
University of New England
College of Osteopathic Medicine

Nociception and Pain: Peripheral and Spinal Cord Levels

The University of New England College of Osteopathic Medicine

Pain

Pain

- Acute Pain – Physiological Pain – Eudynia
  - "Ouch" pain
  - Sensitization
  - Remission

Pain

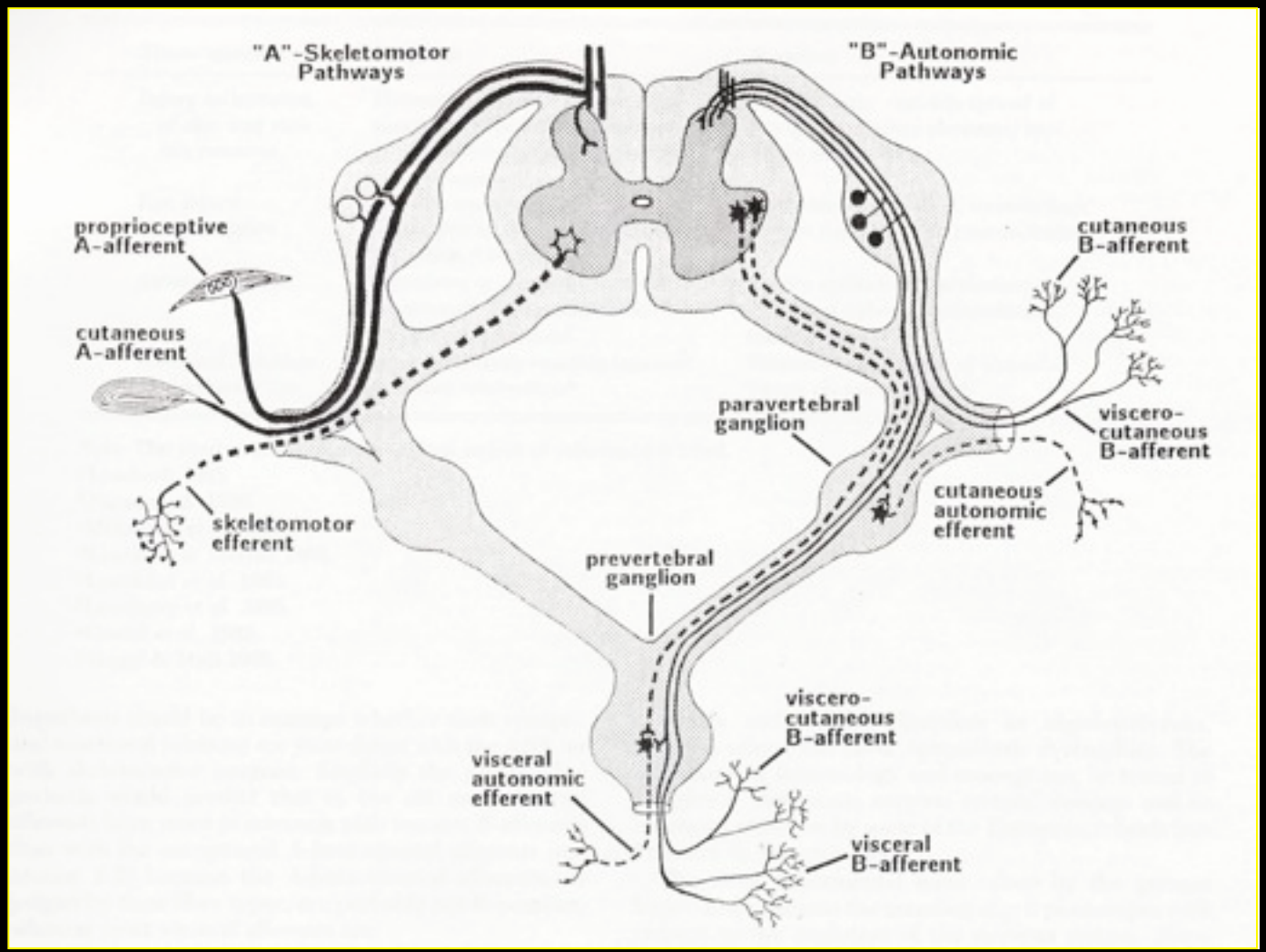
- Acute Pain – Physiological Pain – Eudynia
  - "Ouch" pain
  - Sensitization
  - Remission

