceptive and non-nociceptive afferents

b. activation of non-nociceptive inputs inhibits firing of second-order neurons by activating an inhibitory interneuron (see **Figure 10.8B**)

c. non-nociceptive inputs 'close' the gate and prevent pain transmission

VI. Chronic Pain

1. nociceptive chronic pain

a. results from ongoing stimulation of nociceptors

b. involves both first and second pain

2. chronic pain syndromes

a. typically, chronic pain with no known nociceptive etiology

b. common examples: chronic lower back pain, fibromyalgia

c. etiology remains poorly defined

d. recent proposals include dysregulation of descending modulatory systems (e.g., diminished input to periaqueductal gray)

VII. Neuropathic Pain

A. results from abnormal patterns of activity in nociceptive pathway unrelated to the presence of a noxious stimulus in the periphery

B. peripheral causes (e.g., nerve compression, inflammation)

C. accompanied by abnormal somatic sensations

D. may involve abnormal activity in sympathetic nervous system

E. may have central nervous system causes

1. sustained sensitization of neurons in the nociceptive pathway

2. plasticity at higher levels of somatic sensory and motor representation (e.g., phantom limb pain; see **Box 10D**)