Somatosensory System II: *emphasis on the Pain System*

I. Nociception and Pain

A. Nociception: *all events* following damage or threat of damage to tissue

1. Activity in nociceptors (sensory neurons)

- also activity in non-neuronal cells (inflammatory and immune cells, skin cells)

2. Subsequent activity in CNS neurons

a. reflex and withdrawal behaviors

b. autonomic responses

c. activity of neurons in “pain” pathways and systems

3. Perception of Pain

B. Pain: complex *perceptual experience* usually related to actual/potential tissue damage

1. Many components

a. sensory and discriminative

b. unpleasantness, displeasure

c. suffering, escape

d. learning, memory

2. Normal and pathologic pain

a. acute pain

- persists as long as stimulus
- essential to survival
- sets boundaries in explorationof surroundings

b. persistent (prolonged) pain

- lasts longer than initial insult
- duration usually related to healing/inflammation

c. chronic pain

- abnormal duration; beyond healing period

3. Pain is extremely personal and individualized

II. Some relevant terms

A. Nociception: events that occur after detection of noxious event by nociceptor

B. Pain: perceptual experience

C. Anesthesia: no sensations (touch nor pain)

D. Analgesia: reduced or no pain

E. Hyperalgesia: increased pain, hypersensitivity

F. Allodynia: pain produced by normally innocuous stimuli

G. Paresthesia: tingling sensation

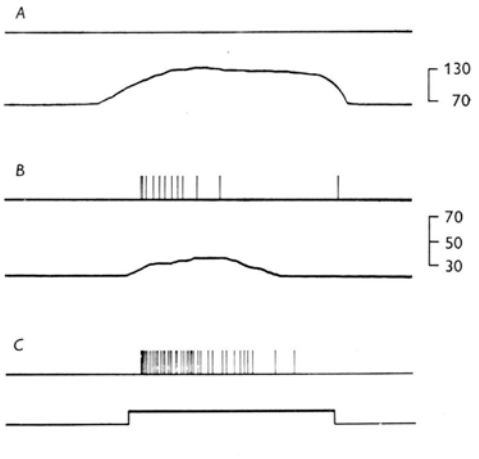
III. Nociceptors

A. Sensory neuron that is *preferentially sensitive to a noxious stimulus*

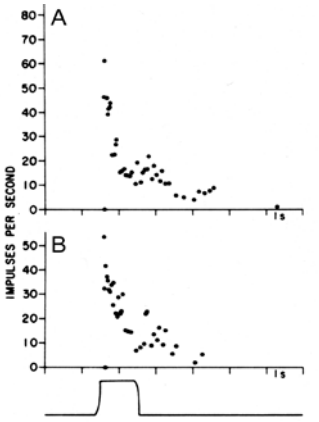
1. Stimulus is an event that is potentially/actually damaging to body tissue
2. Nociceptor distinguishes noxious from innocuous events

B. Types of Nociceptors (modalities)

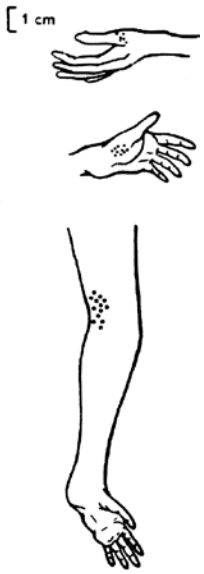
1. Mechanical nociceptors
   a. high threshold (pressure/force)
   b. punctate, spot-like receptive fields



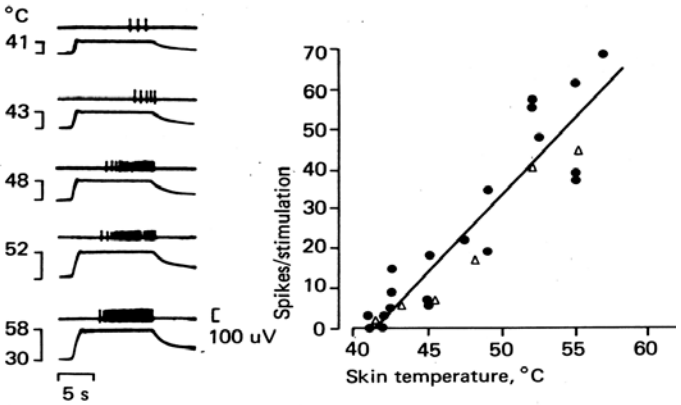
Responses of mechanical nociceptor to (A) probe with blunt tip (B) sharp probe, and (C) squeeze with serrated forceps. *from Burgess and Perl, 1967*.