- Chronic Pain – Clinical Pain – Maldynia
  - Bad tissue / Bad neurons or Both
  - Structural change in the nervous system
  - Functional change in the nervous system

Pain

- Acute Pain – Physiological Pain – Eudynia
  - "Ouch" pain
  - Sensitization
  - Remission
- Chronic Pain – Clinical Pain – Maldynia
  - Bad tissue / Bad neurons or Both
  - Structural change in the nervous system
  - Functional change in the nervous system

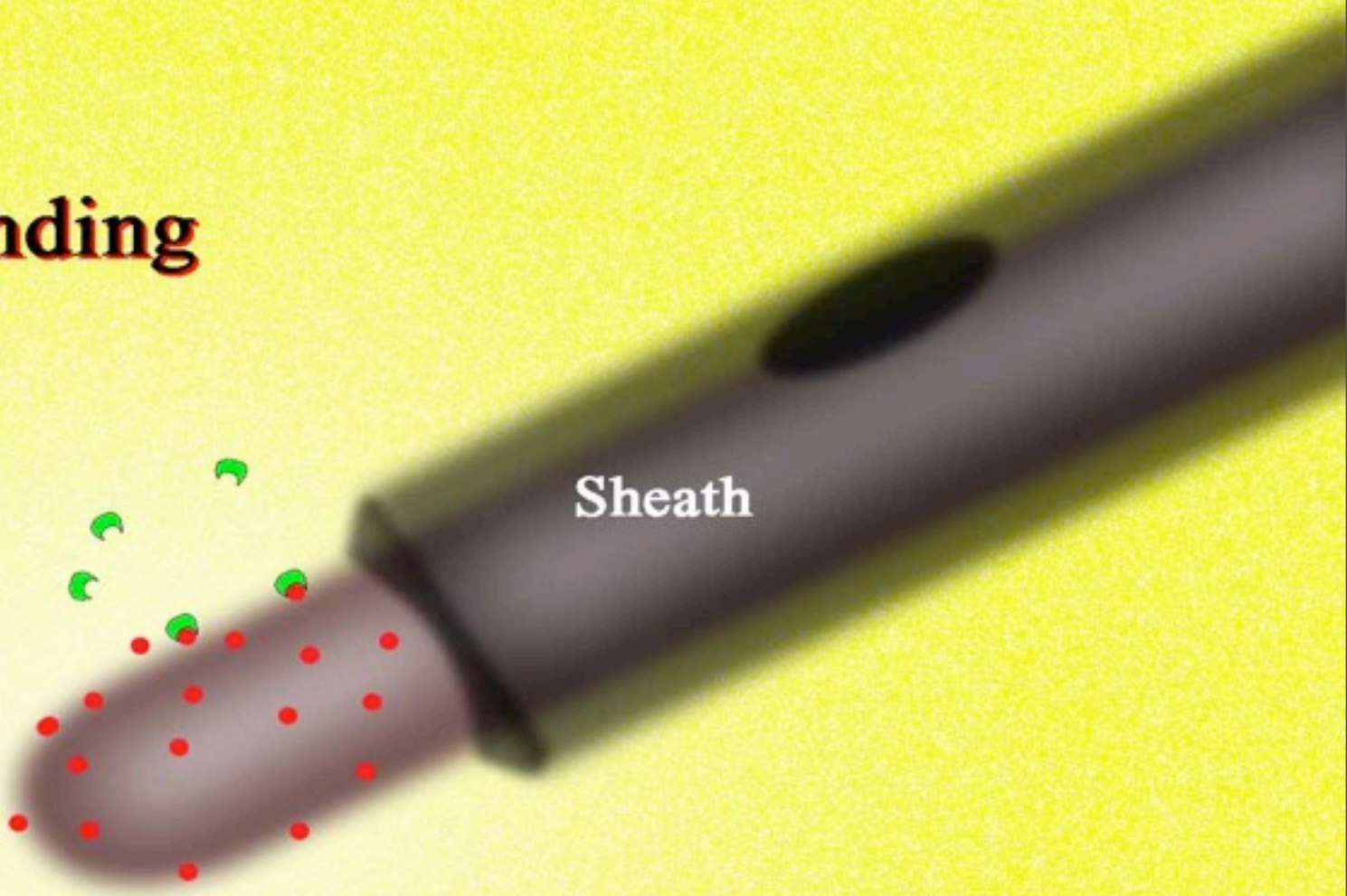
Primary Afferent Fibers



Prechtl and Powley, Behav. Brain Sci. 13:289-331, 1990

