Pain and Analgesic System

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Structures at peripheral endings of afferent neurons
Detect stimuli a variety of energy forms, modalities, such as heat, light, sound, pressure, & chemical.

Convert forms of energy into electrical signals (APs)
  ◦ Process is called transduction
Receptors have differential sensitivities to various stimuli.

- Each type of receptor is specialized to respond to one type of stimulus, its adequate stimulus.
  - e.g., receptors in eye are sensitive to light.
- Some receptors respond weakly to stimuli other than their adequate stimulus
  - e.g., adequate stimulus for eye receptors (photoreceptors) is light, can be activated to a lesser degree by mechanical stimulation. When hit in the eye, a person often “sees stars,” because mechanical pressure stimulates photo-Rs.
Types of Receptors

• Sensory Receptors
  – Can be categorized according to location:
    • **Cutaneous receptors** are near an epithelial surface
    • Respond to touch, pressure, temperature or **pain**

    • **Special sense receptors** are part of a sensory organ
    • Such as hearing, sight, equilibrium
Types of Receptors

- **Photoreceptors**
  - Responsive to visible wavelengths of light

- **Mechanoreceptors**
  - Sensitive to mechanical energy
    - e.g. skeletal muscle receptors sensitive to stretch, receptors in ear containing fine hairs that are bent as a result of sound waves, & blood pressure monitoring baroreceptors.

- **Thermoreceptors**
  - Sensitive to heat & cold

- **Osmoreceptors**
  - Detect changes in concentration of solutes in body fluids & resultant changes in osmotic activity

- **Chemoreceptors**
  - Sensitive to specific chemicals
  - Include receptors for smell & taste & receptors that detect O$_2$ & CO$_2$ concentrations in blood and chemical content of digestive tract
  - **Proprioceptors** signal positional info of body parts

- **Nociceptors**
  - Pain receptors that are sensitive to tissue damage or distortion of tissue
May be

- Specialized ending of an afferent neuron
- Separate cell closely associated with peripheral ending of a neuron
Specialized ending of an afferent neuron

Mechanism of Action

- **Stimulus** alters receptor’s permeability which leads to graded receptor potential (causes nonselective opening of all small ion channels)
- Lead to **influx of sodium** ions. This produces receptor (generator) potentials.
- The magnitude of receptor potential represents intensity of stimulus.
- A receptor potential of sufficient magnitude (reach threshold) can produce an AP.
- This **AP propagated** along an afferent fiber to **CNS**.
Receptors

- Specialized ending of an afferent neuron

1. In sensory receptors that are specialized afferent neuron endings, stimulus opens stimulus-sensitive channels, permitting net $\text{Na}^+$ entry that produces receptor potential.

2. Local current flow between depolarized receptor ending and adjacent region opens voltage-gated $\text{Na}^+$ channels.

3. $\text{Na}^+$ entry initiates action potential in afferent fiber that self-propagates to CNS.
Receptors

- Separate cell closely associated with peripheral ending of a neuron

1. In sensory receptors that are separate cells, stimulus opens stimulus-sensitive channels, permitting net Na$^+$ entry that produces receptor potential.

2. This local depolarization opens voltage-gated Ca$^{2+}$ channels.

3. Ca$^{2+}$ entry triggers exocytosis of neurotransmitter.

4. Neurotransmitter binding opens chemically gated receptor-channels at afferent ending, permitting net Na$^+$ entry.

5. Resultant depolarization opens voltage-gated Na$^+$ channels in adjacent region.

6. Na$^+$ entry initiates action potential in afferent fiber that self-propagates to CNS.
• The larger the receptor potential is, the greater frequency of AP generated in afferent neuron

• **Stimulus intensity** is therefore distinguished both by
  • 1- Frequency of APs generated in afferent neuron & by
  • 2- Number of receptors & thus afferent fibers activated within the area.
Cutaneous Sensations
Cutaneous Sensations

- Include touch, pressure, heat, cold, pain
- Mediated by free & encapsulated nerve endings
- Free nerve endings mediate heat, cold, pain
Pain mediated by nociceptors
  ◦ Use glutamate & Substance P as Neurotransmitters (NT)
    • Substance P called "pain NT"

Heat elicits pain thru capsaicin receptors
  ◦ Capsaicin is "hot" chemical in chili peppers
a protective mechanism
- meant to bring a conscious awareness that tissue damage is occurring or is about to occur

According to The International Association for the Study of Pain (IASP):
- Definition: Pain is an unpleasant sensory & emotional experience associated with actual or potential tissue damage.
Significance:

1) **Warning signal against tissue damage.** Pain is one of the most prominent symptoms of tissue damage.

