Pain

- Submodality of the sense of touch, warns of injury and things that should be avoided
- More subjective than the other senses. The same stimulus can produce different responses in different individuals, or in the same individual in different circumstances

Speaker notes

nociceptive
: of or related to pain arising from stimulation of nerve fibers

Congenital insensitivity to pain

from: http://ghr.nlm.nih.gov/condition/congenital-insensitivity-to-pain

> *20 cases have been reported in the scientific literature*

> *Mutations in the SCN9A gene cause congenital insensitivity to pain. The SCN9A gene provides instructions for making one part (the alpha subunit) of a sodium channel called NaV1.7.*

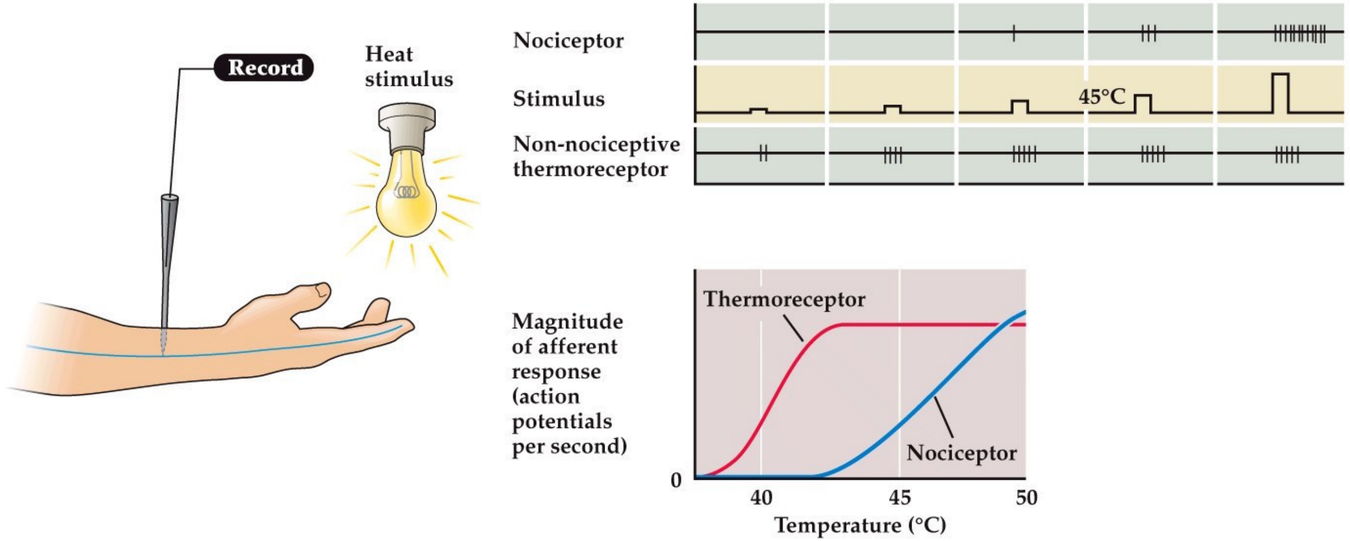
> *NaV1.7 sodium channels are found in nerve cells called nociceptors that transmit pain signals to the spinal cord and brain. The NaV1.7 channel is also found in olfactory sensory neurons, which are nerve cells in the nasal cavity that transmit smell-related signals to the brain.*

> *The SCN9A gene mutations that cause congenital insensitivity to pain result in the production of nonfunctional alpha subunits that cannot be incorporated into NaV1.7 channels. As a result, the channels cannot be formed.*

> *autosomal recessive pattern*

Pain perception involves activation of specialized neurons (not just mechanoreceptors)

- Nociceptor doesn’t fire until pain is felt. Other thermoreceptors fire at all temps and at about the same frequency



Neuroscience 5e Fig. 10.1

Speaker notes

Scheme for transcutaneous nerve recording

How do we detect pain?

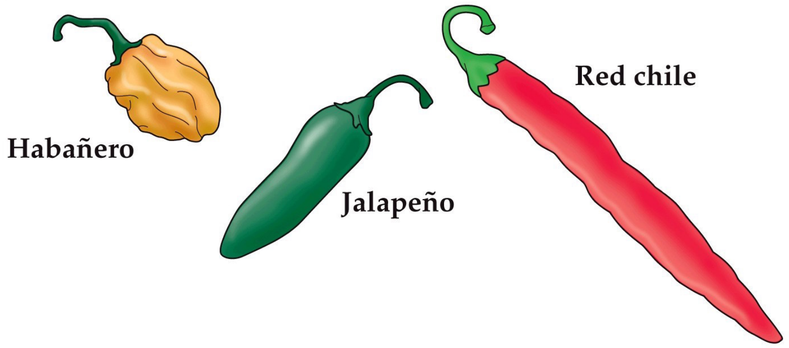
- A family of ion channel receptors have been found that open in response to heat as well as capsaicin called TRP (transient receptor potential) channels
- Structurally resemble voltage-gated K^+ channels, having 6 transmembrane domains that make a pore
- When open allows Ca^{2+} and Na^+ across membrane to generate a receptor potential

Speaker notes

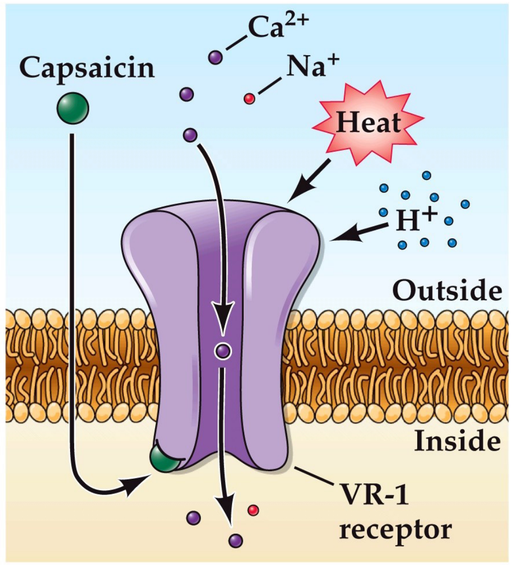
No notes on this slide.