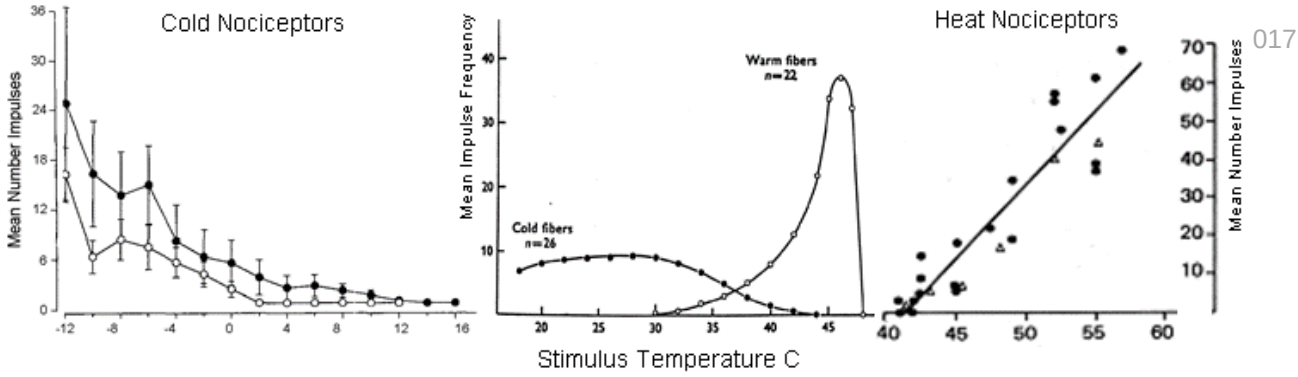
Responses of C mechanoreceptor (low threshold) to noxious and innocuous mechanical stimulation. (A) Response to displacement (1.2 mm) with 1 mm probe that caused no physical damage to skin. (B) Response to same displacement with needle probe. *from Bessou et al., 1971.*



2. Polymodal nociceptors
   a. mechanical + heat + chemical
   b. thermal thresholds ~ 43-45° C
   c. high mechanical thresholds
   d. algesic agents; e.g acids



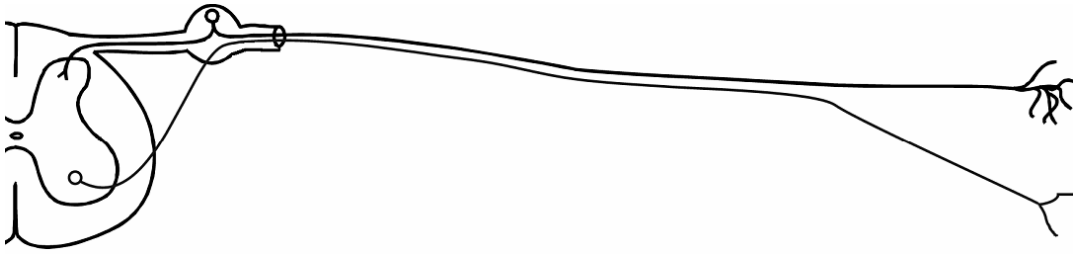
Stimulus-response relationship for C polymodal nociceptors. Left: recordings of C-fiber supplying skin of cat illustrating progressively greater responses to graded noxious heat stimuli. Right: linear relationship between stimulus temperature and number of discharges. *from Beck et al., 1974*