Small Fiber Location

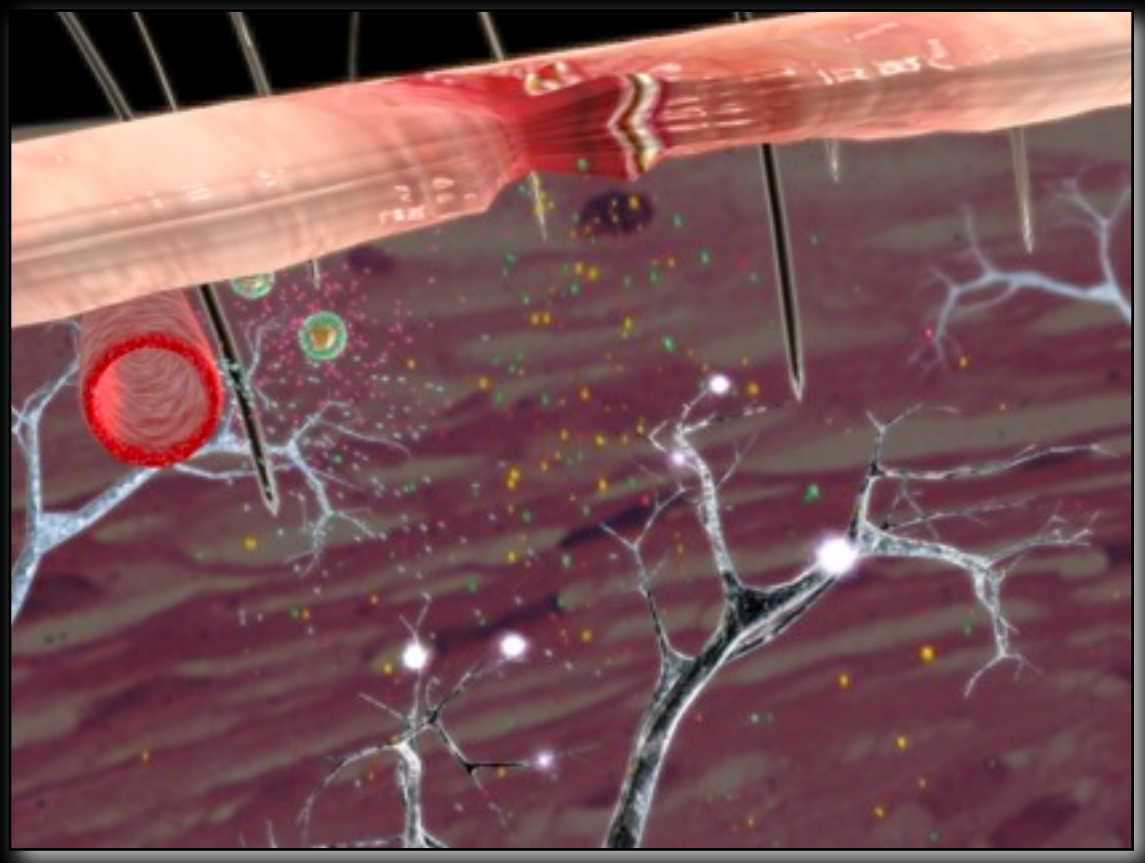
PAN Ending



Chemoreceptors

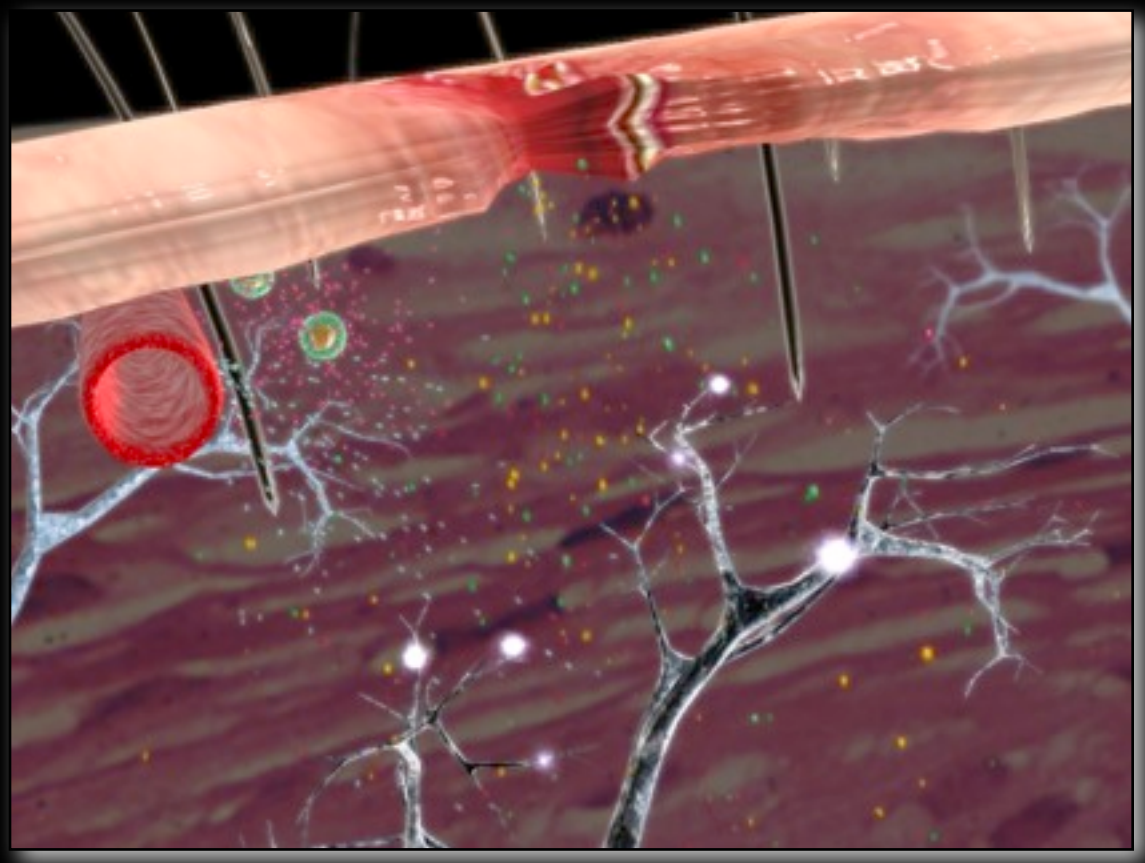
Factors Activating PANS

- Bradykinins
- Histamines
- Prostaglandins
- Serotonin
- H^+ and K^+
- Cytokines
- ATP
- Neuropeptides



