Pain Physiology

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Pain Physiology

- Objectives:
  - Explain how pain is transmitted through the body
    - Peripheral nervous system
    - Central nervous system
  - Match pharmacological approaches to pain processes

Pain Process

- **Definition of pain process:**

  -The neural mechanisms by which pain is perceived involves a process that has four major steps:

  - **Transduction**
  - **Transmission**
  - **Perception**
  - **Modulation**

Transduction

- **Definition:**

A conversion of a

mechanical

thermal

chemical

stimulus to a neuronal **action potential**

Facilitating Transduction

- **Biochemical mediators: "Chemical Soup"**

Prostaglandins
Bradykinins
Serotonin
Histamines
Cytokines
Leukotrienes
Substance P
Norepinephrine

Tissue Injury

- Tissue injury causes release of inflammatory pain mediators resulting in peripheral sensitization

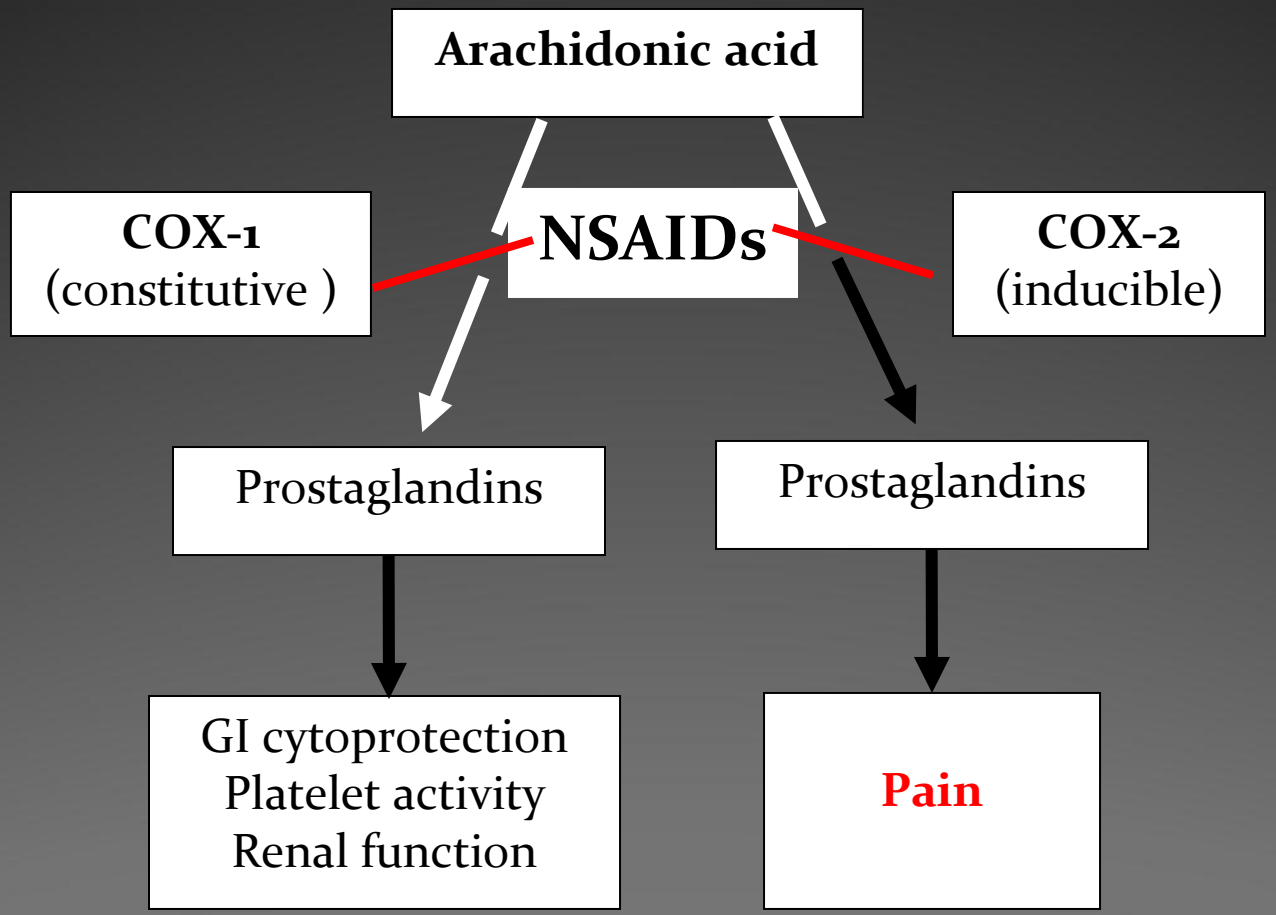
- Sensitization results in more frequent action potential along nociceptive neurons.
  - -Threshold for activation of nociceptor neurons is decreased at the synapse level
  - -Hyper-excitable transmission occurs

Central sensitization results from prolonged pain

Peripheral Excitatory Mediators (Pain)

Substance	Receptor	Mechanism
Substance P (SP)	NK_1	↑ neuronal excitability, edema
Prostaglandin (PG)	?	Sensitize nociceptors, inflammation, edema
Bradykinin	B_2 (normal) B_1 (inflammation)	Sensitize nociceptors ↑ PG production
Histamine	H_1	C-fiber activation, edema, vasodilatation
Serotonin	5-HT_3	C-fiber activation, release SP
Norepinephrine (NE)	α_1	Sensitize nociceptors Activate nociceptors

NSAIDs Mechanism of Action



COX = Cyclooxygenase; NSAID = Nonsteroidal anti-inflammatory drug; GI = Gastrointestinal.

Adapted from Solomon GD. In Tollison CD, Satterthwaite JR, Tollison JW, eds. Practical Pain Management, 3rd edition. Philadelphia, PA:Lippincott Williams & Wilkins, 2002: 243–252.

Cyclooxygenase inhibitors

- COX found in all tissues, encourages synthesis of prostaglandins
- COX 1: present in all tissues, protects gastric mucosa, supports renal function, promotes platelet aggregation (good)
- COX 2: at site of tissue injury & brain Mediates inflammation, pain, fever response (bad)

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Inhibit both COX 1 & 2
- Initial analgesic effect - 1 hour
- Maximum anti-inflammatory effect - 2 wks
- Uses - rheumatoid arthritis, OA, pain, fever, bursitis, tendonitis
- ADRs - GI upset, ulceration, bleeding, renal failure, anaphylaxis

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

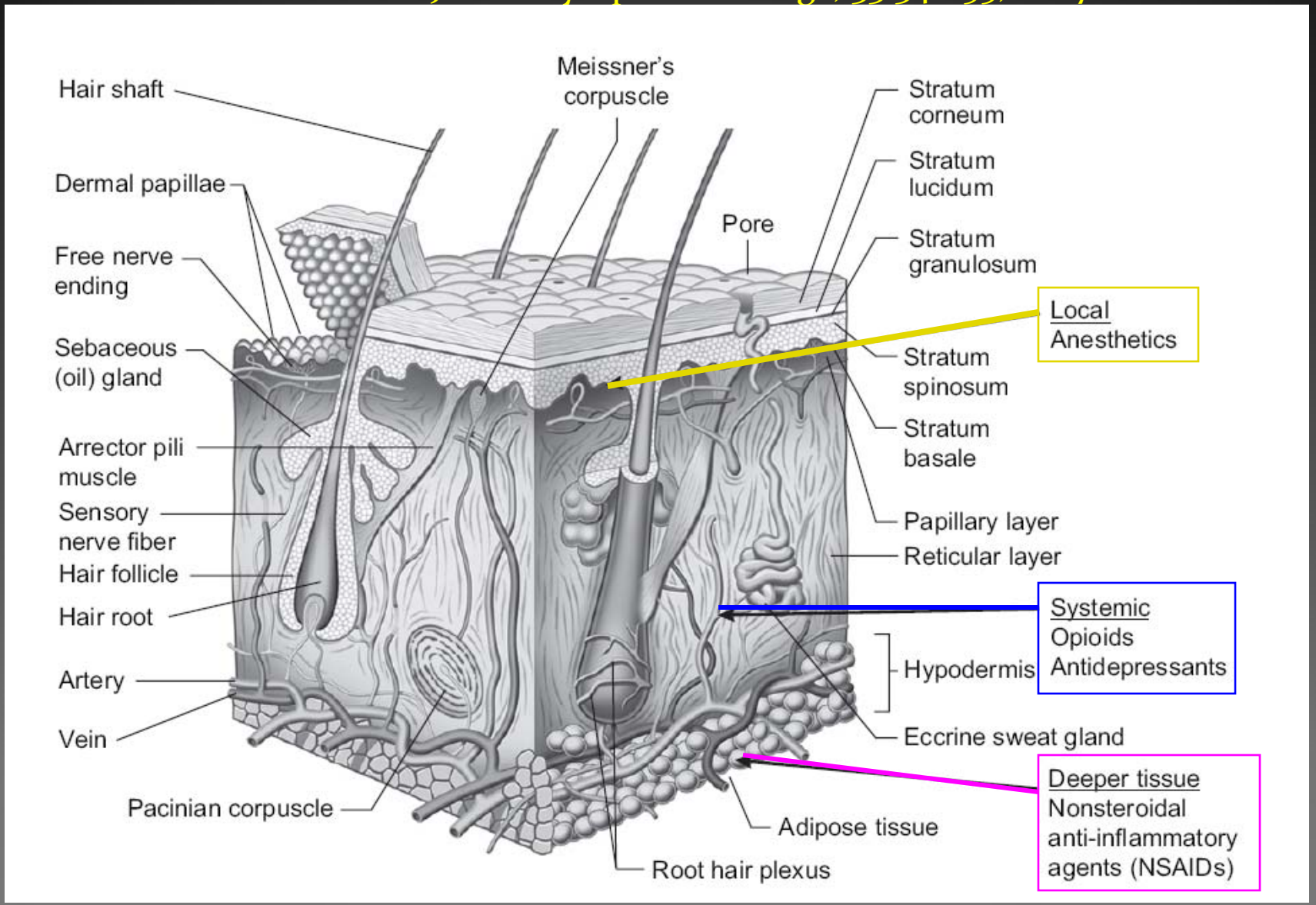
- Prostaglandin-mediated sensitization in cutaneous terminals of primary afferent nociceptors may be blocked by aspirin, diclofenac and indomethacin
  - Diclofenac (Flector) 1.5% transdermal bid - FDA approved for treatment of acute pain associated with sprain and strains
  - Diclofenac (Solaraze) 3% solution bid – FDA approved for actinic keratosis