Heat gated ion channels

- Capsaicin receptors are nonselective cation channels opened by heat, low pH, and capsaicin (the hot in hot peppers) [^Caterina1997]
- Mice without TRPV1 (VR1) have impaired sensitivity to pain. Can drink capsaicin as if it were water[^Caterina2000]



Neuroscience 5e Box10A



Neuroscience 5e Box10A

Speaker notes

[^Caterina1997]: Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997 Oct 23;389(6653):816-24. doi: 10.1038/39807. PMID: 9349813.

[^Caterina2000]: Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Koltzenburg M, Basbaum AI, Julius D. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science. 2000 Apr 14;288(5464):306-13. doi: 10.1126/science.288.5464.306. PMID: 10764638.

transient receptor potential cation channel subfamily V member 1 (TrpV1), also known as the capsaicin receptor or the vanilloid receptor 1 (VR1)

function of TRPV1 is detection and regulation of body temperature. In addition, TRPV1 provides a sensation of scalding heat and pain (nociception).

43ºC threshold (110ºF)

There is recent evidence for endovanilloids that are released by other cells that can stimulate TRPV1 and contribute to nociception

receptors for transduction of mechanical and chemical forms of nociceptive stimulation are not well understood, candidate include

- TRP family (TRPV2 and TRPA1)
- ASIC acid sensing family (ASIC3 cardiac pain)
- TRPV3 TRPV4 warm temperatures
- TRPM8 cold temperatures

repeated applications of capsaicin desensitize pain fibers, preventing neuromodulatiors like sub P, VIP, and somatostatin from being released by PNS and CNS nerve terminals

NAV 1.7 and NAV 1.8 are sodium channels especially important for transmission of nociceptive information

2021 Nobel Prize David Julius (UCSF, TRP channels) and Ardem Patapoutian (Scripps, piezo receptors)

https://www.universityofcalifornia.edu/news/david-julius-wins-nobel-prize-work-pain-sensation

https://www.nobelprize.org/prizes/medicines

> *“for their discoveries of receptors for temperature and touch”*

Nociceptors

- Transfer information about pain
- Three major classes of nociceptors: Aδ mechanosensitive nociceptors, Aδ thermal nociceptors, and polymodal nociceptors
- Aδ mechanosensitive nociceptors-activated by intense pressure, are lightly myelinated and have speeds of 5-30 m/s
- Aδ thermal nociceptors are activated by very hot or very cold temperatures. Are lightly myelinated
- Polymodal nociceptors (C fibers) respond to temperature, pressure, or chemicals, are unmyelinated and conduct at speeds of 1 m/s
- Aδ and C fibers have cold temperature gated ion channels. When they fire they are perceived as pain
- Pain receptor receptive fields are generally pretty large, presumably because the detection of pain is more important than its exact location

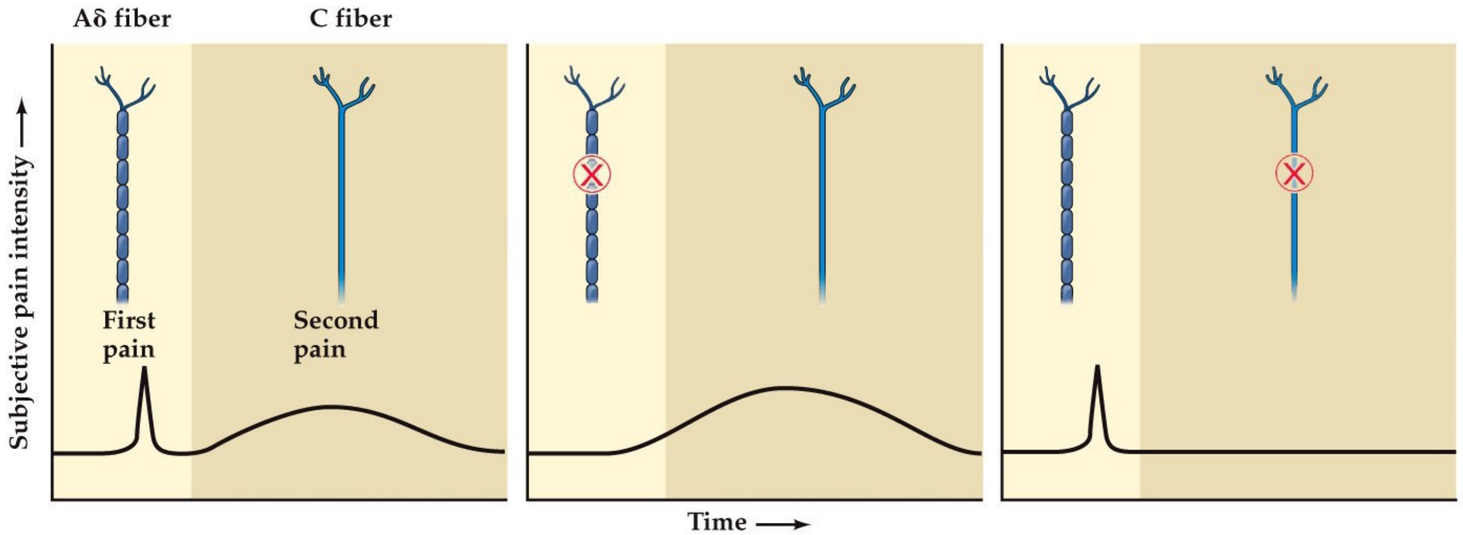
Speaker notes

No notes on this slide.

