1. Describe the various types of pain receptors.
2. Know the peripheral and central anatomical pathways involved in nociception.
3. Understand the cellular basis that underlies normal fast and slow pain sensation compared with innocuous mechanical sensation (light touch).
4. Understand the molecular basis by which nociceptors can respond to mechanical, thermal, and chemical stimuli.
   - no single receptor class is dedicated to one percept, and no one percept relies on a single receptor class
5. Understand the molecular mechanisms responsible for the development of pain hypersensitivity (allodynia or hyperalgesia) in response to tissue or nerve injury.
6. Understand the cellular and molecular basis that underlie abnormal (chronic) pain sensation.
7. Understand how the body normally alleviates pain (analgesia).
8. Define the terminology related to pain according to the IASP classification.

**PAIN:**
An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. **Superficial pain** is a “call to action.” The motor response to superficial pain includes withdrawal from the noxious stimulus, orienting to a (potentially) noxious stimulus, and escape from the noxious stimulus. **Deep (chronic) pain** is inescapable. We respond by becoming immobile, withdrawing from social interaction, and we stop eating. Cardiac output decreases; resources shift to the immune system.

**Nociceptors** respond only to noxious, high intensity stimuli. At the peripheral (distal) end of the nociceptor, noxious stimuli generate currents that, above a given threshold, send signals along the nerve fiber to the spinal cord.
- The "specificity" (whether it responds to thermal, chemical or mechanical features of its environment) of a nociceptor is determined by which ion channels it expresses at its peripheral end.
- Dozens of different types of nociceptor ion channels have so far been identified, and their exact nature & functions are still being determined.
- The smallest myelinated and unmyelinated fibers carry pain and temperature information.
**PATHWAYS OF NOCICEPTION:**

**The Spinothalamic Tract:**

A. The peripheral processes of dorsal root ganglion cells end as receptors sensing pain, temperature, and complex (chemical) sensations.

B. The central processes of these dorsal root ganglion cells synapse with the neurons of the nucleus proprius.

C. The axons of these second-order neurons cross via the anterior white commissure, enter the contralateral white matter, ascend in the lateral funiculus, and synapse on third-order neurons located in the ventral posterolateral nucleus of the thalamus.

D. The axons of third-order neurons project to the primary somatosensory cortex (3,1,2).

Other pain pathways include:

- Spinoreticular tract
- Spinomesencephalic tract

**STRATIFICATION OF AFFERENTS:**

- **Peptidergic C fibers** & **Aδ fibers** terminate superficially; synapse on large *projecting neurons* in lamina I & interneurons in outer lamina II (express TrkA receptors)

- **Non-peptidergic C fibers** terminate in the inner part of lamina II (express c-RET neurotrophin receptors)

- **Innocuous Aβ fibers** terminate on PKCg-expressing interneurons in the ventral half of lamina II

- *Projection neurons* in lamina V receive **direct** input from both Aδ and Aβ fibers; **indirect** from C fibers (referred pain via interneurons)

**PERCEPTION OF PAIN:**

**NOCICEPTION:** the transduction and conveyance of signals from specialized sensory receptors concerning tissue damage.

Nociceptors are the LEAST specialized of sensory receptors. They are free nerve endings with little or no specialized structures.

- Thermal or Mechanical - small diameter, thinly myelinated axons (Aδ); moderately slow conduction velocities (5-30m/s); convey sharp pain.
• Polymodal - respond to a variety of stimuli (temperature, chemical, mechanical); small diameter, Unmyelinated axons (C); slowest conduction velocities (0.5-2m/s); convey dull or diffuse pain.

• Silent – receptors found in viscera which are unresponsive to normal stimuli; respond only to inflammatory stimuli (sensitized); alter both peripheral & central pathways.

Both Aδ and C fibers are distributed in skin & deep tissues. First pain causes a fast, sharp, well-localized sensation (Aδ). Second pain causes a less well-defined aching, or burning (C). Nociceptors are the common entry point for pain pathways. However, pain pathways diverge upon entering the CNS.