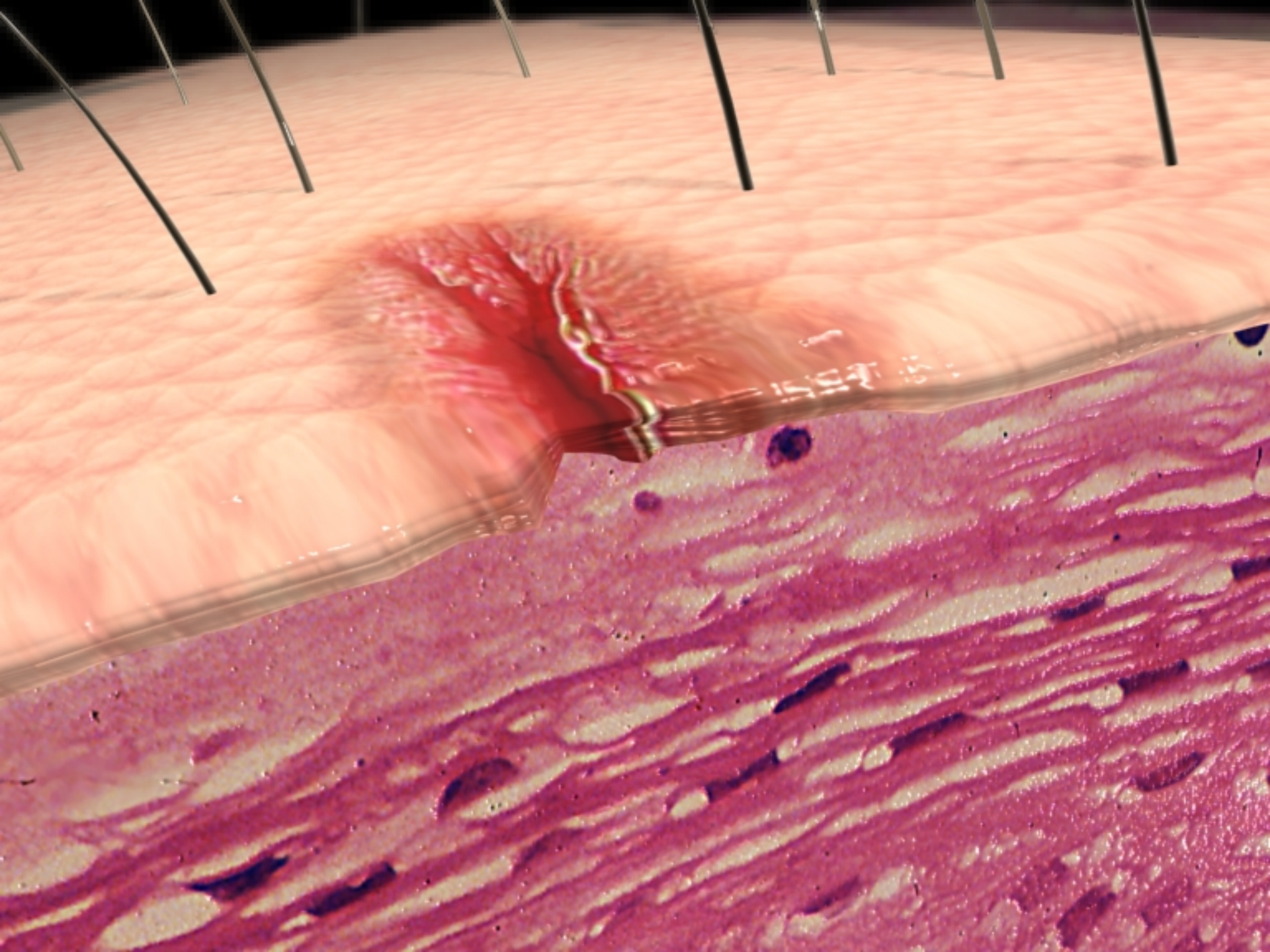
- Ketoprofen 10% gel TID off label use
  - Some efficacy noted in literature
  - Compounded by pharmacy

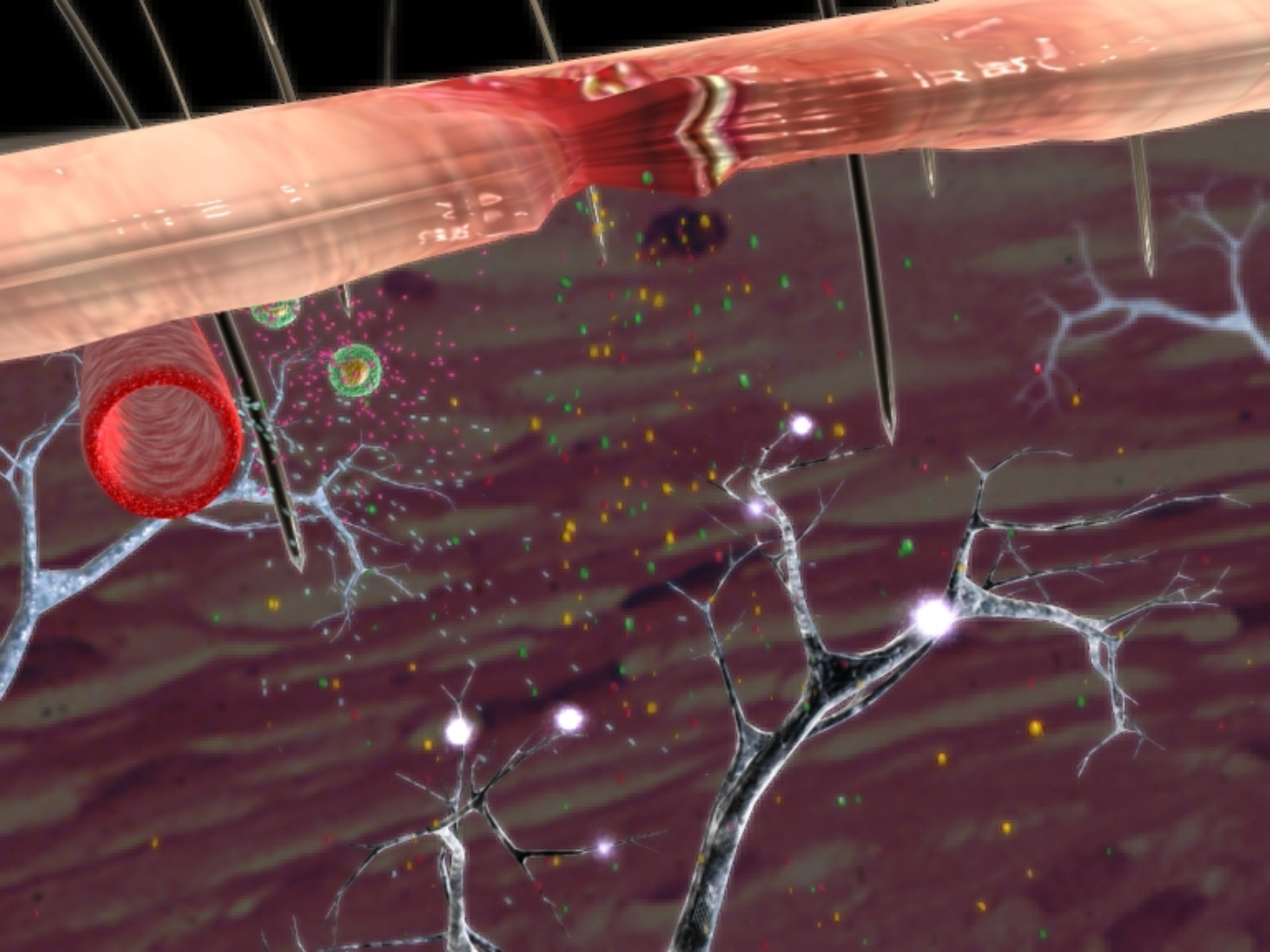
Reference: J. Pain Symptom Manage, 33:356-64, 2007