Two categories of pain perception

- first pain (sharp), Aδ fibers
- second pain (dull, longer lasting) C-fibers

selective block of either Aδ or C fibers



Neuroscience 5e Fig. 10.2

Speaker notes

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Hyperalgesia

- Enhanced sensitivity and response to stimulation of the area around the damaged tissue. Stimuli that would not ordinarily be perceived as pain now is. For example after a sunburn a normal shower now feels painful
- Due to the release of substances from the damaged cells (e.g. prostaglandins, bradykinin, histamine, serotonin, ATP) that increase sensitivity by interacting with the nociceptor ion channels (directly or indirectly). and making it open easier, or by interacting with other receptors on nociceptive fibers to potentiate activity of TRP channels
- Aspirin and ibuprofen inhibit cyclooxygenases (COX-2 inhibitors), necessary for prostaglandin synthesis
- Shows that pain and injury are inter-related

Speaker notes

- allodynia (hyper sensitization), clinically relevant pain from normally unpainful stimuli. Contrast with nociceptive pain (actual response to real tissue injury associated with inflammation like aches, sprains, arthritis, cancer pain, headache). Clinical issue is shifting noxious stimuli in pain sensation-stimulus intensity activation curve to the left into innocuous stimuli
- injury to a nerve is called neuropathic pain (phantom limb pain falls into this category), nerves in limbs, spinal cord, or brain can all call neuropathic pain. Also shingles, MS, spinal cord injury, cancer pain. Often severe burning sensation pain and chronic.
- phantom limb pain, often severe grip sensation (nails digging into hand)

Nice talk on pain from Allan Basbaum UCSF. Argues against the existence of a 'pain' pathway. Can't just cut nerve to abolish pain--maybe for acute pain but not chronic pain. peripheral sensitization.

tissue injury --> arachidonic acid, cyclooxgenase--> prostaglandins --> C fiber threshold lowered --> allodynia

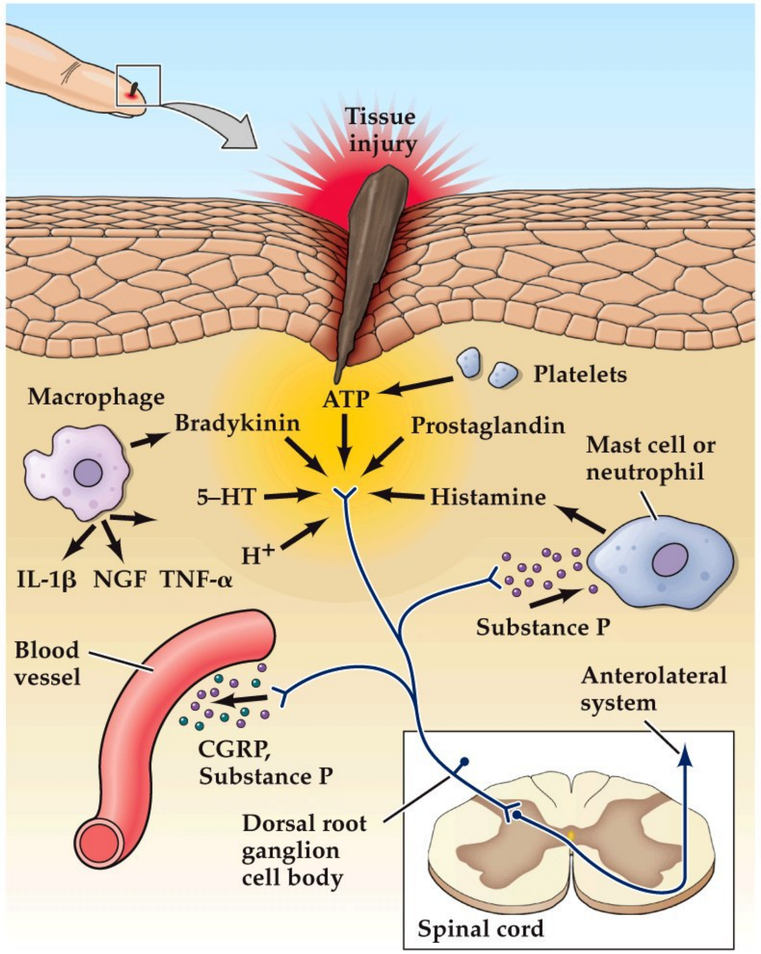
central sensitization (pain memories)-- is a CNS disease, not a symptom of other diseases it is argued (A. Basbaum)

Sensory discriminative (SI and SII) and affective motivational (limbic system activated, including cortical areas anterior cingulate gyrus, insular cortex (between parietal and temporal lobes ventral to S1)) dimensions of the pain experience. (MC Bushnell, Basbaum lecture). **Anterior cingulate gyrus positively correlates with unpleasant experience**

More fMRI brain activation (amplitude and size of activation) in parts of brain with same painful stimulus for females vs males. Pain threshold almost the same (45degs hot) between the sexes but is a little bit lower for women. But pain tolerance is much higher in women. (Casey et al, Basbaum lecture). Who can tolerate delivering a baby.