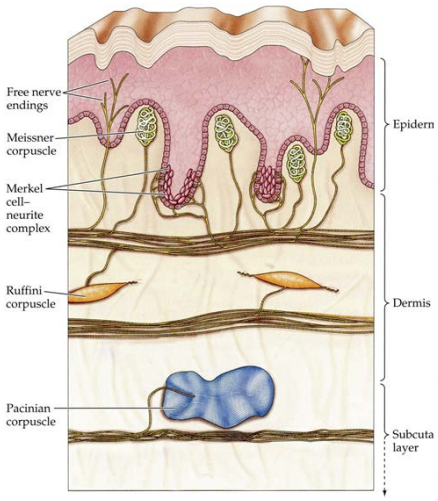


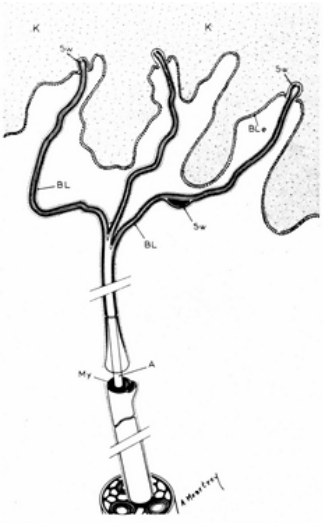
3. Cold Nociceptors: respond to noxious cold
    a. thresholds near 0° C
    b. no overlap with cooling receptors

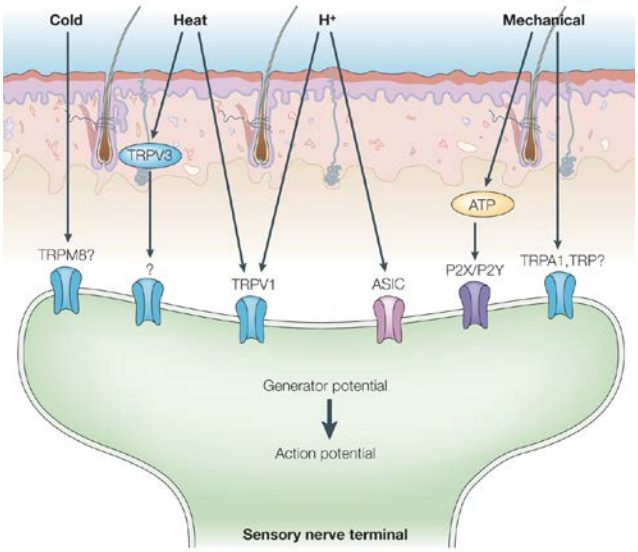
C. Anatomy of Nociceptors

1. Sensory neuron: peripheral and central axonal processes
2. Unmyelinated or thin myelinated axons
3. Peripheral processes
    a. naked (free) endings in superficial layers of skin
    b. terminals contain transduction channels and proteins





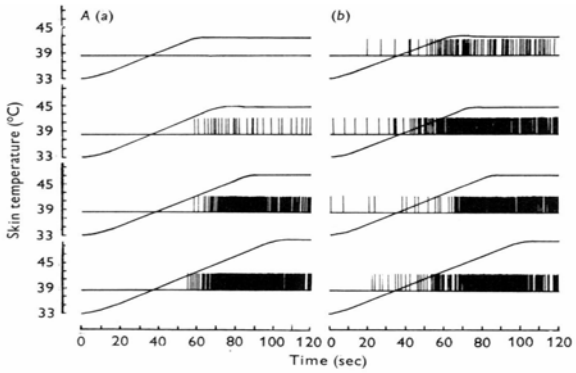




IV. Sensitization of Nociceptors

A. Enhanced responsiveness of nociceptors

1. Lowered threshold (Increased excitability) and larger response
2. Contributes to hyperalgesia



Sensitization of C-polymodal nociceptor in monkey skin by repeated heat stimulation. Left: 43, 45, 47, and 50° C from adapting temperature of 33° C. Right: Repetition of same series of stimuli. Note lowering of threshold and increased response to same temperatures. from Croze et al. 1976.