Skin Anatomy

Reference: J. Pain Symptom Manage, 33:342-55, 2007



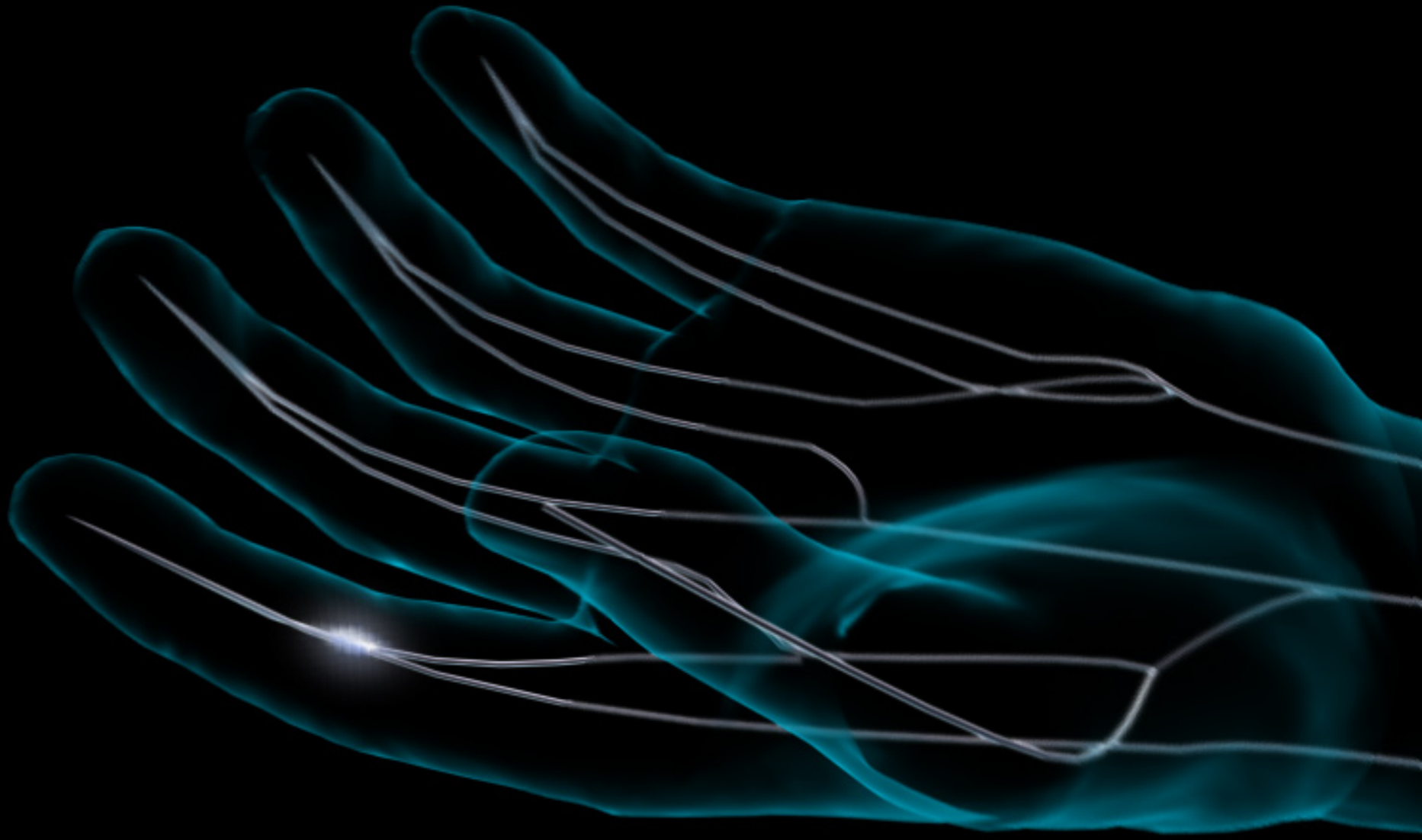




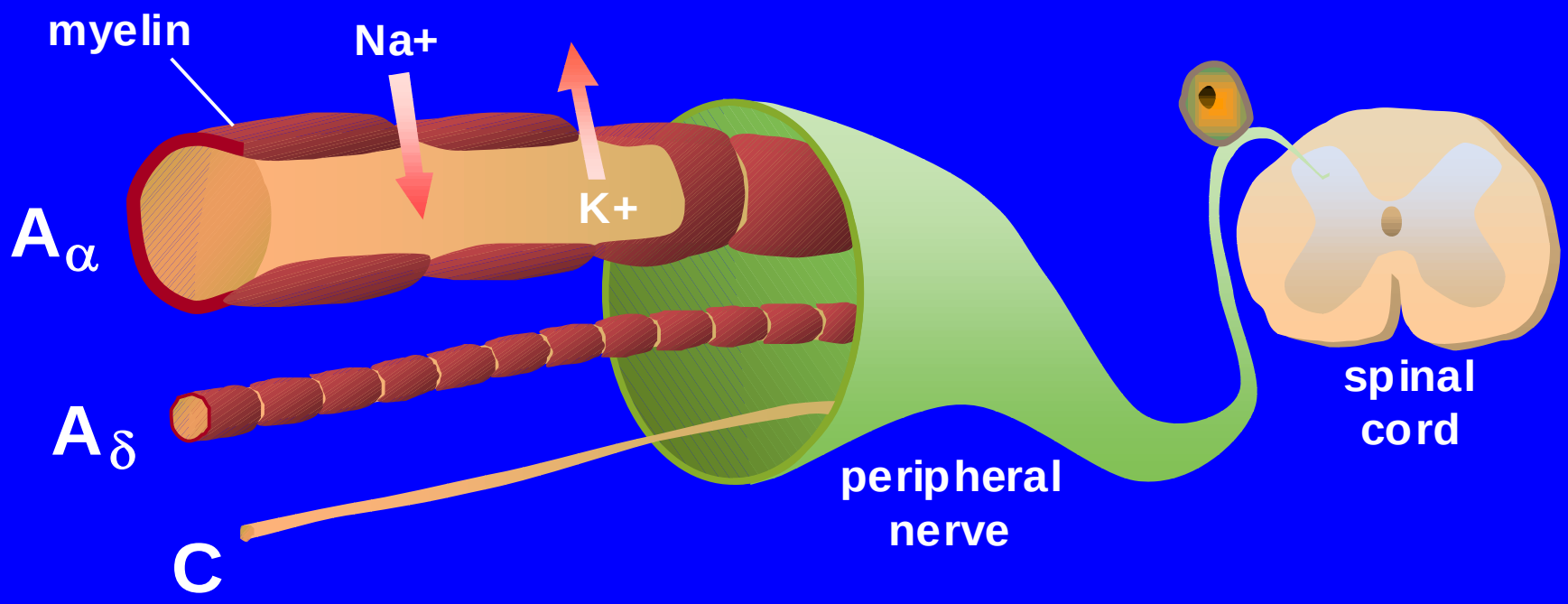
Transmission of pain

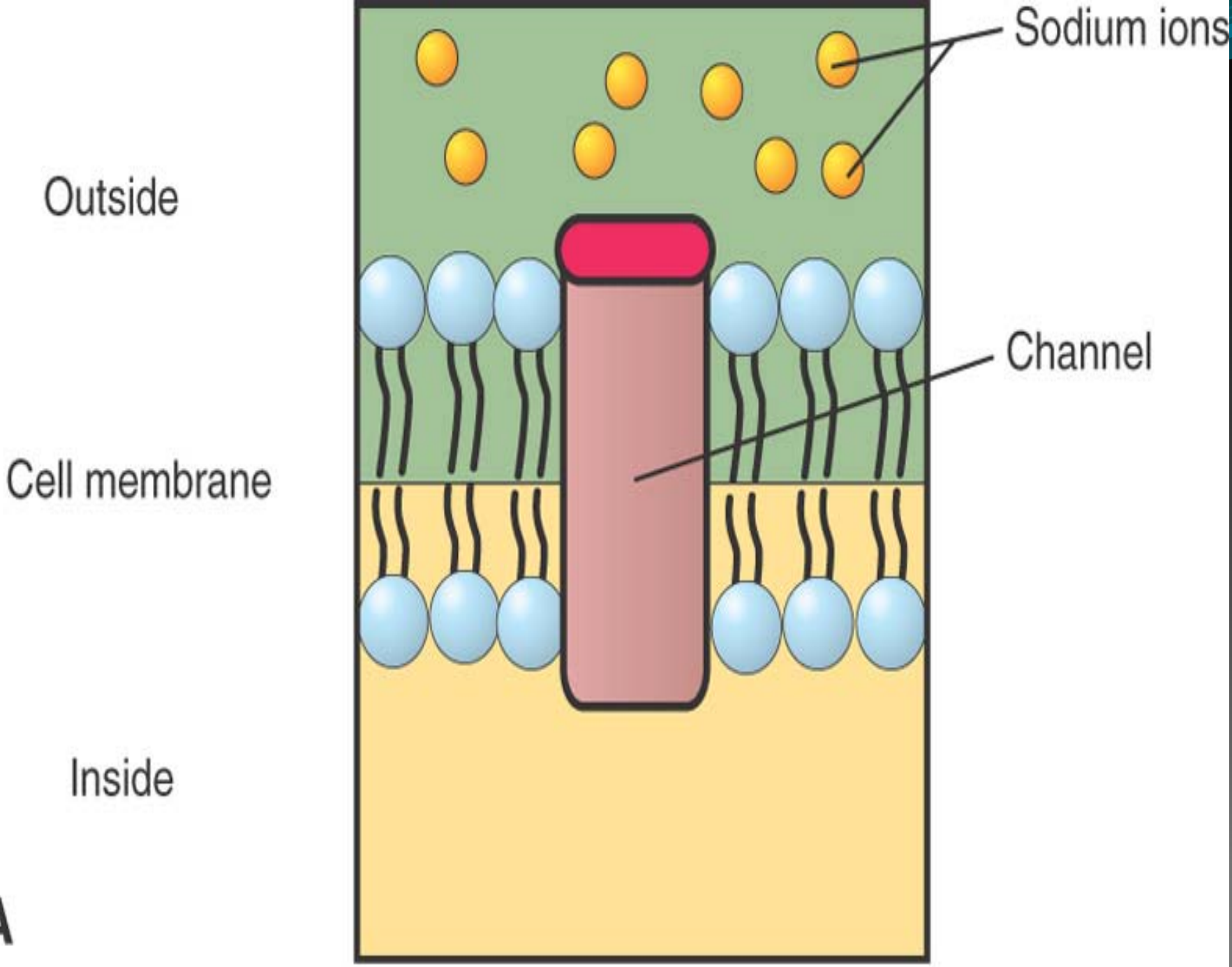
- **Defined as:**

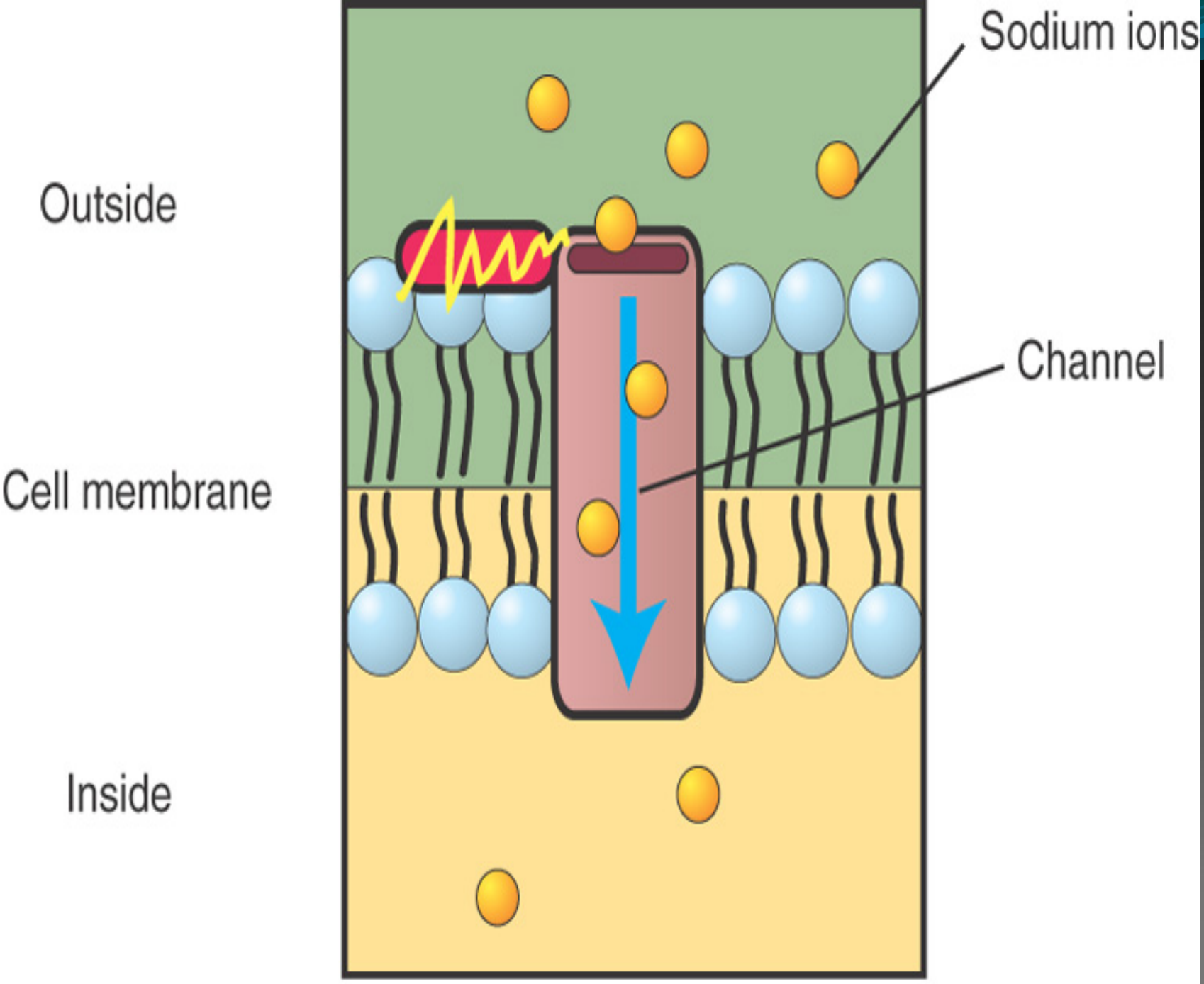
Projection of pain into the Central Nervous System