Expectancy can alter pain (sawamoto 2000 interesting fMRI study, after Basbaum lecture 51:07). Imaging the brain of an empathetic spouse (female) reveals activity patterns characteristic of a spouse that is in pain (no citation someone from germany, Basbaum lecture 52:27)

Inflammatory response to tissue damage



Neuroscience 5e Fig. 10.7

Speaker notes

Another type of peripheral sensitization can occur due to substances released within damaged tissues can modulate the response of nociceptive fibers. A host of molecules that can augment the activity of free nerve endings like…

Most interact directly with the receptors or ion channels of the nociceptive fibers. e.g. TRPV1 capacin receptor can be potentiated form the channels direct interactions with extracellular protons that are released by immune cells or through indirect interaction with other enzyme receptors like TrkA for NGF or bradykinin receptors.

Prostaglandins reduce the threshold depolarization needed for AP generation by phosphorylation of special TTX resistant Na+ channels expressed in nociceptor afferents and also incr levels of cAMP.

Cells that contribute to this inflammatory soup include mast cells, patelets, basophils, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts. Cells are responsible for releasing protons (lowering the pH), arachidonic acid, bradykinini, histamine, serotonin, prostaglandins, neucleotides, NGF, cytokines (interleukin 1beta, and TNF-alpha). COX2 inhibitors, NSAIDs -- or nonsteroidal anti-inflammatory drugs block Cox-1 and Cox-2 enzymes so that prostaglandins can't be made.

nociceptive
: of or related to pain arising from stimulation of nerve fibers

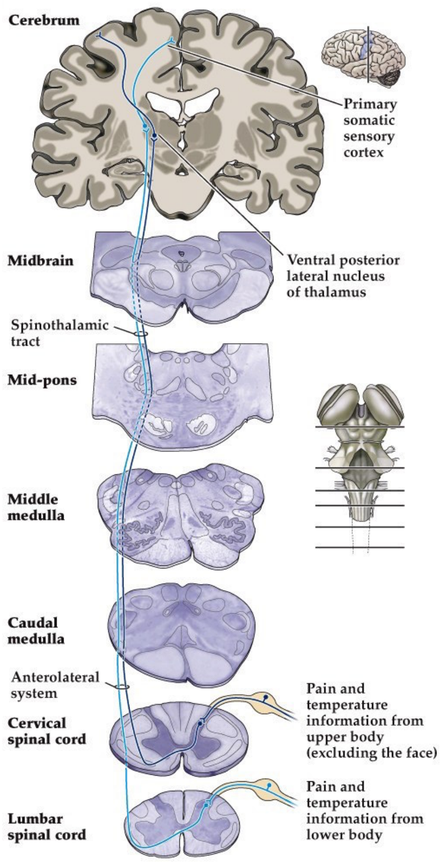
Pain pathways

- Spinothalamic tract
- Cell bodies found in the most lateral parts of the dorsal root ganglia, but not discretely localized.
- Innervate neurons in the dorsal horn of the spinal cord.
  - Some of these neurons project within the spinal cord. These are important for reflex behaviors.
  - Others project axons that cross the midline in the same segment and then go up to the brain.

Speaker notes

No notes on this slide.

Major pathways for pain (and temperature) sensation of the body



Neuroscience 5e Fig. 10.6

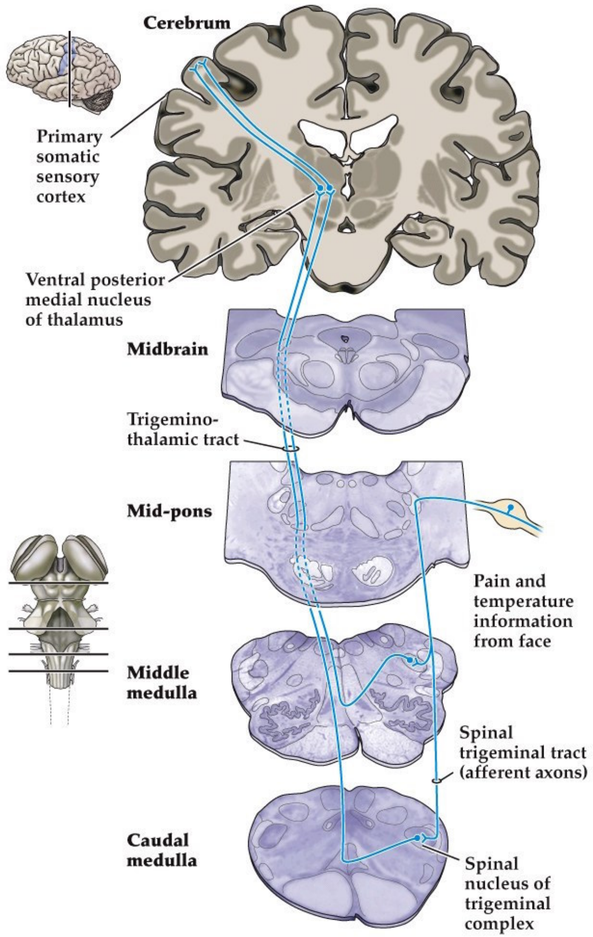
Speaker notes

nociceptive projections into dorsal horn branch into ascending and descending collaterals forming the dorsolateral tract of Lissauer (named after 19th c. German neurologist).

C fibers (slow pain) terminate in layer 1 (Rexed's laminae, named after anatomist who first described spinal gray matter layers in 1950s) of dorsal horn.