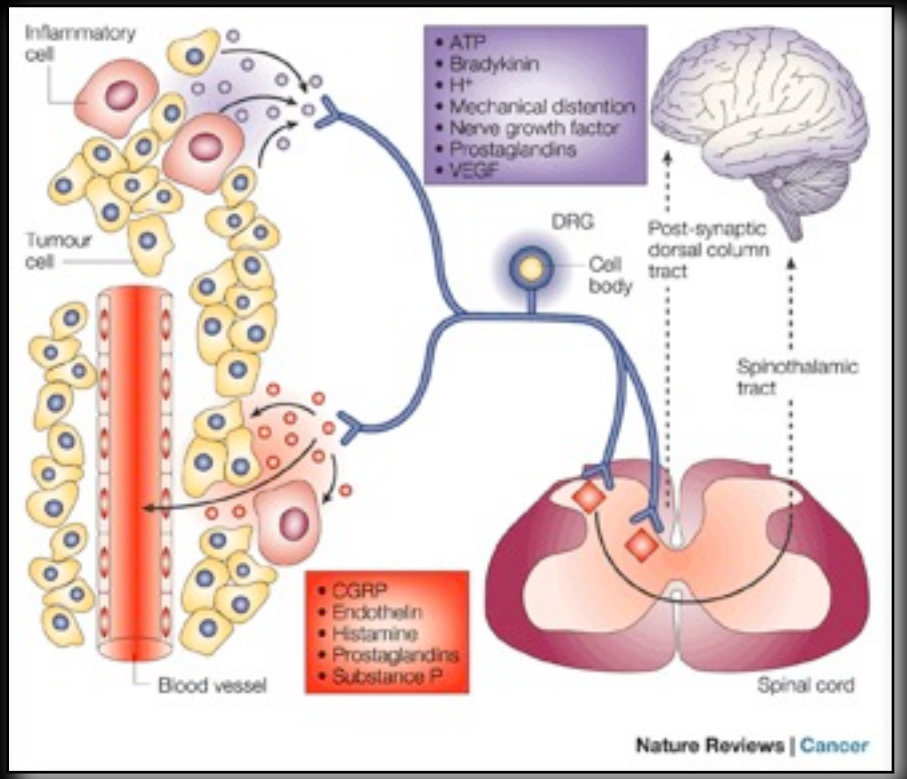
Factors Mediating Vasodilation

- Bradykinins
- Histamines
- Prostaglandins
- Serotonin
- H^+ and K^+
- Cytokines
- ATP
- Neuropeptides



Neurosecretory Function of PANS

- Substance P
- Calcitonin gene-related polypeptide
- Somatostatin

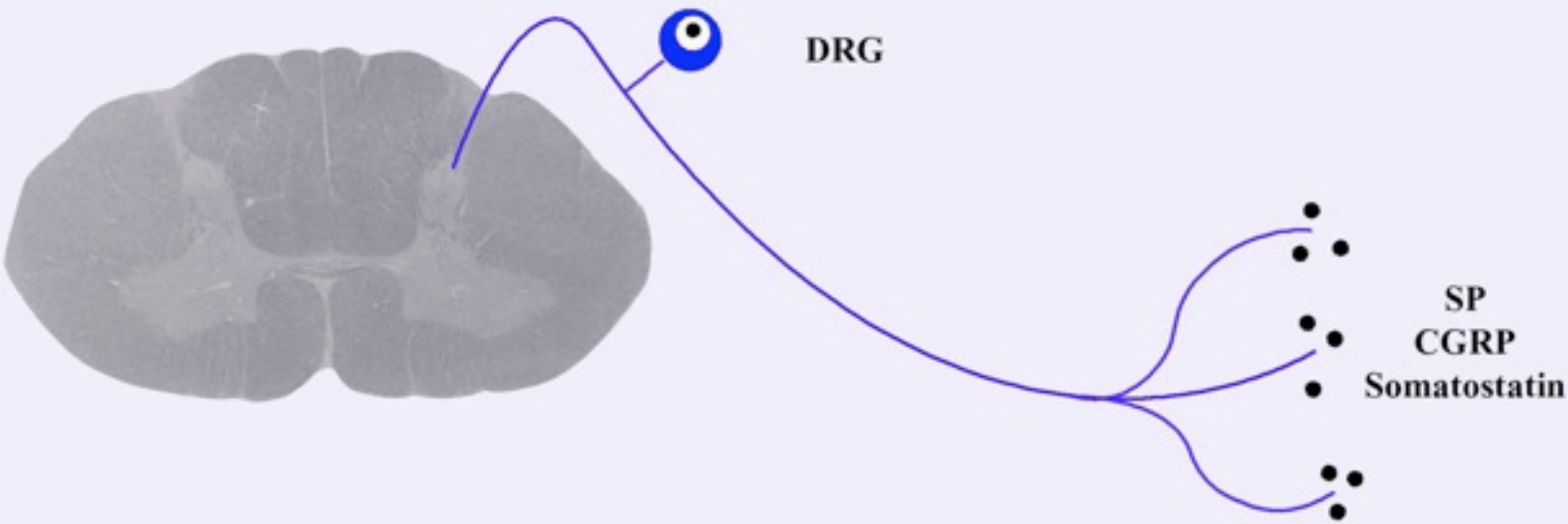


Molecular mechanisms of cancer pain

Patrick W. Mantyh, Denis R. Clohisy, Martin Koltzenburg & Steve P. Hunt

Nature Reviews Cancer **2**, 201-209 (March 2002)