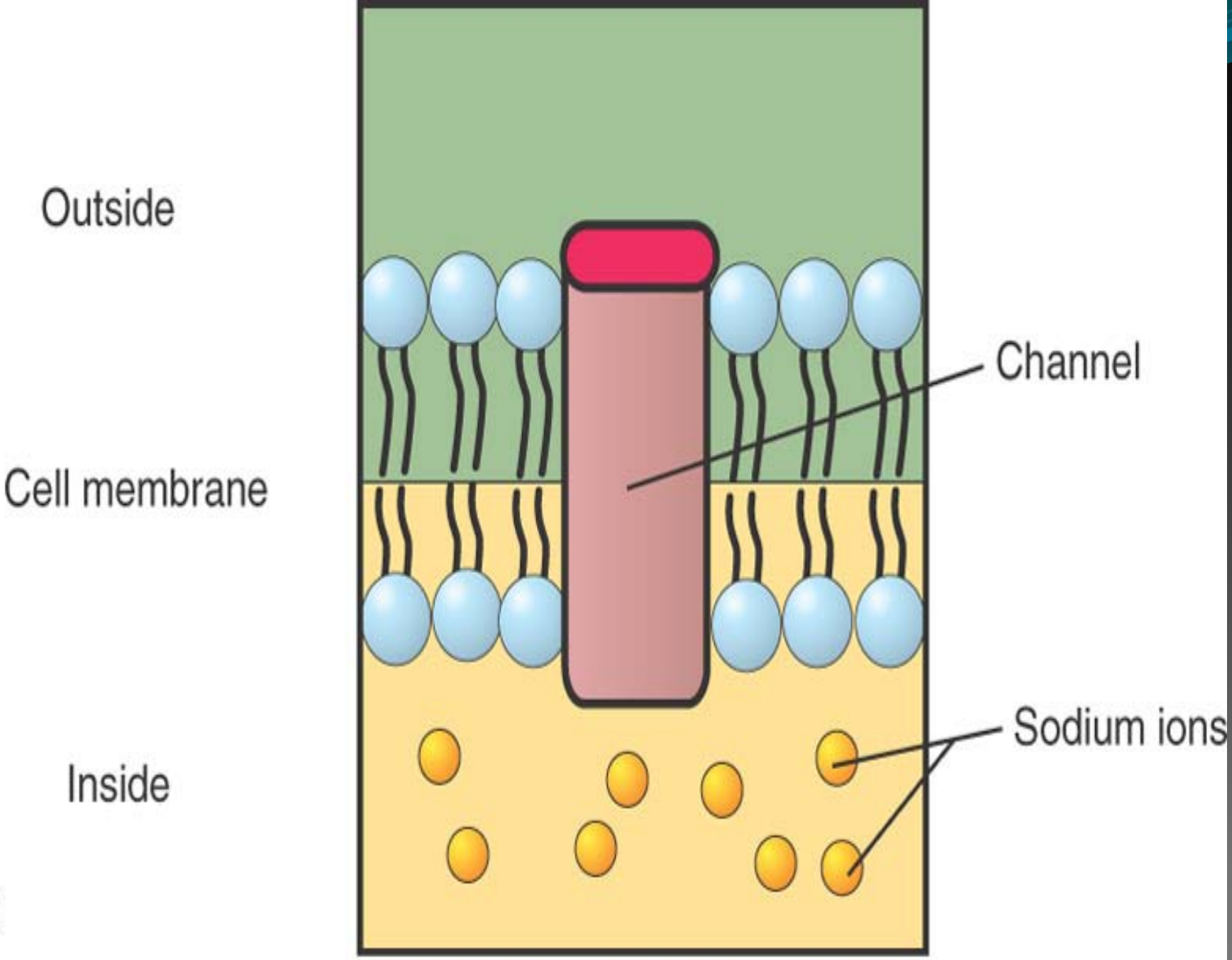


Peripheral Nerves: Transmission of Action Potential



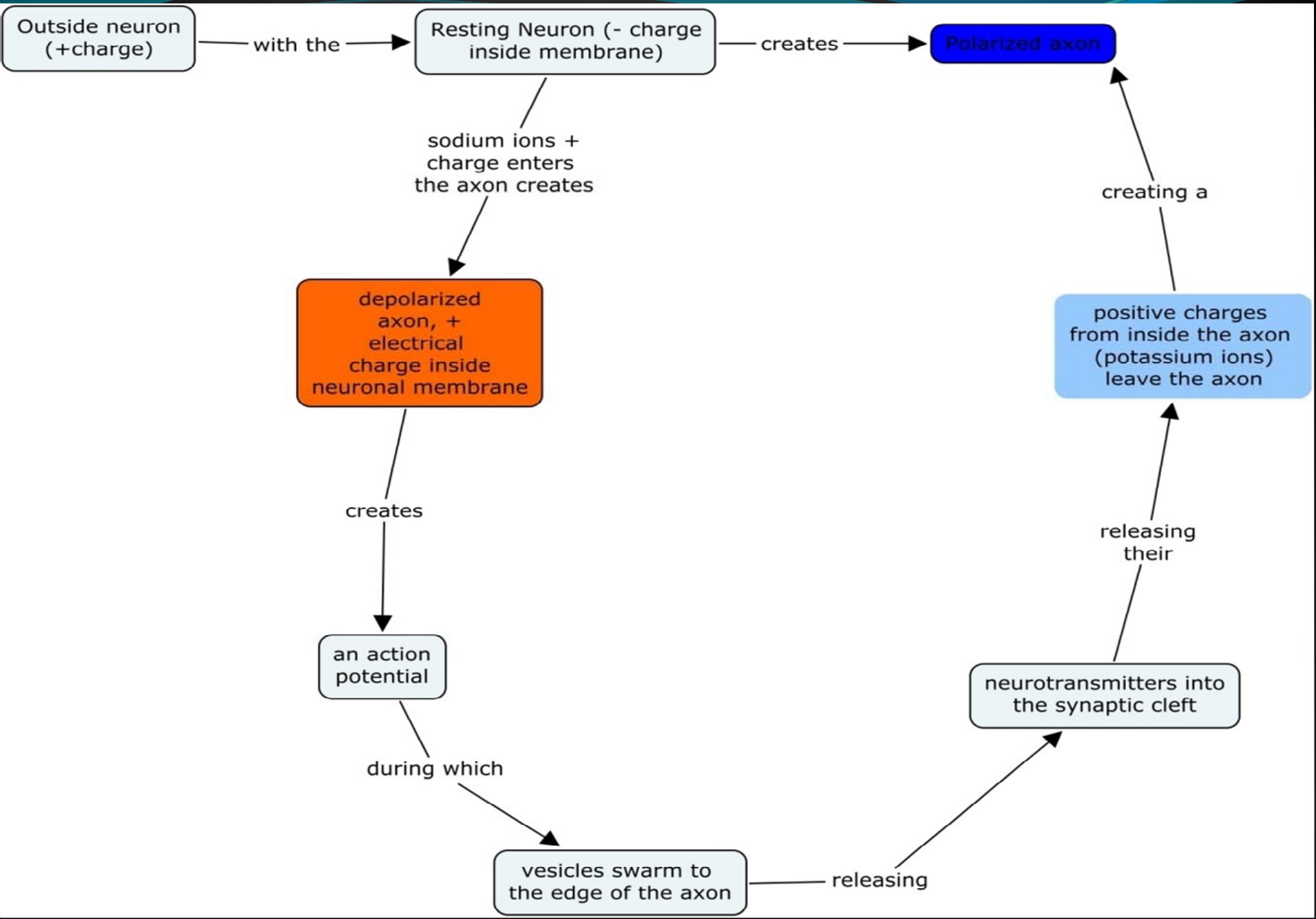






C

Figure 4. Ion exchange along the neuronal membrane creating action potential.