Adelta (fast pain) terminate in layer 5 of dorsal horn where Abeta mechanosensory terminals innervate.

Pathways for pain (and temperature) sensation of the face



Neuroscience 5e Fig. 10.6

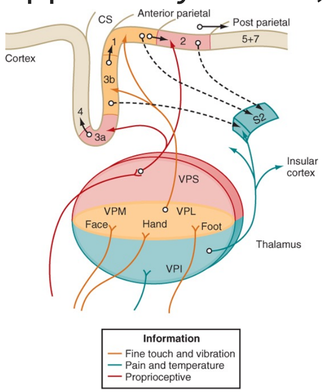
Speaker notes

No notes on this slide.

Nociceptive component in the ventral posterior nuclei in the thalamus

- Pain and temp go to VPM and VPL nuclei just like the mechanosensory axons
- VPM from the face, VPL from the body
- Presumably responsible for our ability to locate a pain with respect to body position

upper body medial, lower body lateral



Berne and Levy, Physiology 6e Elsevier

Speaker notes

No notes on this slide.

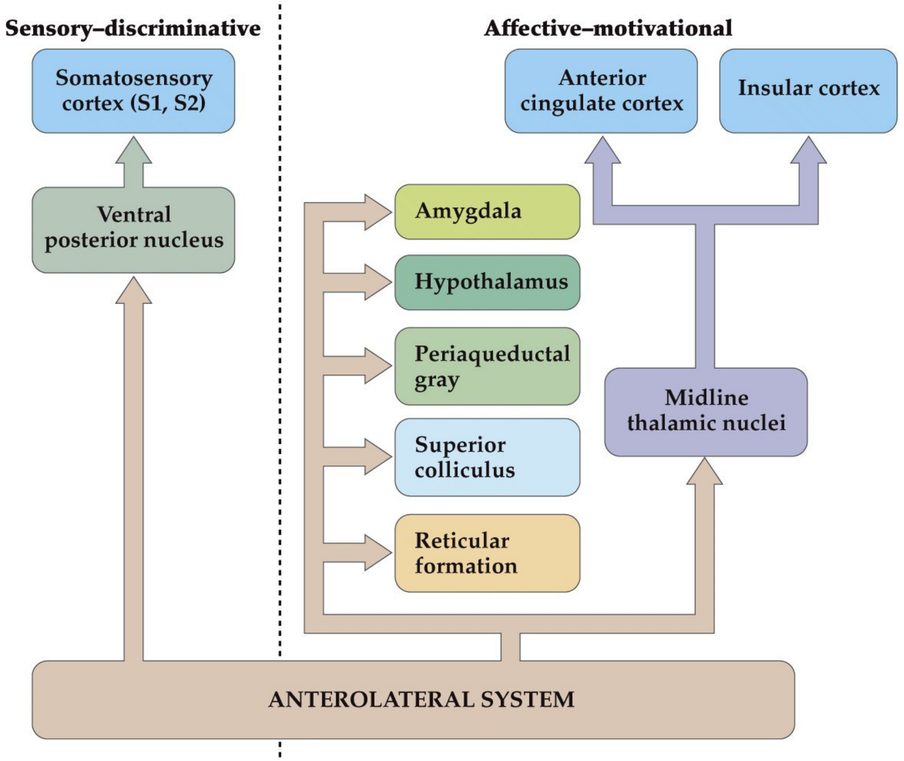
Cerebral cortex

- VPM and VPL neurons project to primary somatosensory cortex. These thalamic neurons have small receptive fields and are likely used to locate where the pain is, but are not responsible for dull aches that are associated with chronic pain as ablation does not reduce pain
- There are also direct projections to the reticular formation (in medulla), and the midline thalamic nuclei. These neurons project to areas of the limbic system and are responsible for the emotional aspects of pain

Speaker notes

No notes on this slide.

Anterolateral system sends information to different parts of the brainstem/forebrain



Neuroscience 5e Fig. 10.5

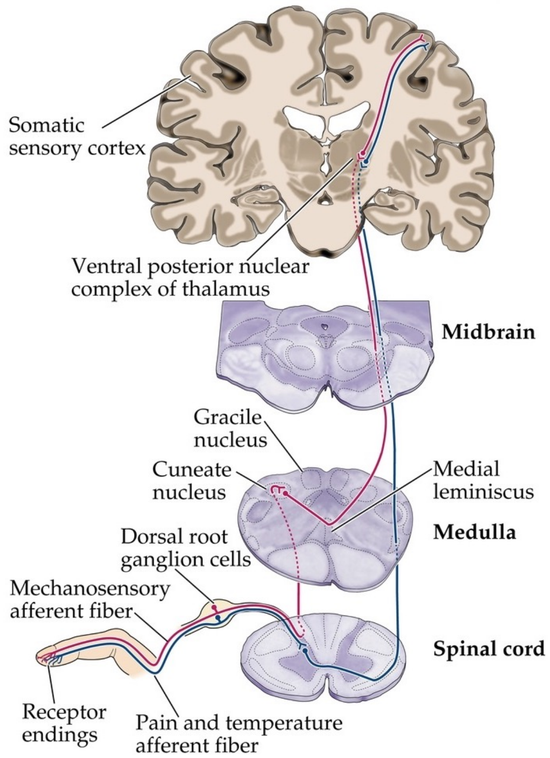
Speaker notes

sensory discrimative: location, intensity, and quality of noxious stimulation

affective-motivational: unpleasant feeling, fear, anxiety, autonomic activation for fight-flight