Properties of the Primary Afferent Nociceptor



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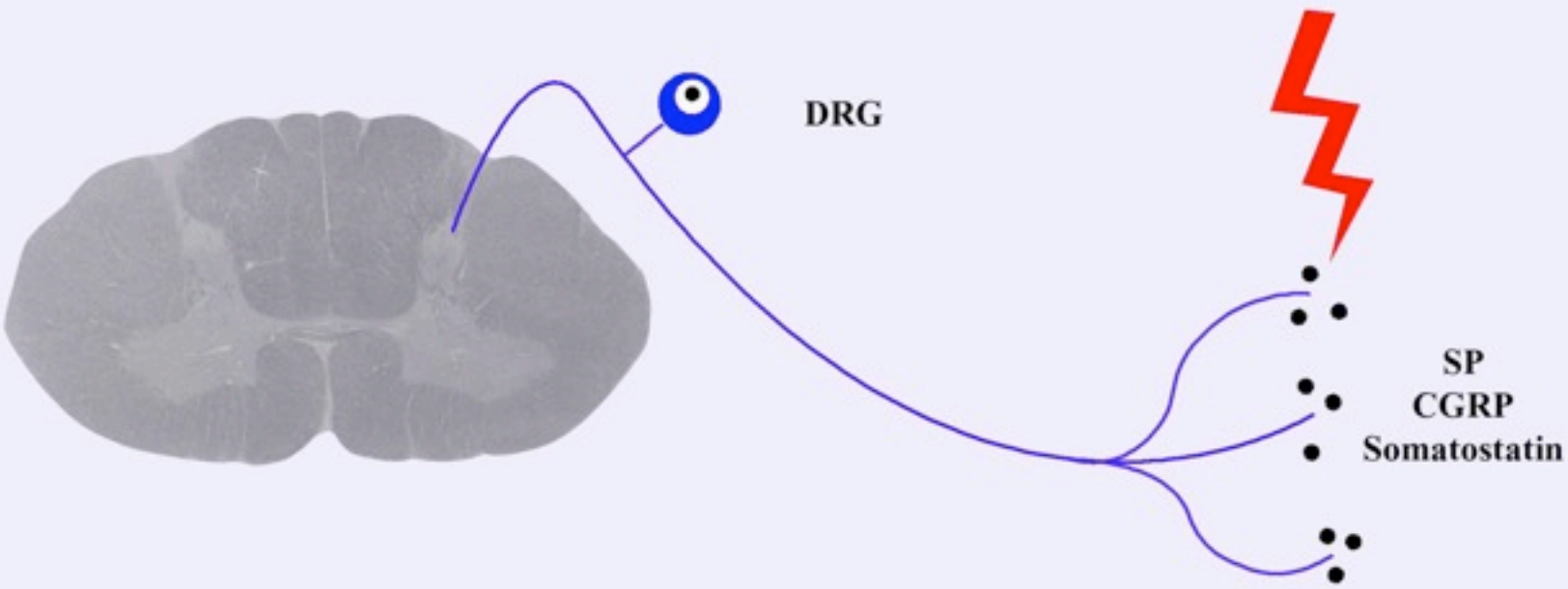
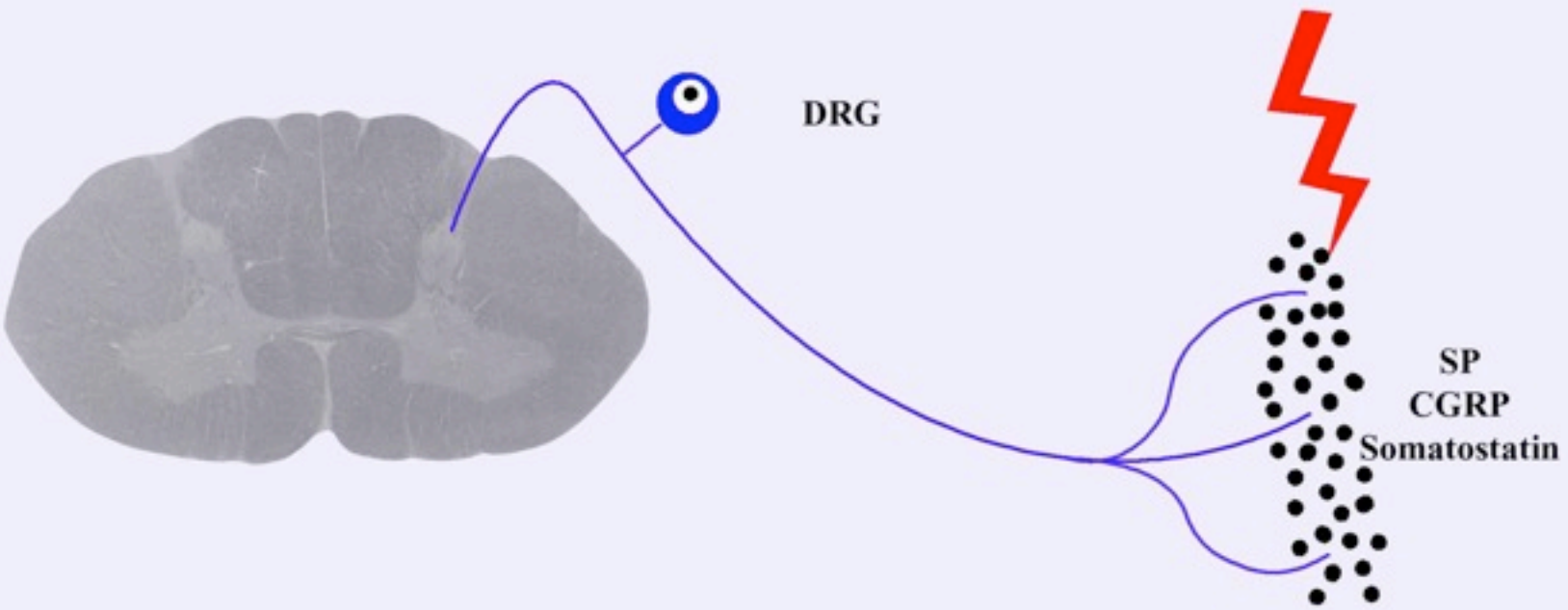
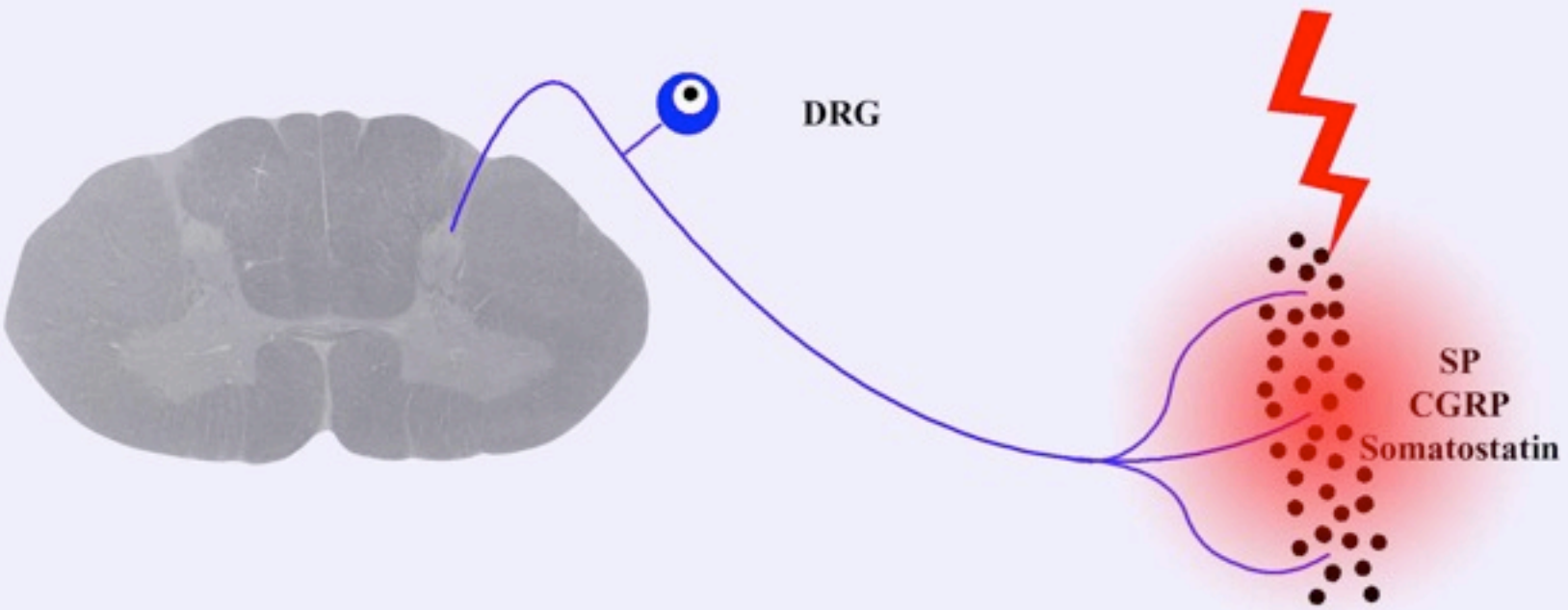