B. Sensitizing events and agents

1. Previous activity: noxious chemical, thermal, or mechanical stimulation
2. Inflammatory mediators and algesic agents
   a. e.g. bradykinin, serotonin, cytokines, prostaglandins
   b. efferent release of neuroactive substances from neighboring nociceptors

V. Efferent Actions of Nociceptors

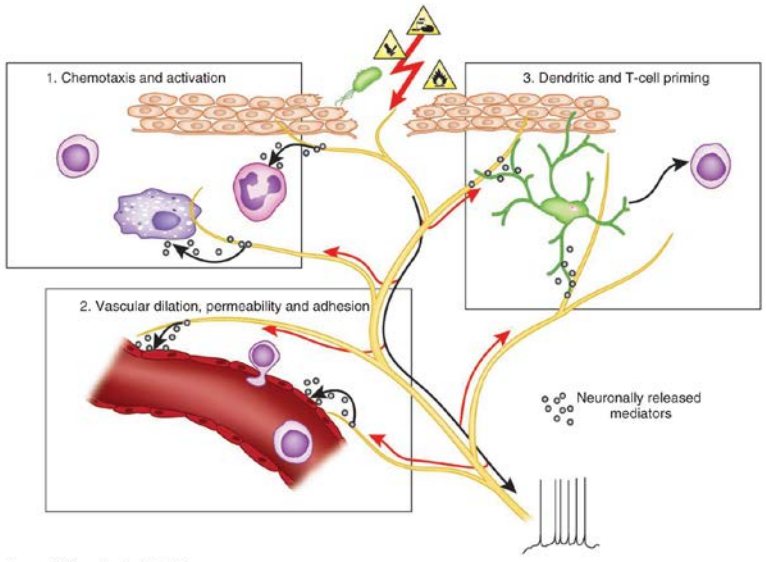
A. Axon Reflex: antidromic (efferent) conduction, local branches in periphery

B. Neurogenic Inflammation

1. Reddening (flare): vasodilation of arterioles
2. Edema (swelling): plasma leaks from local venules
3. nociceptors become sensitized (more pain)

C. Antidromic AP's cause release of neuroactive/vasoactive substances

1. CGRP (vasodilation) and SP (edema and neuroactive
2. Inflammatory mediators; attract innate immune cells
3. Immune cells release



from Chiu et al., 2012

algesic and inflammatory agents

D. Inflammatory Pain

1. Most common persistent pain
2. Accompanies all injuries: skin, joints, muscle, bones, post-surgery
3. Paradox
   a. inflammation promotes healing
   b. inflammation causes more pain
4. Non-steroidal anti-inflammatory Drugs (NSAIDs)
   a. blocks production of algesic agents, e.g. prostaglandins
   b. unclear effect on healing

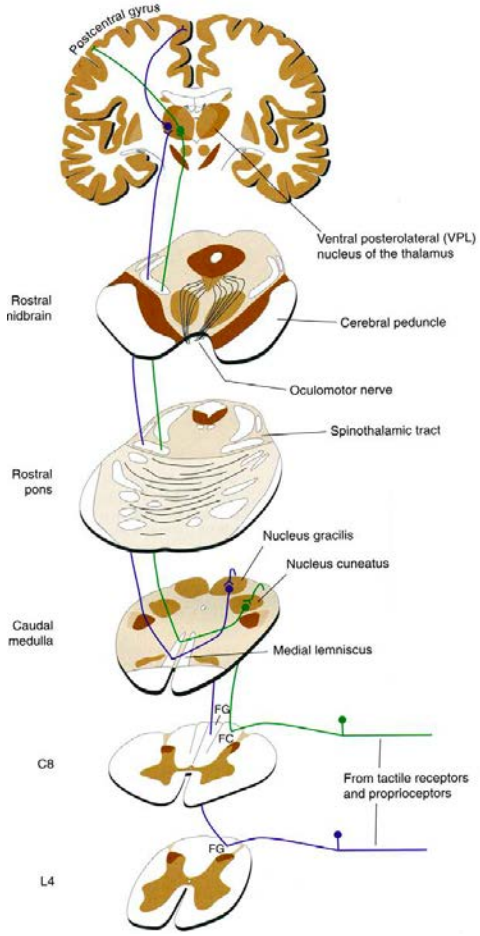
VI. Review Touch/Proprioception and Pain/Temperature Pathways

