Somatosensory System II: Pain
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• The somata of somatosensory primary afferent neurons are in:
  • dorsal root (spinal) ganglia
  • cranial nerve sensory ganglia
The somatosensory system detects multiple sensations.

- Touch
  - fine touch
  - pressure
  - Vibration
  - hair movement
  - movement against the skin
- Proprioception
  - limb & trunk position
  - limb movement
  - load
- Thermoception (temperature)
  - heat
  - cold
- Nociception (pain – tissue damage)
- Pruriception (itch)
Pain

• “An unpleasant sensory and emotional experience associated with actual or potential tissue damage.” (International Association for the Study of Pain)
Pain

• Carried into CNS by small primary afferent axons with slow conduction velocities
  – Myelinated: <10 meters/sec
  – Unmyelinated: < 2 m/sec

• Sensations are carried to the thalamus by spinothalamic tract neurons
Pain can be provoked by activation of nociceptors

- Nociceptors signal *tissue damage or threat of tissue damage*
  - Mechanical injury (e.g., cutting, scraping, etc.)
  - Heat injury (burning)
  - Cold (frost-bite)
  - Gut distension (e.g., gas pains)
  - Chemical injury (e.g., acid)
  - Etc.
Nociceptors

- Free nerve endings
- Thresholds are usually HIGHER than most other sensory receptors
  - Light-touch receptor threshold: <1 g
  - Painful touch threshold: ~70 g
Nociceptors

- Mechanical nociceptors:
  - High threshold
  - Fire more with increased force
  - Small, point-like receptive fields

*Firing responses to stimuli*

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

- Polymodal nociceptors:
  - Respond to mechanical, heat, & chemical stimuli
  - Thermal thresholds 43-45°C
  - High mechanical thresholds
  - Respond to algesic agents, e.g., acid

Heat Nociceptors
Nociceptors

• Cold nociceptors:
  – Thresholds ~0° C
  – No overlap with cooling receptors
Anatomy of nociceptors: free nerve endings
Anatomy of nociceptors

- Free nerve endings in superficial skin
- Terminals have transduction proteins sensitive to
  - Heat
  - Cold
  - Acid
  - Pressure
  - ATP
Sensitization of nociceptors

- Causes decreased threshold & larger response
- Contributes to increased pain after injury

First (sensitizing) trial

- 43° C
- 45° C
- 47° C
- 50° C

Second trial

- Skin temperature (°C) vs. Time (sec)
Sensitizers

• Activity
  – Heat
  – Mechanical stimulation
  – Chemical stimulation

• Inflammatory agents
  – Prostaglandins
  – Bradykinin, serotonin, cytokines

• Etc.
Types of pain

• Acute pain ("normal pain")
  – In response to injury or threat of injury
  – Lasts as long as the stimulus
  – Sets boundaries: what’s safe to explore?

• Persistent pain
  – Outlasts the injury or threat of injury
  – Related to healing
  – Protective during healing process

• Chronic pain
  – Outlasts duration of healing
Inflammatory pain

• Most common persistent pain (e.g., sunburn)
• Accompanies all injuries: skin, joints, muscle, bones, post-surgery
• Paradox:
  – inflammation promotes healing
  – inflammation causes more pain
• Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
  – blocks production of prostaglandins \(\rightarrow\) reduced inflammatory pain
  – Effect on healing is uncertain
Chronic pain

• **Huge public health issue**
  – More than 50% of Americans will experience chronic (> 3 months) pain during lives
  – Chronic pain can lead to helplessness, depression, suicide
  – Cost roughly $600 billion annual (> heart disease, cancer, and diabetes)
    • Cost of treatment
    • Lost productivity

• **Chronic pain remodels brain**
  – Difficult to reverse
  – May underlie long-lasting nature of chronic pain
Neuropathic pain

• Type of chronic pain caused by nerve compression, nerve injury, chemotherapy, diabetes, etc.
• Loss of innervation $\Rightarrow$ anesthesia in affected area
• Loss of growth factors released by cut nerves $\Rightarrow$ adjacent nerves behave abnormally
• Thus light touch can cause pain
• Example: Carpel tunnel syndrome
Pain pathways

VPL of thalamus

Spinothalamic tract

S1 cortex

Dorsal root ganglion

Nociceptive primary afferent axon

Spinal cord
Pain pathway vs. innocuous touch

• Touch/vibration
  – First synapse: dorsal column nuclei (nucleus gracilis or nucleus cuneatus)
  – Point of crossing midline: medulla

• Pain
  – First synapse: spinal cord
  – Point of crossing midline: spinal cord
Light touch/vibration pathway