Spinothalamic tract

- Also called anterolateral column part of the ventral column
- Note where axons cross over the midline
- Touch and pain are on opposite sides below medulla
- Touch and pain are on the same side above medulla



Neuroscience 2e 2001

Speaker notes

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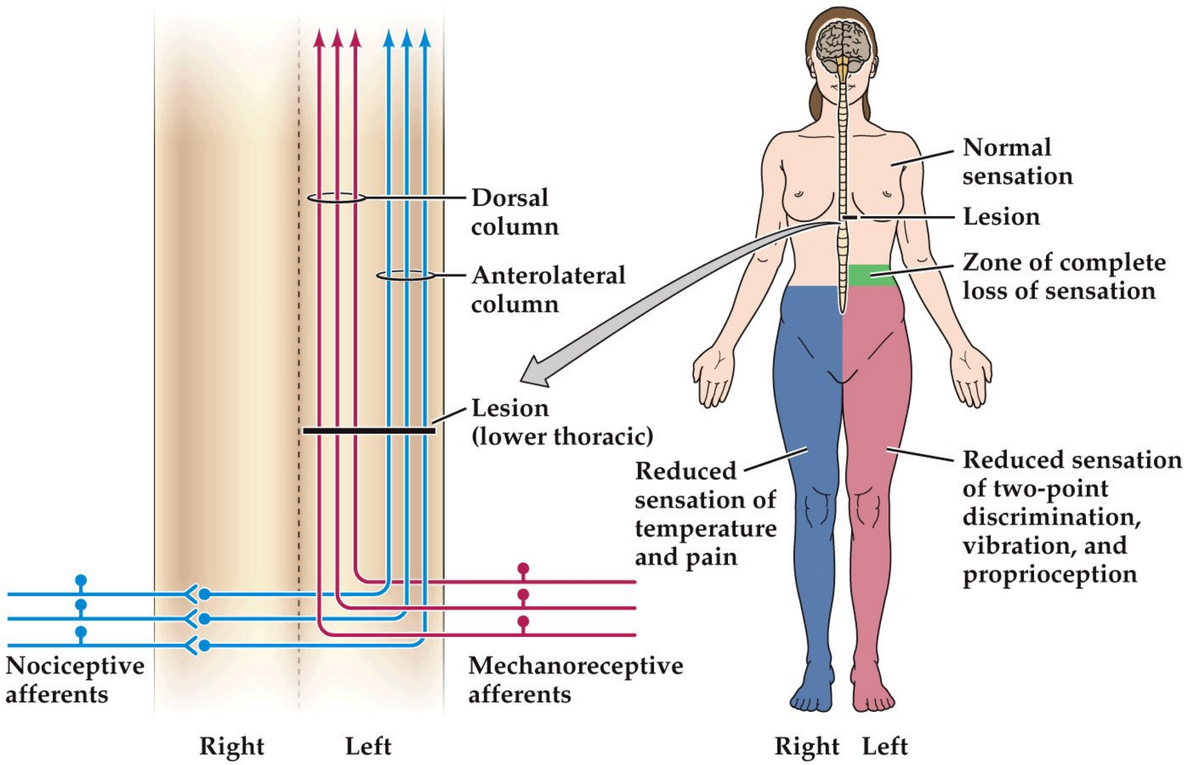
The anterolateral and dorsal column-medial leminiscal systems cross the midline at different sites



Neuroscience 5e Fig. 10.4

Speaker notes

nociceptive and mechanosensory pathways

Pain vs touch

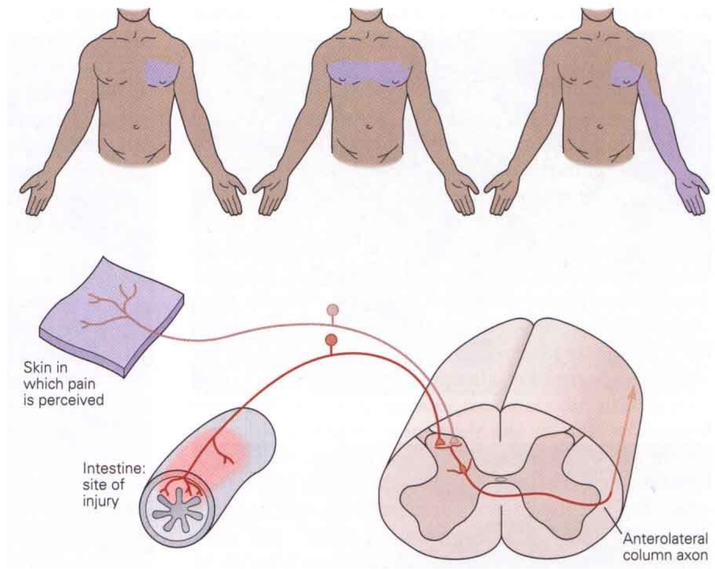
- 2nd order mechanosensory axons cross at the level of the medulla but 2nd order pain axons cross at about the segment their cell bodies are in
- If there is a damage on one side of the spinal cord, below the injury site, there would be no sense of touch on the same side and no sense of pain on the contralateral side

Speaker notes

No notes on this slide.

Referred pain

- Few if any neurons in dorsal horn are specialized solely for the transmission of visceral pain
- It is conveyed to brain via dorsal horn neurons that also get inputs from skin
- Therefore a person may feel pain at a site completely different than its source



referred pain

Speaker notes

anginal pain which is pain arising from heart muscle that is not being adequately perfused with blood. Referred to the upper chest wall, with radiation into the left arm and hand.

Innervation of same neuron in the dorsal horn of the spinal cord.