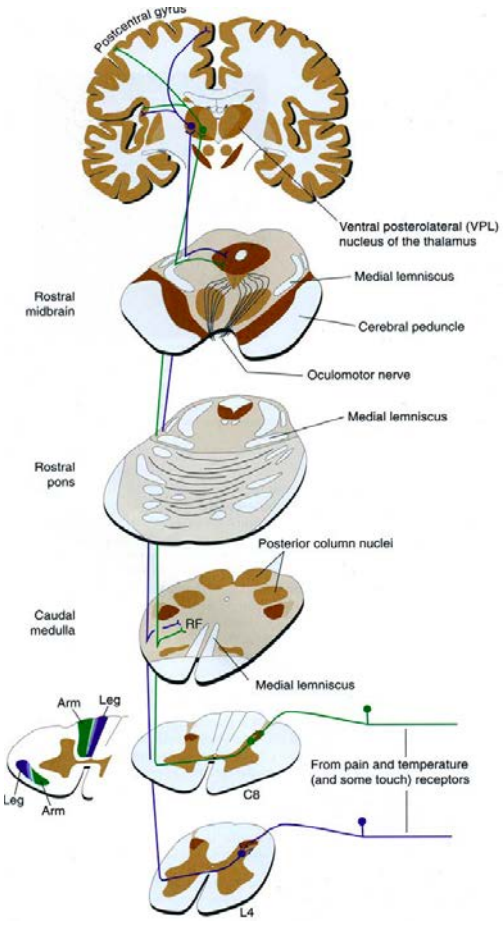
A. Touch (DC) and Pain systems (STT) are parallel pathways to cortex

1. Information from same area of body; different features extracted by each pathway
2. Axons cross midline at different locations
3. Axons ascend different locations, so effects of lesions differ

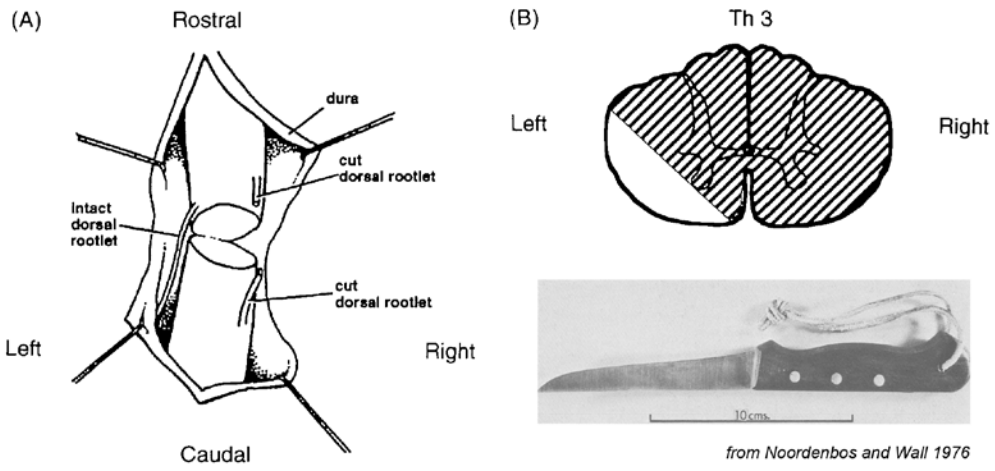
B. Same thalamic and cortical destinations: VPL and primary somatic sensory cortex (S1)

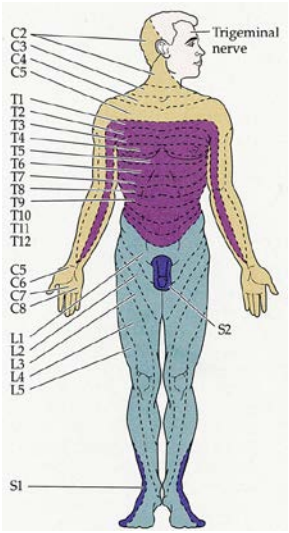
1. Pain and Touch neurons in thalamus and cortex organized as a map of body surface
2. So, a complete map of body maintained to cortex for both Pain and Touch





C. Case Study (1976): stabbing victim
   1. Spinal cord completely cut except for Left ventral-lateral funiculus
      a. touch and proprioception:
      b. pain and temperature:
      c. movement:

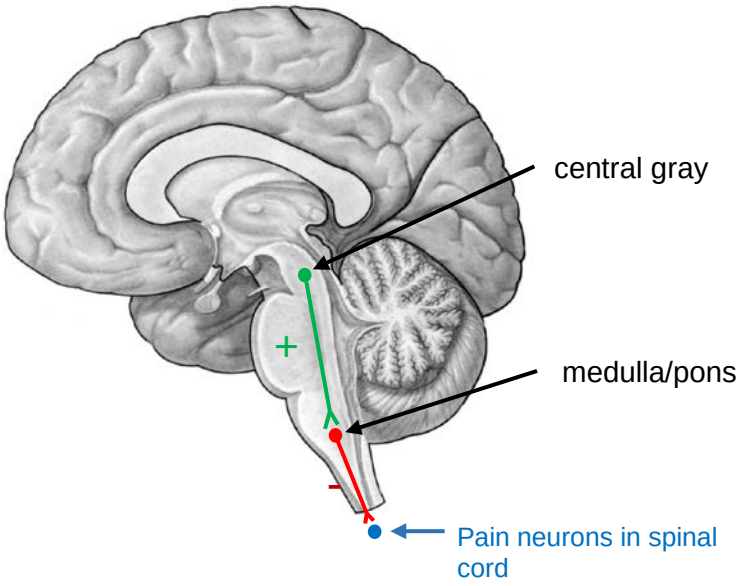




VII. Endogenous modulation of pain processing
   A. Pain can be modified by circumstance
      1. e.g. heat pain threshold is 45°C in almost all people, almost all of the time.
      2. But, in some circumstances in life, *pain perception* can be altered
         a. pain tolerance; perception of meaning/importance of pain
         b. life threatening situations
      3. Placebo effect
         a. "belief" can cause inert procedures or substances to produce analgesia
            - yellow pills more effective than white, injections better than pills, etc.
         b. effective 25-40% of the time
   B. There must be built-in (endogenous) mechanisms in brain capable of reducing pain.
      1. How does the brain do this?
      2. Can this system be manipulated to control pain?
   C. Stimulation Produced Analgesia (SPA)
      1. Electrical stimulation in central gray blocks pain (rats)
      2. Spinal withdrawal reflexes and pain behaviors are inhibited
      3. Rats appear otherwise alert and behave normally
   D. Brainstem sends inhibitory axons down to spinal cord to block pain processing

1. Central Gray neurons (PAG)
   a. receive large wide spread input from cerebral cortex
      - important in the production of analgesia by placebo, etc..
   b. receive collateral input from ascending pain pathways (STT)
      - important for system to know when noxious events occur
   c. send excitatory axons to reticular formation of medulla and pons
2. Neurons in the medulla and pons send inhibitory projections to the spinal cord
   - inhibit reflexes; inhibit pain processing in spinal cord (STT)

E. PAG neurons contain many opioid receptors
1. This is basis for endogenous opioid analgesic system
   - also accessible to exogenous opioids, e.g. morphine from a plant
2. Placebo effect is also mediated by this system; depends on cortex input



VIII. The Problem and Cost of Chronic Pain

A. More than 50% of Americans will experience chronic (> 3 months) pain during lives chronic pain can lead to helplessness, depression, suicide.

B. 116 million Americans have chronic pain condition
1. 10-50% of postsurgical patients develop chronic pain
2. 2.1 million annual ER visits in US for headache alone.
3. 26% of Americans had low back pain > 3 days during last 3 months.

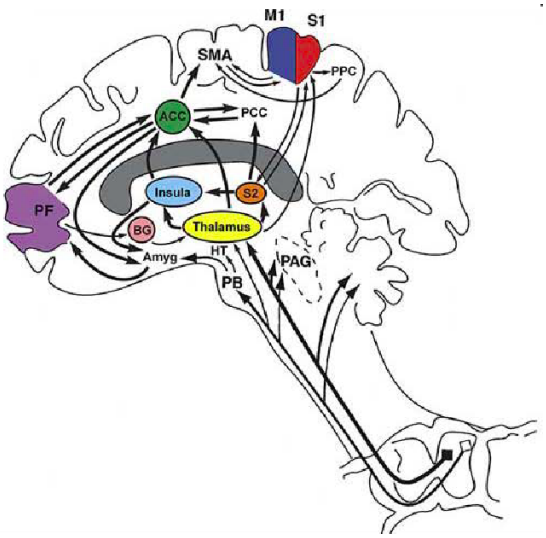
C. Cost roughly $600 billion annual (> heart disease, cancer, and diabetes)
1. Almost $300 billion for treatment