- **Rostral medulla**
  - Internal arcuate fibers
  - Gracile nucleus (pathways from lower body)
  - Cuneate nucleus (pathways from upper body)
- **Caudal medulla**
  - Gracile tract
  - Cuneate tract
- **Cervical spinal cord**
  - Mechanosensory receptors from upper body
- **Lumbar spinal cord**
  - Mechanosensory receptors from lower body
- **Midbrain**
  - Medial lemniscus
- **Mid-pons**
  - Medial lemniscus
- **Cerebrum**
  - Primary somatic sensory cortex
  - Ventral posterior lateral nucleus of the thalamus
Pain/temperature pathway

- Middle medulla
- Caudal medulla
- Anterolateral system
- Cervical spinal cord
- Lumbar spinal cord
- Midbrain
- Spinothalamic tract
- Mid-pons
- Cerebrum
- Primary somatic sensory cortex
- Ventral posterior lateral nucleus of the thalamus
Pain modulation

- Brain circuits exist that can make pain worse or better
Stimulation-produced analgesia

• Stimulation of the region around the cerebral aqueduct ("central gray" or "periaqueductual gray") produces profound analgesia in rats
Stimulation-induced pain facilitation

- Stimulation of parts of the rostral portion of the ventromedial medulla can facilitate pain
Pain modulation

- These circuits may mediate opiate analgesia as well as withdrawal pain
- Endogenous opioid circuits ("endorphins") may be involved in analgesic effects
Pain treatment

• Anesthesia
  – Loss of all sensation

• Analgesia
  – Loss of pain sensation
Anesthesia

• General anesthesia
  – *Causes loss of consciousness: no reaction to pain*
  – Inhalable or injectible
    • Inhalable: isofluorane; nitrous oxide
    • Injectable: propofol
  – Patient is unconscious and may have difficulty breathing and maintaining blood pressure
  – Used mainly for major surgery
  – “Twilight sleep” for more minor procedures
Anesthesia

• Local anesthesia
  – Used for minor or (sometimes) major surgery
  – Injectable
    • E.g., Novocaine
  – Cold temperatures act as a local anesthetic
    • Ice for sprains, burns, etc.

  – Blocks action potential generation/propagation at injection site
Analgesia

• *Selective decrease or loss of pain sensation*

• Used to decrease suffering from pain

• Major categories:
  – Non-steroidal anti-inflammatory drugs (NSAIDs)
  – Cannabinoids
  – Opioids
  – Drugs for chronic pain
    • Gabapentin, etc.
Non-steroidal anti-inflammatory drugs (NSAIDs)

- Aspirin, ibuprofen
- Inhibit synthesis of inflammatory agents (prostaglandins)
- Effective treatment for many kinds of pain
- Better than opioids for bone cancer pain
Cannabinoids

• Cannabinoid = any drug derived from cannabis
• Analgesic effects of cannabinoids reported for centuries.
• Cannabinoid agonists inhibit nociceptive neurotransmission in animal models
• Nevertheless clinical trials haven’t shown consistent benefits to patients
Endocannabinoid system

- Body produces chemicals active at cannabis receptors
  - Anandamide
  - 2-arachidonoylelglycerol
- These compounds are broken down by body’s enzymes
- Drugs that inhibit those enzymes can increase levels of endocannabinoids and are analgesic in rats
Opioids

• Drugs derived from, or related to, those coming from opium
  – Morphine
  – Heroin
  – Fentanyl
  – Codeine
  – Oxycodone (Percoset, Oxycontin)
  – Hydromorphone (Dilaudid)
Actions of opioids

VPL of thalamus

Inhibit spinothalamic tract neurons

Activate pre-frontal (limbic) cortex

Inhibit neurotransmitter release from nociceptors

Spinothalamic tract

S1 cortex
Opioid side-effects

• Constipation
  – Serious problem for chronic users
  – Drugs available for treatment of it

• Tolerance
  – Prolonged drug use → decreased effect

• Dependence
  – Drug abstinence causes pain, diarrhea, etc.

• Addiction
  – A pattern of compulsive drug use
Opioid side-effects

• Constipation
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  – A pattern of compulsive drug use

\textit{NOT} the same things!
Addiction: two-part mechanism

1. The drug makes you feel good

...But eventually...

2. **Lack** of the drug makes you feel bad ("I need it to feel normal")
Factors that promote addiction

• Availability
  – Addicts report that it’s easier to quit cocaine than it is to quit nicotine (smoking)

• Potency/delivery method
  – Gin > beer; heroin > opium
  – Crack cocaine (smoked) > cocaine (snorted)

• Living where you’ve used drugs
  – Simply visiting a street where you’ve often bought heroin, can be sufficient to induce withdrawal
Oxycontin: an addiction flow-chart

Oxycontin = sustained-release form of oxycodone
Advertised for treatment of chronic pain (i.e. increased availability)

Users became addicted
Users discovered it could be crushed, and then injected or snorted → enhanced “rush”
Popularity increased, and new users asked for their own prescriptions
Will cannabinoids be a panacea?

- As potency increases, addictive potential will increase
- Potent cannabinoid drugs may be found to be addictive