2) **Initiate protective reflexes** which causes the subject to get rid of the painful stimulus, or at least, to minimize tissue injury or damage.
Storage of painful experiences in memory helps us avoid potentially harmful events in future.

Stimulation of nociceptors elicits perception of pain.

Sensation of pain is accompanied by motivated behavioral responses (such as withdrawal or defense) & emotional reactions (such as crying or fear).

Subjective perception can be influenced by other past or present experiences.

- e.g., feeling more pain perception associated fear of dentist OR lowered pain perception in an injured athlete during a competitive event.
Pain

Classification

- Pain is classified into nociceptive, neuropathic & psychogenic
  - All can be either acute or chronic.
  - Pain is defined as chronic if persists more than 7 weeks.

- Nociceptive: pain caused by tissue damage (inflammation) which stimulate pain receptors (nociceptors).

- Neuropathic: pain due to injury of nerve pathway

- Psychogenic: difficult to differentiate whether secondary to or actual cause of pain.
  - E.g anxiety, depression (30% of depressives complain of pain on initial presentation).
Nociceptors

- Specialized sensory receptors that provide information about tissular damage
- Are “free nerve endings”, localized at skin, underlying tissue and viscera
- The least differentiated of sensory receptors
- Do not adapt to sustained or repetitive stimulation (because of their value to survival)
Free nerve endings which are morphologically similar but functionally specific.

They are classified according to their sensitivity into:

4 categories of nociceptors
- Mechanical nociceptors
- Thermal nociceptors
- Chemical nociceptors
- Polymodal nociceptors
4 categories of nociceptors

- **Mechanical nociceptors**
  - Respond to mechanical damage such as cutting, crushing, or pinching or even firm pressure on tissues.

- **Thermal nociceptors**
  - Respond to temperature extremes (above 45° C and below 10° C).

- **Chemical nociceptors**
  - Respond to noxious chemical stimuli.
    - Irritating chemicals released from injured tissues

- **Polymodal nociceptors**
  - Respond equally to all kinds of damaging stimuli (combination) (mechanical, thermal, & chemical noxious stimuli).
Pain

- **Stimulation of Pain Receptors:**
  - Noxious stimuli are **strong enough** →→ tissue damage →→ release of chemical agents from destructed cells into surrounding interstitial spaces which are called “pain producing compounds“ (PPCs) →→ stimulate pain receptors in the affected tissues.

- **Pain Threshold:**
  - Pain threshold is the lowest intensity of stimulus that can cause pain when the stimulus is applied for sufficient period of time.
The Pain Producing Compounds” (PPCs) may be classified into:

- **Direct stimulators**
  - When substances (as K\(^+\) ions, H\(^+\) ions, Serotonin, Histamine, Bradykinin) reach specific threshold, directly stimulate pain receptors →→ pain signals propagate

- **Sensitizers**
  - Substances which lower threshold for stimulation of pain receptors by direct stimulators →→ facilitate pain production. They include:
    - a) Substances released by injured tissues as: PGE2 & IL-1
    - b) Substances released by pain receptors as: substance P

- Substance P also stimulate mast cells to release histamine which is a direct stimulator.
Presence of PGs

- (lower nociceptors threshold for activation) greatly enhances receptor response to noxious stimuli (i.e. it hurts more when PGs present)

- **Tissue injury**, can lead to local release of PGs.

- Aspirin–like drugs **inhibit synthesis of PGs**, accounting at least in part for analgesic (pain–relieving) properties of these drugs.
Types of fibers:
3 types of fibers (A, B, & C).

A fibers
- Myelinated
- Subdivided into 4 main groups by conduction velocity,
  - A(alpha): largest & fastest velocity, acts as motor & sensory fibers
  - A(beta): next largest, acts as motor & sensory.
  - A(gama): next largest, acts as motor only.
  - A(delta): next largest, acts as sensory only.