**HYPERALGESIA:**

“An increased response to a stimulus which is normally painful.” Due to the lowering of the nociceptor’s threshold by either peripheral (primary) or central (secondary) mechanisms, resulting in an increase in the number of action potentials sent to the CNS.

**Primary Hyperalgesia:** “This occurs at the site of the lesion when the nociceptive fiber is sensitized or directly activated by chemical agents released by the damaged tissue, nearby cells, or the neuron itself.”

Injury can release chemical mediators, such as bradykinin, serotonin, prostaglandin, etc. which sensitize the receptor and release of substance P, which can interact with many sites. (Aspirin is now known to specifically interact with an enzyme which makes prostaglandins, and therefore can reduce inflammation & algesia).

When tissue damage occurs, the damaged cells release chemical agents which depolarize the pain fiber, which send APs into the CNS AND get conducted (retrogradely) through each branch point. When the AP reaches the nerve ending, peptides (SubP, CGRP, NkA) are released.

• CGRP causes vasodilation (flare).
• SubP & NkA render vessels more permeable (edema).
• SubP stimulates mast cells to degranulate (histamine), stimulates leukocytes into area (cytokines, prostaglandins, NO, leukotrienes).
In addition to the TRP (transient receptor potential) family of channels, other receptors and ion channels participate in the transduction of stimuli expressed by nociceptors. These include a class of Na channels (Nav1.7), purinergic receptors activated by ATP (PTX3), and Mas-related G protein-coupled receptors (Mrg).

* Individuals lacking the Nav1.7 receptor (due to a gene mutation which inactivates the channel) are completely insensitive to pain. All other sensations, however, are normal. Other mutations can make the channel hypersensitive.

Many nociceptors are polymodal, activated by thermal, mechanical, and/or chemical stimuli

**Secondary Hyperalgesia:** “This occurs during severe or persistent injury, where the nociceptors fire repeatedly, thereby increasing the firing of neurons in the dorsal horn (called "wind-up"), which results in long-term changes to the overall excitability of these cells, or the target neurons (post-synaptic neurons).”

The resulting long-term changes in excitability/sensitivity of these dorsal horn neurons is called **Central Sensitization**. These long term changes in the excitability of the dorsal horn neurons (and interneurons) has been attributed to the induction of immediate early genes, resulting in the up-regulation in the expression of neuropeptides (NAPs), neurotransmitters, and corresponding receptor populations. In a sense, the dorsal horn neurons have a “stored memory” for pain which can lead to spontaneous pain, decreased threshold for pain, and an overall increase in the excitability of these neurons. This leads directly to an overall increase in the amount and severity of pain perceived.

The initial response of interneurons and 2° neurons in the spinal cord may include activation of 2nd messenger systems, resulting in the formation/increase of second messengers (cAMP), thereby releasing/increasing protein kinase activity (PKA) and the activation or inactivation of various ion channels, thus temporarily altering the excitability of these neurons.

Continuous or tonic stimulation can also result in protein kinases crossing the nuclear envelope, interacting with regulatory proteins (Enhancer) and immediate early genes to stimulate the formation of new/additional channels. These new/additional channels, when inserted into the membrane, can permanently alter the excitability properties of interneurons and 2° neurons. This may result in a “memory” for pain long after the initial injury has healed.

**NEUROTROPHINS:**
BDNF further increases excitability and facilitates the activation of dorsal horn neurons.

**Aδ vs. C fiber NEUROTTRANSMITTERS:**
**REFERRED PAIN:**
“Referred Pain” is due to convergence of somatic sensory afferents and visceral afferents from pain & stretch receptors onto common interneurons and 2° neurons. The cortex typically interprets the pain coming from somatic sources rather than visceral. The neurotransmitters used differ between the two types:
- Aδ fibers use small vesicles and excitatory amino acids (glutamate).
- C fibers use both large & small vesicles, (amino acids, substance P & NAP’s); therefore they can have fast and slow EPSPs at the dorsal horn.