Transmission

- A synapse contains three elements:

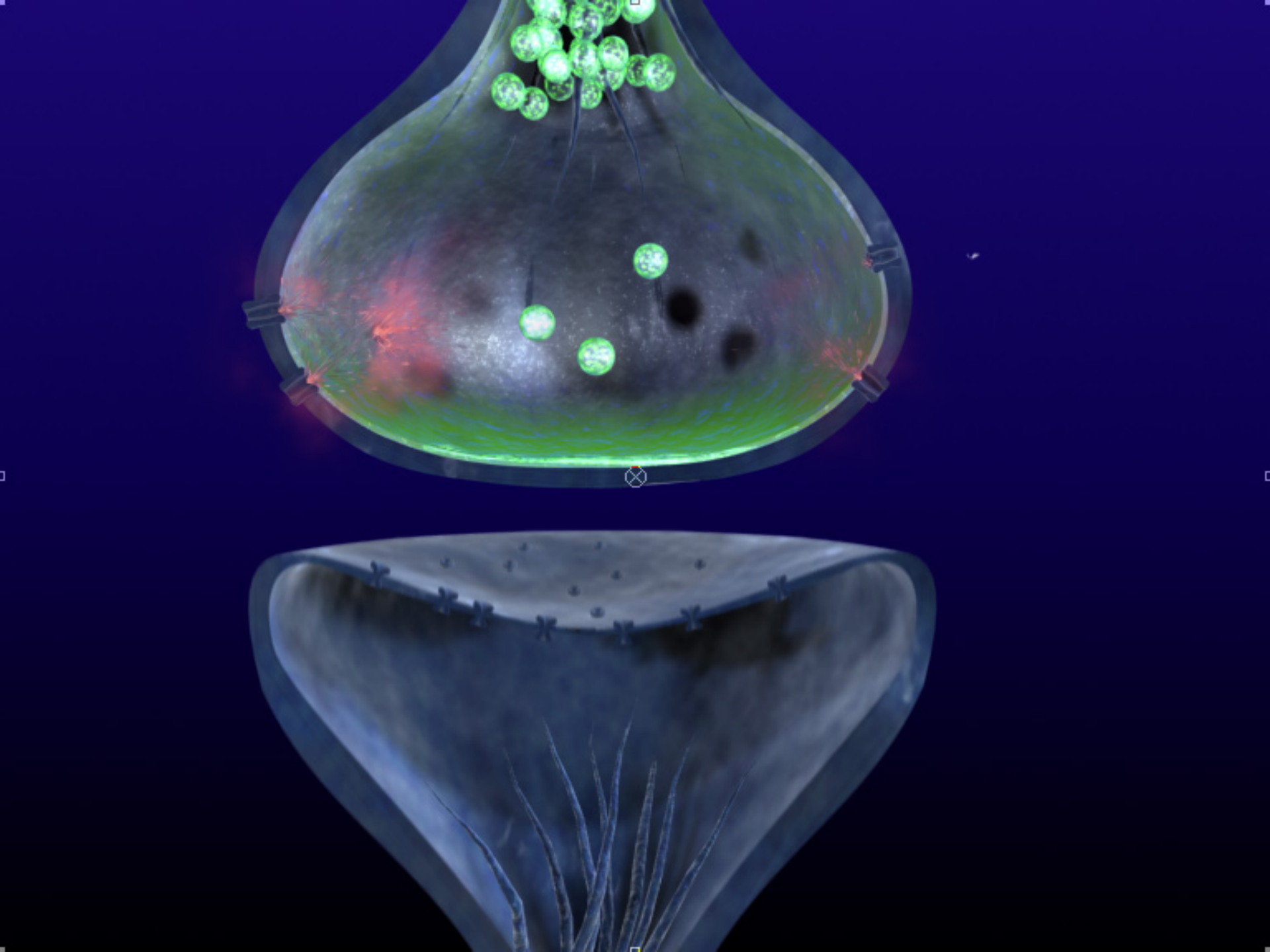
  the presynaptic terminal

  the synaptic cleft

  the receptive membrane

Transmission

- The presynaptic terminal is the axon terminal of the presynaptic neuron
- Here that the presynaptic neuron releases neurotransmitters which are found in vesicles

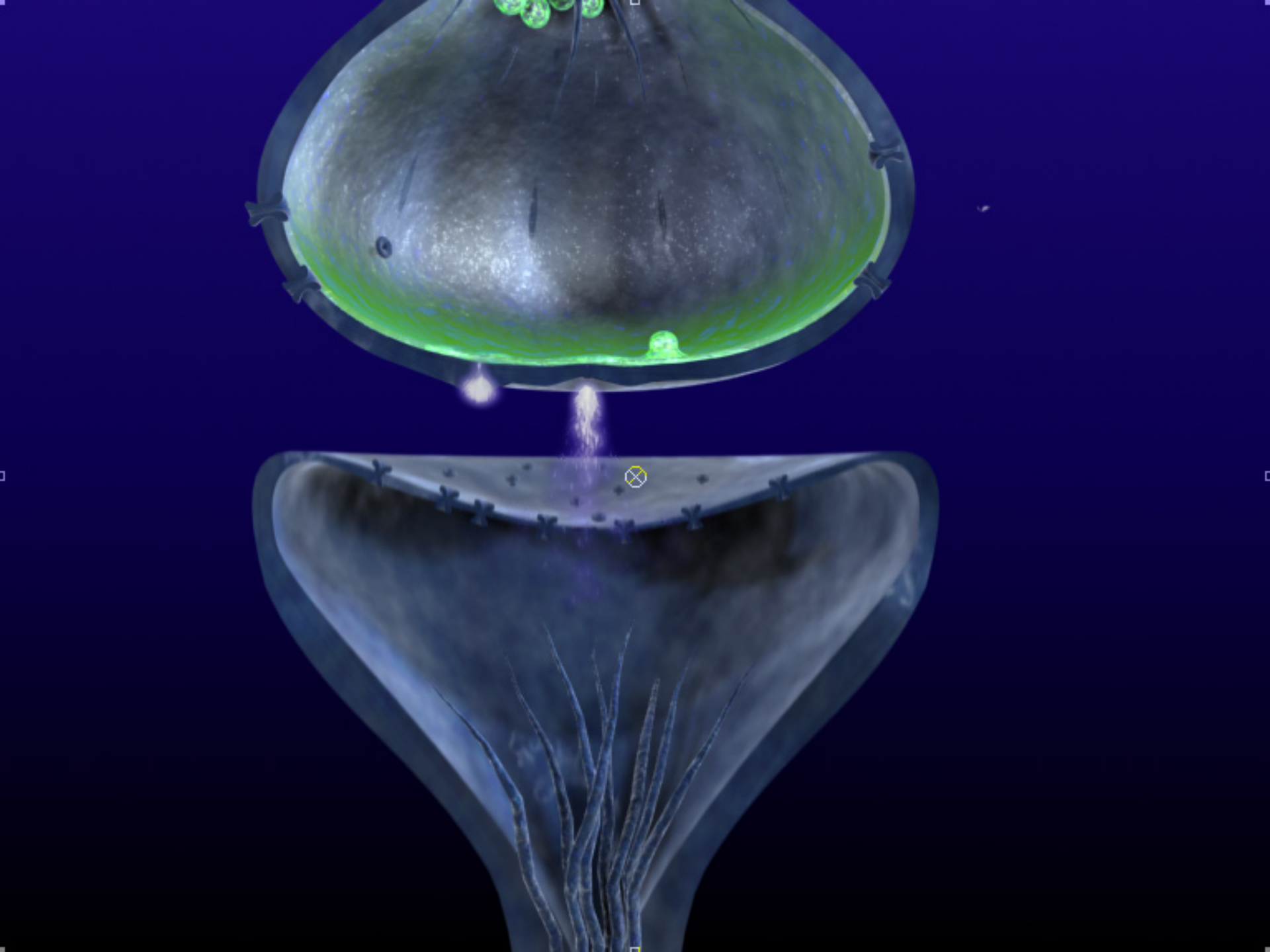


Capsaicin

- Hot peppers
- May deplete & prevent re-accumulation of substance P in primary afferent neurons responsible for transmitting painful impulses from peripheral sites to the CNS.
- Absorption, distribution, metabolism & excretion, half life – unknown
- May produce transient burning with application, usually disappears in 2-4 days, but may persist for several weeks.

Transmission

- The synaptic cleft is the narrow intercellular space between neurons.
- Neurotransmitters cross the synaptic cleft and bind to specific receptors on the postsynaptic neurons
- This will excite or inhibit the postsynaptic neurons.

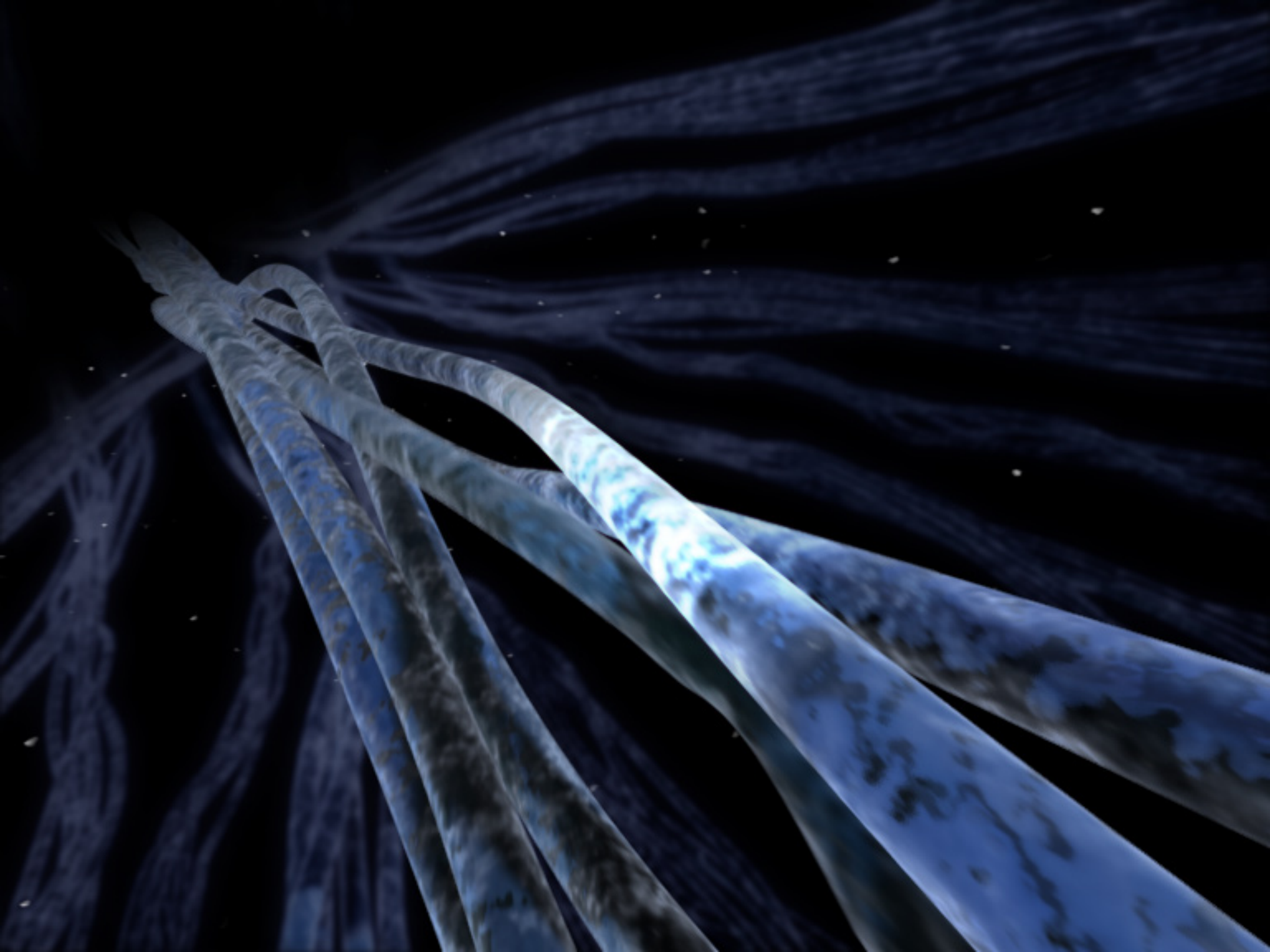


Transmission

- What stimulates the presynaptic neuron to release the transmitters?
- Neurotransmitters are amino acids (glutamate and GABA), acetylcholine, norepinephrine and serotonin.
- Larger molecules such as enkephalin and substance P serve as neurotransmitters.