B fibers
- Myelinated
- smaller than A fibers, only acts a motor &

C fibers
- Unmyelinated.
- Smallest, acts as motor & sensory.
Fast & Slow Afferent Pain Fibers

- Pain impulses originating at nociceptors
- Transmitted to CNS via one of 2 types of afferent fibers which correspond to the 2 different types of pain; a fast–acute (pricking) pain & a slow–chronic (burning or aching) pain.

- 1– Fast Afferent Pain Fiber
- 2– Slow Afferent Pain Fibers

depending on type of nociceptors
• **Types of Nociceptors:**
  - **Thermal or mechanical,**
    - associated with **fast, sharp** pricking pain
    - transmitted on **small diameter,** compare to other A fiber, myelinated A–Delta fibers; at rates of up to 30 m/sec
    - Release **excitatory amino–acid–glutamate** (Fast EPSP)
  - **Polymodal nociceptors,**
    - activated by **variety** of high intensity mechanical & thermal stimuli,
    - transmitted **slowly** on **small unmyelinated** C fibers, rate of 12 m/sec
    - release excitatory **amino acid–glutamate** & neuropeptides (Substance P = slow EPSP)
Fast Afferent Pain Fibers

- It is well **localized** sensation that is well matched to noxious stimuli
- **Start & stops abruptly** *(change without preparation or warning)* when stimuli is applied or removed
- Is strictly **associated to the skin** *(prick, sharp pain)*
- Transmitted by **A–Delta** fibers
Slow Afferent Pain Fibers

- Is a sore, tender, burning or aching sensation, is poorly localized & less specifically related to the stimuli
- The pain continues for hours or days after removal of the stimuli
- Is associated with cutaneous and deep tissues
- Is transmitted by C fibers
Do you recall the last time you cut or burned your finger. What you felt?

1 – **Pain** perceived initially as a brief, sharp, prickling sensation, easily localized;

- This is fast pain pathway originating from specific **mechanical or heat** nociceptors.
Do you recall the last time you cut or burned your finger. What you felt?

- This feeling followed by dull, aching, poorly localized sensation, persists for a longer time & more unpleasant;
  - This is slow pain pathway.
Do you recall the last time you cut or burned your finger. What you felt? continue

This **slow pain pathway activated** by chemicals, especially bradykinin that stimulate polymodal nociceptors, normally inactive that is **activated** by enzymes released into ECF from damaged tissue.

The persistence of these chemicals **explain** long–lasting, aching pain that continues after removal of mechanical or thermal stimulus that caused tissue damage.
Do you recall the last time you cut or burned your finger. What you felt?

Peripheral receptors of afferent C fibers, that conduct slow pain, activated by capsaicin, (ingredient in hot chili peppers)

Capsaicin also binds with thermal receptors that activated by heat—hence burning sensation when eating hot peppers.
## Characteristics of Pain

<table>
<thead>
<tr>
<th>Fast Pain</th>
<th>Slow Pain</th>
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<tbody>
<tr>
<td>Occurs on stimulation of mechanical and thermal nociceptors</td>
<td>Occurs on stimulation of polymodal nociceptors</td>
</tr>
<tr>
<td>Carried by small, myelinated A-delta fibers</td>
<td>Carried by small, unmyelinated C fibers</td>
</tr>
<tr>
<td>Produces sharp, prickling sensation</td>
<td>Produces dull, aching, burning sensation</td>
</tr>
<tr>
<td>Easily localized</td>
<td>Poorly localized</td>
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<tr>
<td>Occurs first</td>
<td>Occurs second; persists for longer time; more unpleasant</td>
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Higher-Level Processing of Pain Input

- Primary afferent pain fibers synapse with 2nd-order excitatory interneurons in dorsal horn of spinal cord by releasing neurotransmitters that influence these next neurons in line.

- 2 best known pain neurotransmitters
  - Substance P
  - Glutamate
Higher-Level Processing of Pain Input

**Substance P**
Activates ascending pathways that transmit nociceptive signals to higher levels for further processing

- Ascending pain pathways have different destinations in:
  - 1 – Cortex
  - 2 – Thalamus,
  - 3 – Reticular formation &
1- Cortical somatosensory processing areas localize pain.
2- Other cortical areas participate in conscious components of pain experience, such as deliberation about incident.

3- Pain can still be perceived in absence of cortex, presumably at level of thalamus.