**ANALGESIA: the modulation or reduction of pain**
Pain perception can be modified at the first synapse in the spinal cord by MANY other afferents AND descending projections from higher centers in the CNS.

**The “GATE CONTROL” Theory:**
A “balance” exists between myelinated and unmyelinated fibers in the dorsal horn. There are 4 primary classes of spinal neurons which can interact to modulate pain:
1. Unmyelinated nociceptive afferents (pain fibers).
3. Projection neurons to the CNS (2° via ALS).
4. Spontaneously active inhibitory interneurons (the “gate”).

If you stimulate the pain pathway, this results in inhibition of the inhibitory interneuron and excitation of the projection neurons, resulting in the perception of pain.

By stimulating the non-nociceptive Aβ fibers (2) of the somatosensory system (i.e. touch, temperature, proprioceptive fibers), you will also excite the inhibitory interneurons (4), resulting in a decreased output of the projection fiber and a suppression of the pain. That is why ice, heat, “shaking it out,” and rubbing a mildly painful stimulus (bumping your knee) is effective in reducing the amount of perceived pain.
This type of regulation is only effective in *mildly* painful stimuli, and can **NOT** overcome the pain associated with severe injuries. Remember, this is a “balance” that is being moved back and forth between the nociceptive and non-nociceptive fibers.

**CORTICAL CONTROL OF SEVERE PAIN:**

Pain synapses can also be modified by descending pathways in the CNS. Direct stimulation of the PeriVentricular and PeriAqueductal Gray (PVG & PAG) results in excitation of the rostroventral medulla, which then stimulates cells in the dorsal horn of the spinal cord. These connections in the spinal cord are inhibitory, and suppress the nociceptive neurons.

The PAG and PVG are extremely sensitive to morphine, and therefore the primary site of action of morphine and morphine-like drugs (opiates). *Endogenous opiodes* (enkephalins, proopiomelanocortins & dynorphins) are present at the sites associated with processing of nociceptive input, and therefore stimulate the PAG and PVG.

Other descending pathways from the pons (locus ceruleus) and the medulla (raphe magnus) also terminate in the dorsal horn and suppress nociceptive neurons. The descending inputs to the dorsal horn result in the modulation of the primary pain afferent onto the projection neurons either directly (A; via an inhibitory connection) or indirectly (B) by stimulation of enkephalin interneurons via 2 possible mechanisms: *Presynaptic Inhibition* and *Postsynaptic Inhibition*.

*Presynaptic inhibition* (indirect; extrinsic form of synaptic plasticity) of the pain fibers in the dorsal horn via opiate receptors on the presynaptic cell, which results in an increased K+ conductance and **hyperpolarization of the presynaptic terminal**. This hyperpolarization of the presynaptic terminal results in a decrease in the duration of the AP, decreased Ca$^{2+}$ influx and a decrease in the amount of neurotransmitter released onto the post-synaptic cell (projection neuron).

*Postsynaptic (direct) modification* of the EPSP via hyperpolarization of the postsynaptic membrane via opiate receptors on the postsynaptic cell (intrinsic method of synaptic plasticity – hyperpolarizes the resting membrane potential of the postsynaptic neuron, taking it farther from threshold). The net result is a **significant (albeit temporary) reduction in output** from the 2nd order neuron into the CNS, and a reduction in perceived pain.
Remember that there is a limited supply of endogenous opioids and enkephalins in the spinal cord!

Please look over the “Pain Terminology” handout related to this lecture and familiarize yourself with the definitions of the following terms. Be able to differentiate between the various types of pain described.

- Allodynia
- Analgesia
- Causalgia
- Central Pain
- CRPS Type I & II
- Hyperalgesia (Primary & Secondary)
- Hyperpathia
- Hypoalgesia
- Neuralgia
- Neurogenic Pain (Deafferentation & Sympathetically Maintained)
- Neuropathic Pain
- Neuropathy
- Nociceptive Pain (Nociceptor)
- Pain
- Pain Threshold
- Paresthesia & Dysesthesia
- Sensitization