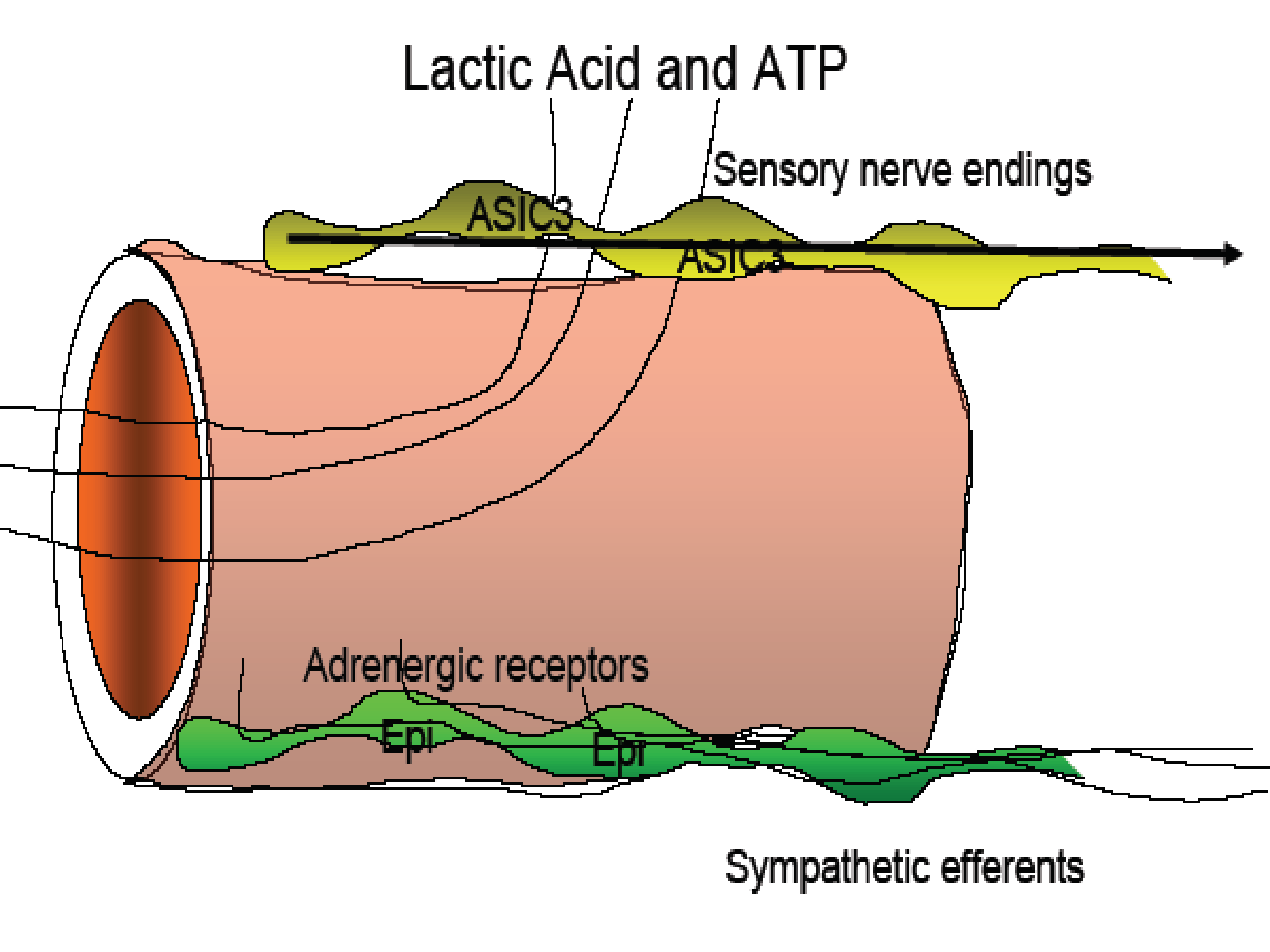
Neurotransmitter activity

- Sodium ions flow into the postsynaptic neuron and excites or depolarizes the neuron
- Chloride ions flow into a neuron and inhibits or hyperpolarizes the neuron
- Glutamate excites neurons
- GABA inhibits neurons



Muscle Pain

- Correlated with Lactic acid levels
- Lactic acid levels in the blood vessels of the muscle influence neuronal noxious stimuli
- What might that tell us about intervening with muscle pain?


Lactic Acid and ATP
Sensory nerve endings
ASIC3
ASIC3
Adrenergic receptors
Epi
Epi
Sympathetic efferents

Peripheral Nervous System

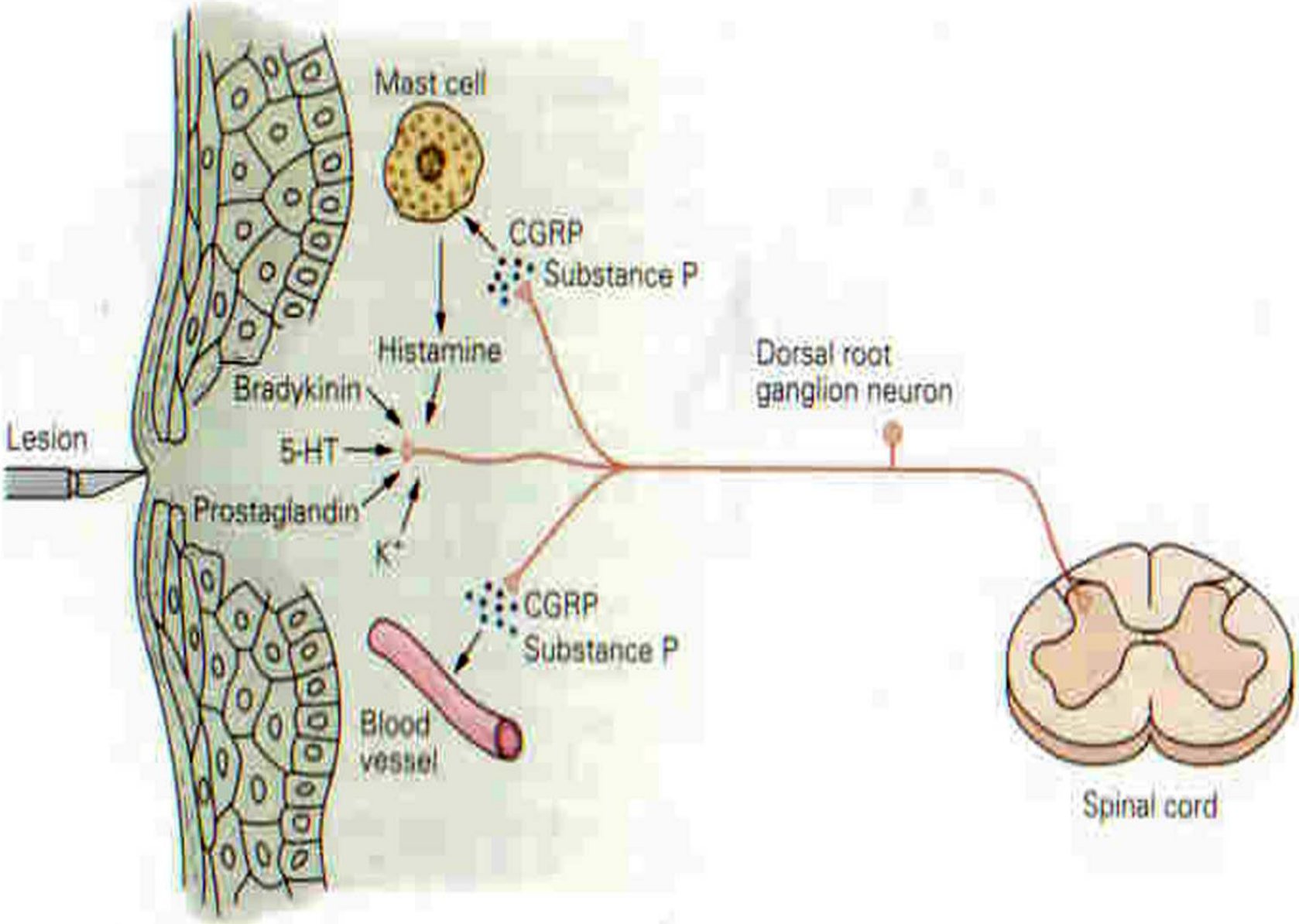
- **Two divisions**
  - **Autonomic division**
    - **Regulates body function**
      - **sympathetic**
      - **parasympathetic**

Autonomic Divisions

- Sympathetic system
  - Release of norepinephrine
    - Increase BP
    - Increase pulse
    - Increase respirations
    - Vasoconstriction
    - Decrease GI motility

Autonomic Divisions

- Parasympathetic system
  - Acetylcholine
    - Decrease BP
    - Decrease pulse
    - Decrease respirations
    - Vasodilatation
    - Increase GI motility