2. Similar cost for lost productivity

D. 60% of patients in ERs receive analgesic agents

E. Understanding chronic pain is huge challenge

1. Long-lasting changes in spinal cord and brain circuitry during chronic pain
2. Pain Network in the brain: seen with functional imaging and EEG (brain waves)
   a. network and spinal cord naturally changes state during different stages of pain
   b. states of network involved in suffering, learning/memory etc. aspects of pain
3. During chronic pain, this network and spinal cord circuity are remodeled
   - semi-permanent changes; difficult to reverse; e.g. using drugs etc.
4. These changes are both the response to and the cause of chronic pain



IX. How to Treat Pain?

A. Activate existing endogenous analgesic systems

1. e.g. opioid and cannabinoid systems
2. receptors already exist in CNS and PNS
   a. several sub-types of receptors
   b. each responsible for different effects, depending on location
      - euphoria, analgesia, movement, respiration etc

B. Central endogenous analgesic systems (within CNS)

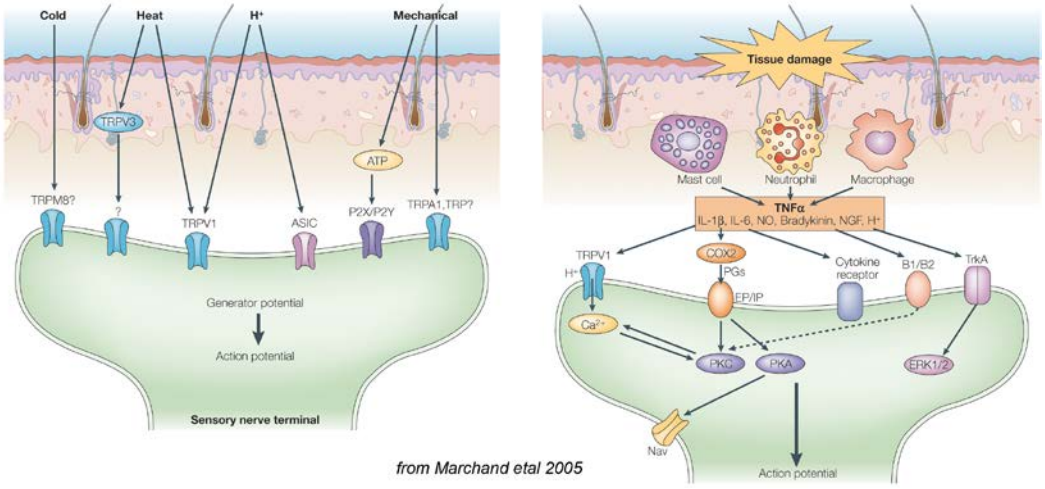
1. e.g. opioid compounds (morphine, oxycodone, codeine)
   a. activates PAG-brainstem descending inhibitory pathways
   b. extremely effective
2. But like all drugs, there are unwanted side-effects

a. sedation, dizziness, nausea, vomiting, constipation
b. respiratory depression
c. physical dependence, tolerance

C. Peripheral endogenous analgesic systems (within PNS)
1. e.g. activate opioid receptors on nociceptor terminals
2. drugs can be delivered by injection or absorbed through skin
3. best if drug cannot enter the brain
- minimizes central (brain) effects; so fewer unwanted side-effects

D. Block inflammatory pain cycle in the periphery
1. NSAID's interfere with Cox2 pathway to prostaglandins
2. e.g. ibuprofen (advil), naproxen (aleve), aspirin

E. Block transduction channels on nociceptor terminals



from Marchand etal 2005

F. Alternative and Complementary Approaches
1. Acupuncture
2. Hypnosis
3. Meditation/Relaxation/Mindfulness
4. most-effective Pain Clinics combine approaches