4- Reticular formation increases level of alertness associated with noxious encounter.

5- Interconnections from thalamus & reticular formation to hypothalamus & limbic system elicit behavioral & emotional responses to painful experience. Limbic system perceive unpleasant aspects of pain.
Higher-Level Processing of Pain Input

- 2 best known pain neurotransmitters
  - **Glutamate**
    - Major *excitatory* neurotransmitter
    - Acts on 2 different plasma membrane receptors
      - AMPA & NMDA
  - Binds to **AMPA receptors** on dorsal horn excitatory interneurons, *permit net entry of Na^+*, *result in generation of APs*, which *transmit* pain message to higher centers
    - (AMPA– R) = \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Higher-Level Processing of Pain Input

- 2 best known pain neurotransmitters
  - **Glutamate**
    - Acts on 2 different plasma membrane receptors
      - AMPA & NMDA
    - Binds to NMDA (N-methyl-D-aspartate) receptors on dorsal horn excitatory interneurons, leads to Ca\(^{2+}\) entry, that make dorsal horn cells more excitable than usual. (not involved in transmission of pain messages.

  - This **hyperexcitability** resulted in make an injured area more sensitive to subsequent exposure to painful or non-painful stimuli, such as a light touch. e.g how sensitive your sunburned skin is, even to clothing
Brain has Built in Analgesic System

- Suppresses transmission in pain pathways as they enter spinal cord
  - i.e Relief of pain (analgesia)

This may be done by:
- Physiological method (endogenous analgesic system).
- Pharmacological.
- Surgical by many methods as cutting of the peripheral nerves.
Brain has Built in Analgesic System

Also called the *endogenous analgesic system*

- Consists of special *areas in brain & spinal cord*, which *when activated can greatly reduce or even completely abolish pain sensation*.
- Three brain–stem regions part of this descending analgesic pathway:
  - 1 – *Periaqueductal gray matter (PAG)* (a narrow canal that connects third & fourth ventricular cavities),
  - 2 – *Specific nuclei in medulla &*
  - 3 – *Reticular formation.*

Nucleus raphe magnus NRM in medulla
Brain has Built in Analgesic System

- **Opiate**: a drug (as morphine, heroin, & codeine) containing or derived from opium & tending to induce sleep & to alleviate pain
  - **Endogenous**:
    - Naturally-occurring, physiologic peptides which are similar in structure & function to opium (=morphine).
    - They can bind to the morphine receptors → produce long-lasting analgesic effect.

- **The opioid peptides consist of 3 major groups**:
  - Enkephalins
  - Endorphins &
  - Dynorphins.
Opioid Receptors

- 3 different types of opiate receptors have been characterized:
  - delta (δ),
  - kappa (k), &
  - muta (μ)

- Binding of opioid peptides with opiate receptors at specific sites in nervous system functions to stop synaptic transmission of pain impulses through central pathways of pain.

- Can be blocked by naloxone, which is a morphine antagonist
**Brain has Built in Analgesic System**

- **Enkephalin** binds to opiate receptors in:
  - Central terminal of 1st order neuron → opening of Cl\(^{-}\) channel → Cl\(^{-}\) influx → hyperpolarization → block of Ca\(^{+2}\) influx → inhibit release of chemical transmitter from 1st order neuron
Brain has Built in Analgesic System

- **Enkephalin** binds to opiate receptors in:
  - Postsynaptic 2nd order neuron in pain pathway → opening of $K^+$ channels → hyperpolarization → inhibit their response to the pain chemical transmitter.
1- Stimulates particular neurons whose cell bodies lie in medulla & reticular formation & that terminate on inhibitory interneurons in dorsal horn of spinal cord.

2- Release enkephalin, binds with opiate receptors at afferent pain-fiber terminal.

3- Thus, suppresses release of substance P, thereby blocking transmission of pain signal.
Brain has Built in Analgesic System

- Factors known to modulate pain include exercise, stress, & acupuncture.

- **Acupuncture**
  - Acupuncture has been practiced in China for more than 4000 years as a method for pain relief.

- **Mechanism:**
  - **Needles** in appropriate **body regions** are thought to excite certain sensory neural pathways which **feed into the brain stem centers** (such as the PAG; Periaqueductal gray matter) involved in the pain control system, with release of endogenous opioid peptides.
Thank You