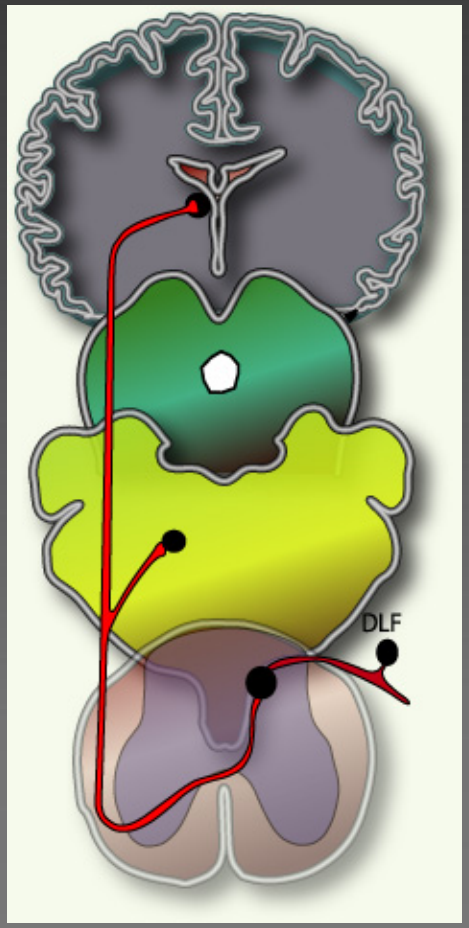

Mast cell
CGRP
Substance P
Histamine
Bradykinin
5-HT
Prostaglandin
K+
Lesion
Dorsal root
ganglion neuron
CGRP
Substance P
Blood
vessel
Spinal cord

Ascending Facilitation of Pain

- Nociceptive impulses proceed into the dorsal horn of the spinal cord (mainly in laminae I through laminae V)
- Secondary neurons in the laminae become excited and send the impulse to brain via chemical transmission
- “Pain” is perceived after nociceptive information reaches the cerebral cortex

Ascending Pain Pathways

Ascending fibers



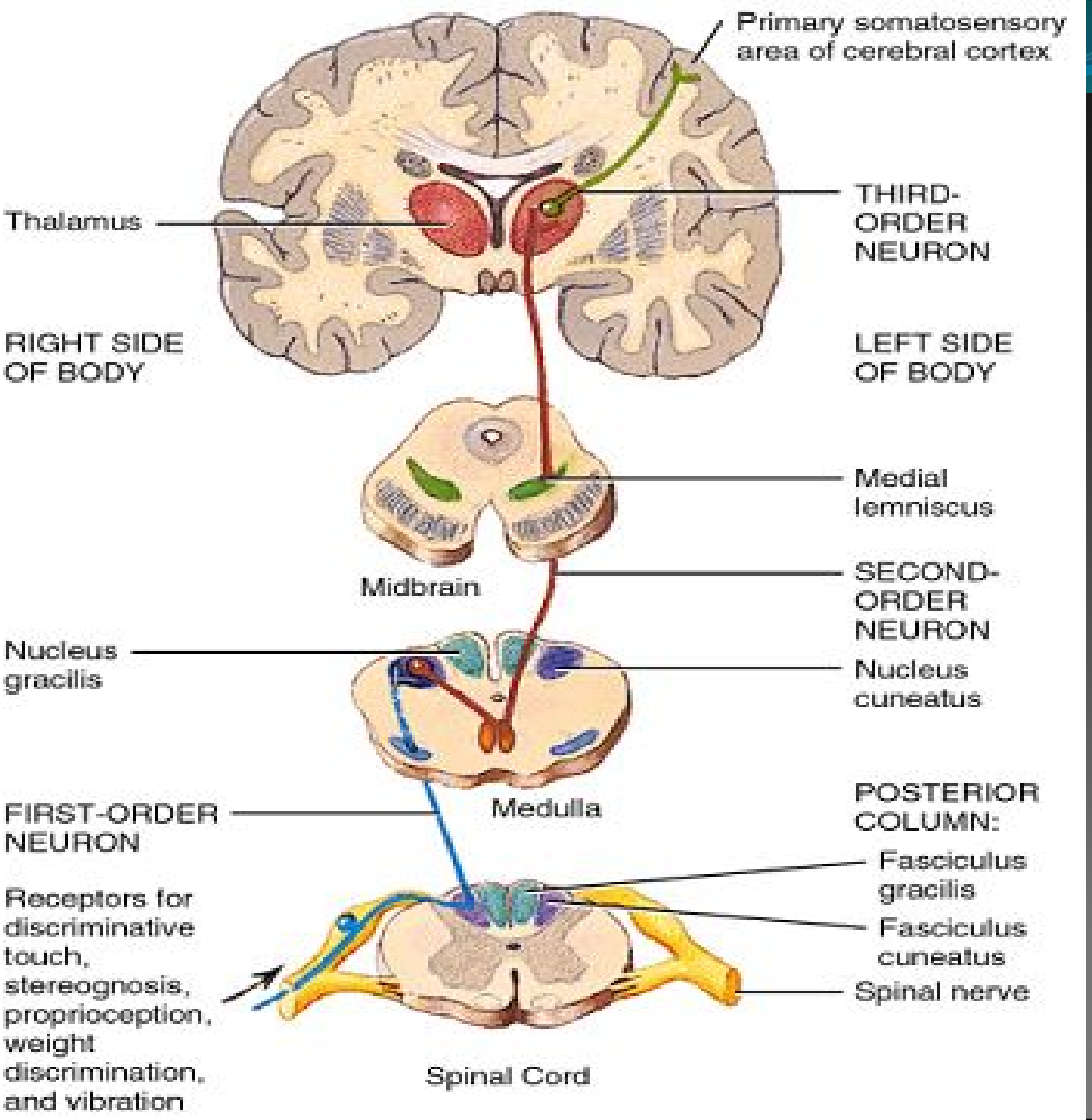
Spinothalmic Tract

Intraspinal Noxious Stimuli

- Received by receptor neurons through the anterolateral system of the spinal cord.
- Dorsal root ganglion (to Lissauer's tract)
  - Small diameter fibers terminate at laminae I, II, and V.
  - Substantia gelatinosa (laminae II) - opioid receptors

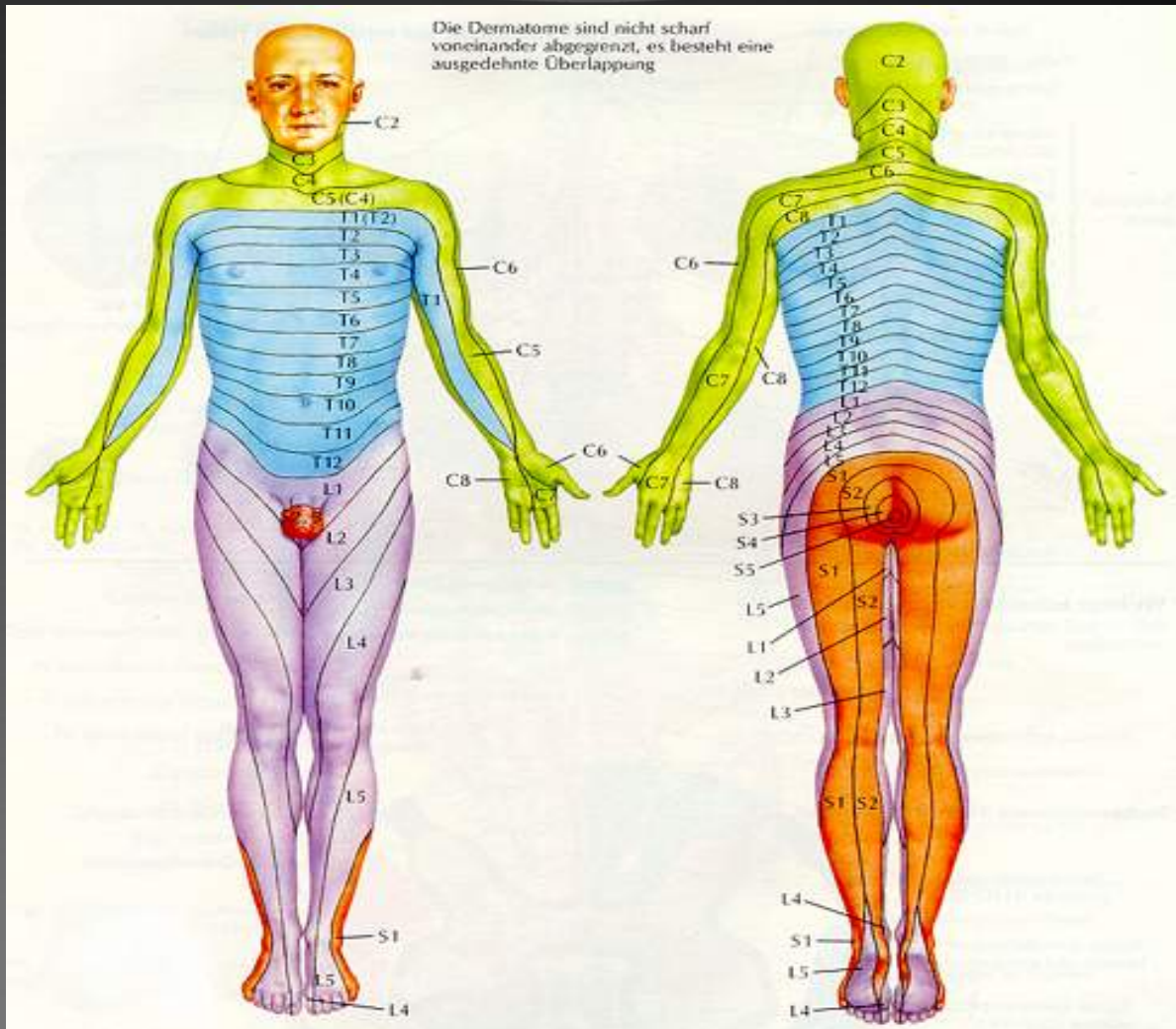
Intraspinal Noxious Stimuli

- The laminae in the dorsal horn
  - Projection to the brain stem
  - Projection to the Thalamus


Primary somatosensory area of cerebral cortex
Thalamus
THIRD-ORDER NEURON
RIGHT SIDE OF BODY
LEFT SIDE OF BODY
Medial lemniscus
Midbrain
SECOND-ORDER NEURON
Nucleus gracilis
Nucleus cuneatus
Medulla
FIRST-ORDER NEURON
POSTERIOR COLUMN:
Fasciculus gracilis
Fasciculus cuneatus
Spinal nerve
Receptors for discriminative touch, stereognosis, proprioception, weight discrimination, and vibration
Spinal Cord

Sensory Stimuli from Spinal Neurons

At each vertebral body level, nerve roots exit from the spinal cord bilaterally. Specific skin surface areas are innervated by a single spinal nerve or group of spinal nerves. These skin area are called dermatomes