Pain perception is subjective

- Pain can be subjective. Depends on context.
  - Rubbing the site of injury can make pain less severe.
  - Soldiers wounded in battle feel less pain than if one gets the same injury at home
- Why? There is a descending pain pathway that can impinge on the dorsal horn to quiet neurons

Speaker notes

e.g. prostaglandins lower threshold by phosphorylation of TTX resistant sodium channels.

TrPV1 receptor potentiations.

cox2 inhibit prostaglandin syn

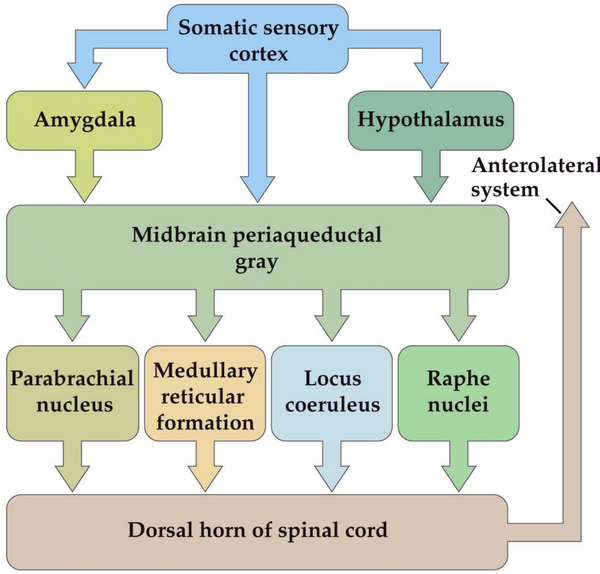
Brain modulation of ascending pain signals

- Stimulation of periaqueductal grey (in midbrain) or rostral medulla reduces pain, producing analgesia
- Stimulation only reduces pain sensation, animal/person still responds to touch, temp etc, just feels less pain
- Cerebral cortex and hypothalamus project to periaqueductal gray which then projects to nuclei in the medulla (Raphe nuclei, reticular formation), which project to the dorsal horn and inhibit ascending pain fibers, forming a descending pathway that modulates pain

Speaker notes

No notes on this slide.

Modulation of ascending pain signal transmission



Neuroscience 5e Fig. 10.8

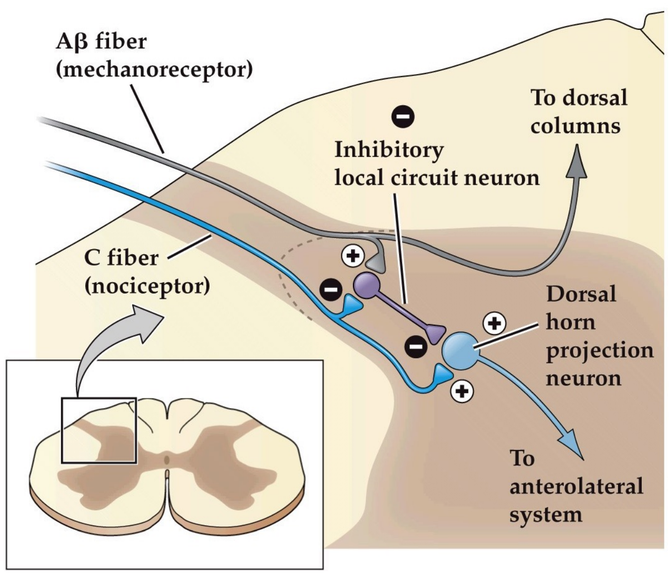
Speaker notes

enkephalins, endorphins, dynorphins— present in the periacq. gray matter, ventral medulla, and in spinal cord regions in dorsal horn.

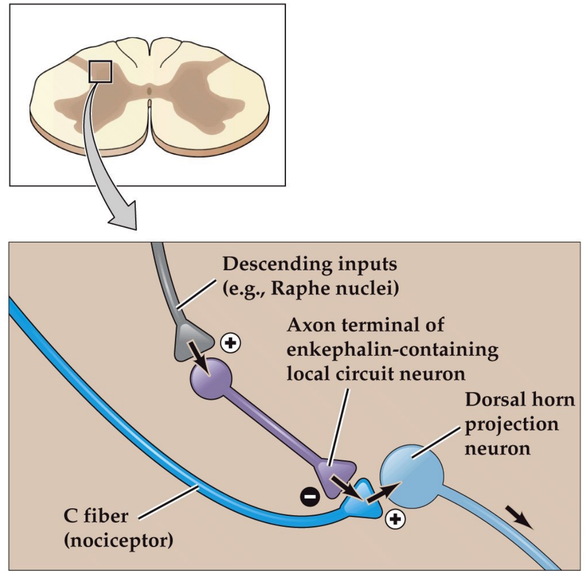
Also CB1 and endocannabinoids work similiarly here in the dorsal horn. CB1 on presynaptic terminals of dorsal horn nociceptive terminals can be activated by endocannabinoid release in a retrograde fashion and decrease the release of neurotransmitters such as GABA and glutamate. *Interestingly, the analgesic effecs of PAG stimulation is blocked if CB1 antagonists are administered* highlighting the importance of endocannabinoids in descending control of pain transmission.