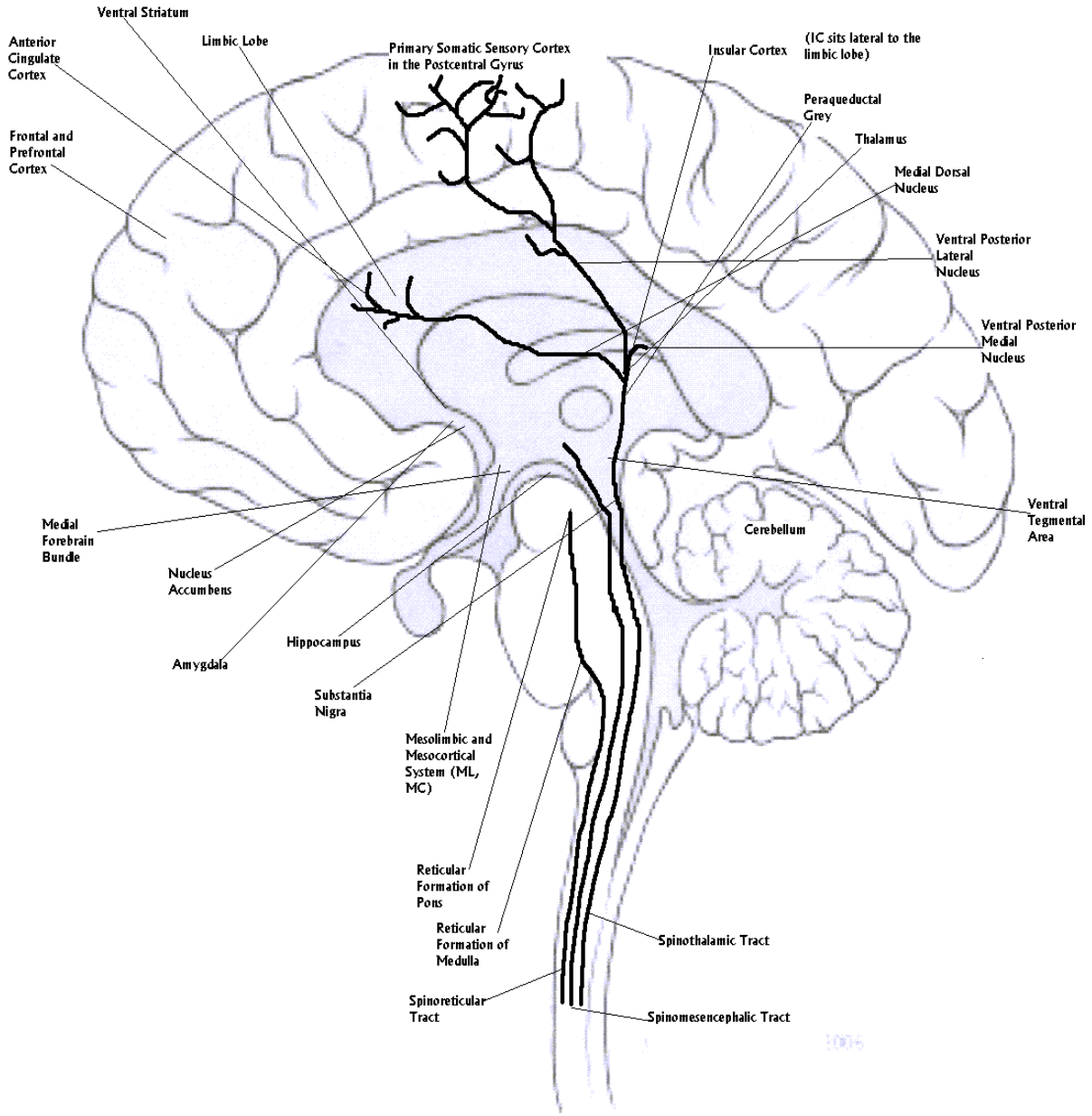
Perception

- Review:
  - Impulses go through the postsynaptic junction
  - Cross the dorsal horn
  - To the spinothalamic tract

Perception

- Axons in the spinothalamic tract synapse in three nuclei of the thalamus
  - Ventral posterior lateral nucleus
  - Ventromedial posterior nucleus
  - Medial dorsal nucleus

- Each play role in pain perception


Ventral Striatum
Anterior Cingulate Cortex
Limbic Lobe
Primary Somatic Sensory Cortex in the Postcentral Gyrus
Insular Cortex
(IC sits lateral to the limbic lobe)
Peraqueductal Grey
Thalamus
Frontal and Prefrontal Cortex
Medial Dorsal Nucleus
Ventral Posterior Lateral Nucleus
Ventral Posterior Medial Nucleus
Ventral Tegmental Area
Cerebellum
Medial Forebrain Bundle
Nucleus Accumbens
Amygdala
Hippocampus
Substantia Nigra
Mesolimbic and Mesocortical System (ML, MC)
Reticular Formation of Pons
Reticular Formation of Medulla
Spinothalamic Tract
Spinoreticular Tract
Spinomesencephalic Tract

Ventral Posterior Lateral Nucleus

- These neurons project to the primary somatic sensory cortex

Ventromedial Posterior Nucleus

- These neurons project to the insular cortex
  - important in behavioral and autonomic responses to pain
  - important to emotions and memories of pain

- Mediates pain perception
  - Projects into the limbic system (emotional center)

Medial Dorsal Nucleus

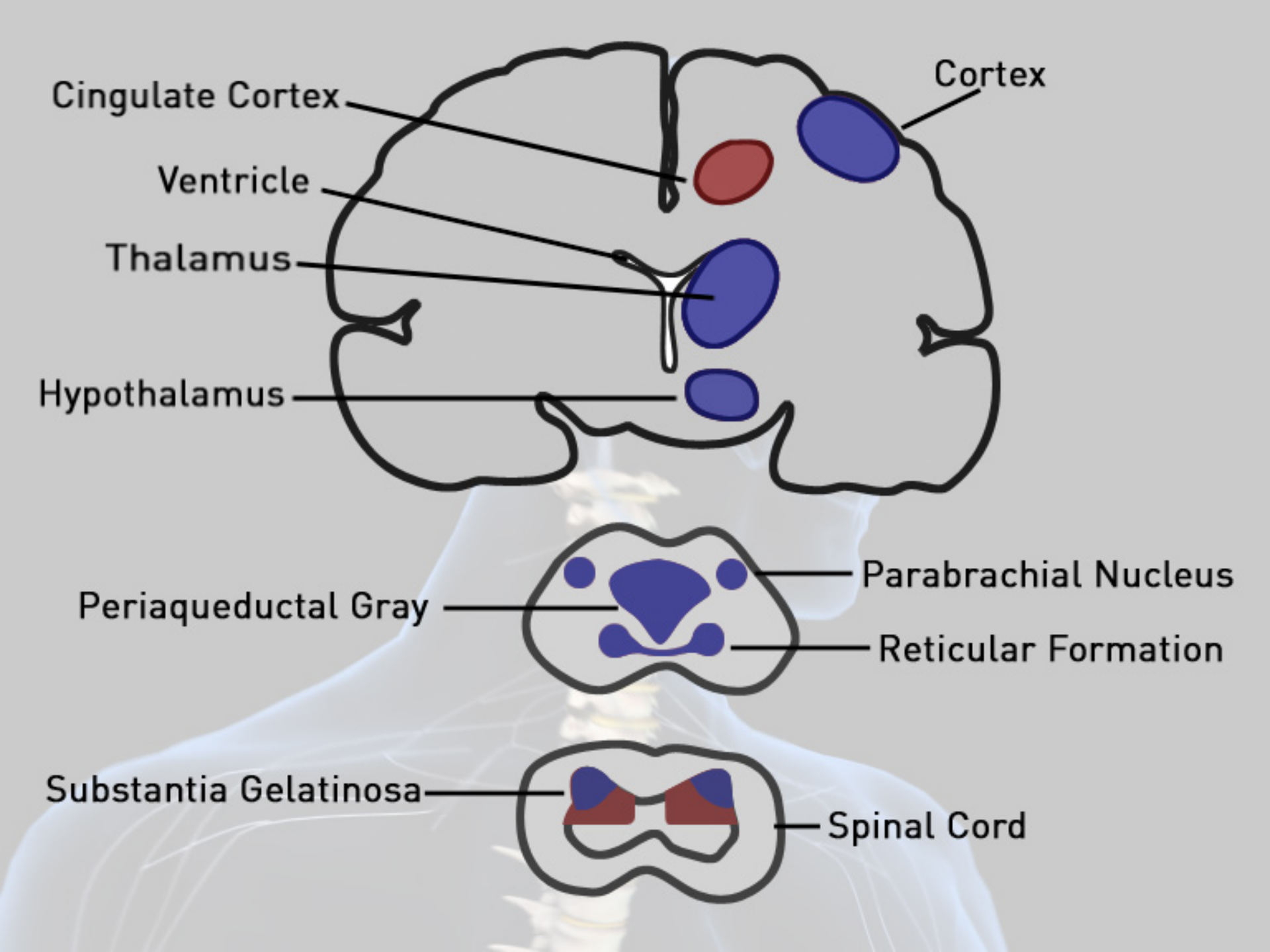
- Neurons project to the cingulate cortex
- Mediates the emotional responses to pain

Descending Pathway

- Mediates voluntary and involuntary motor control
- Regulates somatic sensory processing
- Regulates the autonomic nervous system

Descending Pathway

- Anatomic path
  - From cerebral cortex
  - Brain stem
  - To dorsal horn
- Pain inhibition
  - Enkephalin excites inhibitory interneurons in the dorsal horn


Cingulate Cortex
Cortex
Ventricle
Thalamus
Hypothalamus
Parabrachial Nucleus
Periaqueductal Gray
Reticular Formation
Substantia Gelatinosa
Spinal Cord

Descending Serotonergic Pathway

- Serotonin
- Norepinephrine
- Enkephalin

Anandamine

- Binds to the cannabinoid (CB_1) receptor
- CB_1 receptors are located the hippocampus, cerebellum, and the limbic and mesocortical systems
- Endocannabinoids and CB_1 receptor distributions are not always equal in their locations.

Endocannibinoids

- Found in most brain function
- Equal balance between endocannibinoids and their receptors occur (Fride, 2005)
- Role in brain plasticity leading to
  - long term effects on movement and coordination
  - habit formation
  - reward and addiction

Cannabinoid & Opioid Synergism

- Combination cannabinoid-opioid therapy maybe effective for neuropathic pain
- The two systems may work synergistically in converging brain pathways.
- The cannabinoids have a distinct mechanism of action, targeting ubiquitous cannabinoid (CB) receptors in the central nervous system and periphery
- Opioid analgesics less effective for neuropathic pain

Figure 5. Concept map of endocannabinoids.