Modulation of ascending pain signal transmission

- Axons from neurons with mechanoreceptors can synapse onto inhibitory interneurons in spine to dampen pain response
- Descending pathways from the brainstem can dampen pain response



Neuroscience 5e Fig. 10.8



Neuroscience 5e Fig. 10.8

Speaker notes

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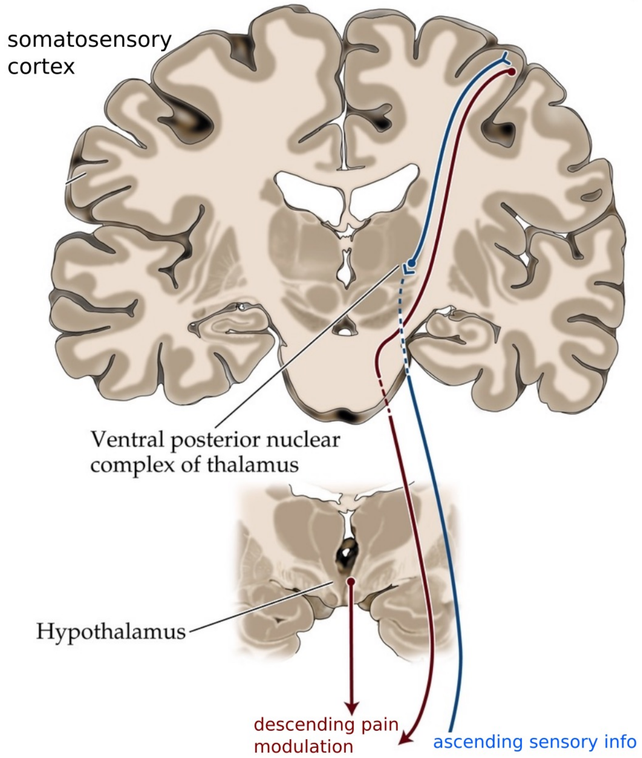
Descending systems modulate the transmission of ascending pain signals

Descending pathways from cortex and hypothalamus



Neuroscience 2e 2001

Speaker notes

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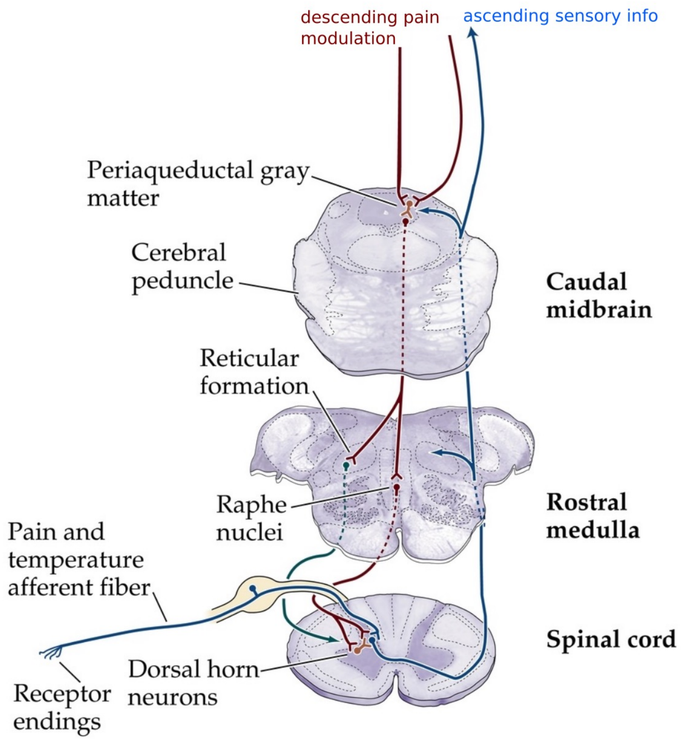
Descending systems modulate the transmission of ascending pain signals

Descending output from periaqueductal gray–rostral medulla reduces activity in spinothalamic tract



Neuroscience 2e 2001

Speaker notes

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Endogenous opioids dampen pain signal transmission

- Opioid receptors (metabotropic) are expressed in the areas of descending pain pathway (also expressed in other areas, such as muscles of the bowel and anal sphincter)
- Ligands– enkephalins, endorphins, and dynorphin. Found in all descending pain areas
- Opioids decrease the chance that a nociceptor afferent will fire by causing inhibition
- Opiate antagonist naloxone (competitive opioid receptor antagonist) blocks stimulation produced analgesia as well as morphine-induced analgesia. Suggests that they are the same thing

Speaker notes

endogenous opioids
: all are 5–30 a.a. long peptides
: enkephalins, endorphins, dynorphins

- leucine-enkephalin
- methionine-enkephalin
- alpha-endorphin
- alpha-neoendorphin
- beta-endorphin
- gamma-endorphin
- dynorphin A
- dynorphin B

- oxycontin, percoset

Placebo effect

- Sugar pills can reduce perception of pain
- Effect can be blocked by naloxone, a competitive antagonist of opioid receptors
- Therefore placebo effect is based on a biochemical change in the brain, as are all perceptions

Speaker notes

- mind separate from body. No– this highlights something that neuroscientists already widely accept, that you cannot separate the mind from the body, the mind is body and vice versa
- what is or is not reality-- philosophers
- highlights descending control and higher order processing of pain
- endogenous opioids
- children are not placebo reactors less than 10 yr old.
- acupuncture works likely as a placebo (needle can be stuck anywhere).

Placebo (wn -over)
: an innocuous or inert medication; given as a pacifier or to the control group in experiments on the efficacy of a drug

Placebo
: not well defined, especially trying to test therapeutic effects of non-pharmacological treatments (acupuncture)
: part of *every* treatment. Human touch, interaction, care compared with isolation and pain

Musial Front Neurosci 2019: https://doi.org/10.3389/fnins.2019.01110 Vincent and Lewith J R Soc Med. 1995: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1295163/