Properties of the Primary Afferent Nociceptor



Properties of the Primary Afferent Nociceptor



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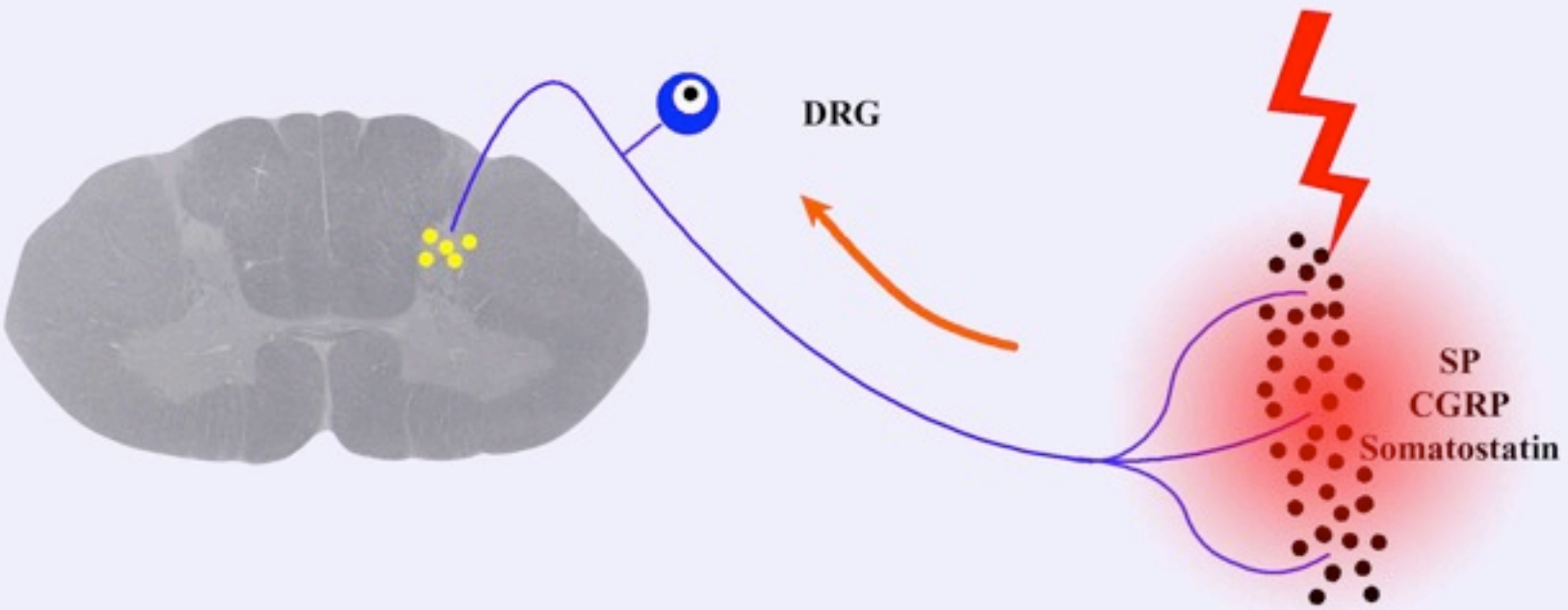
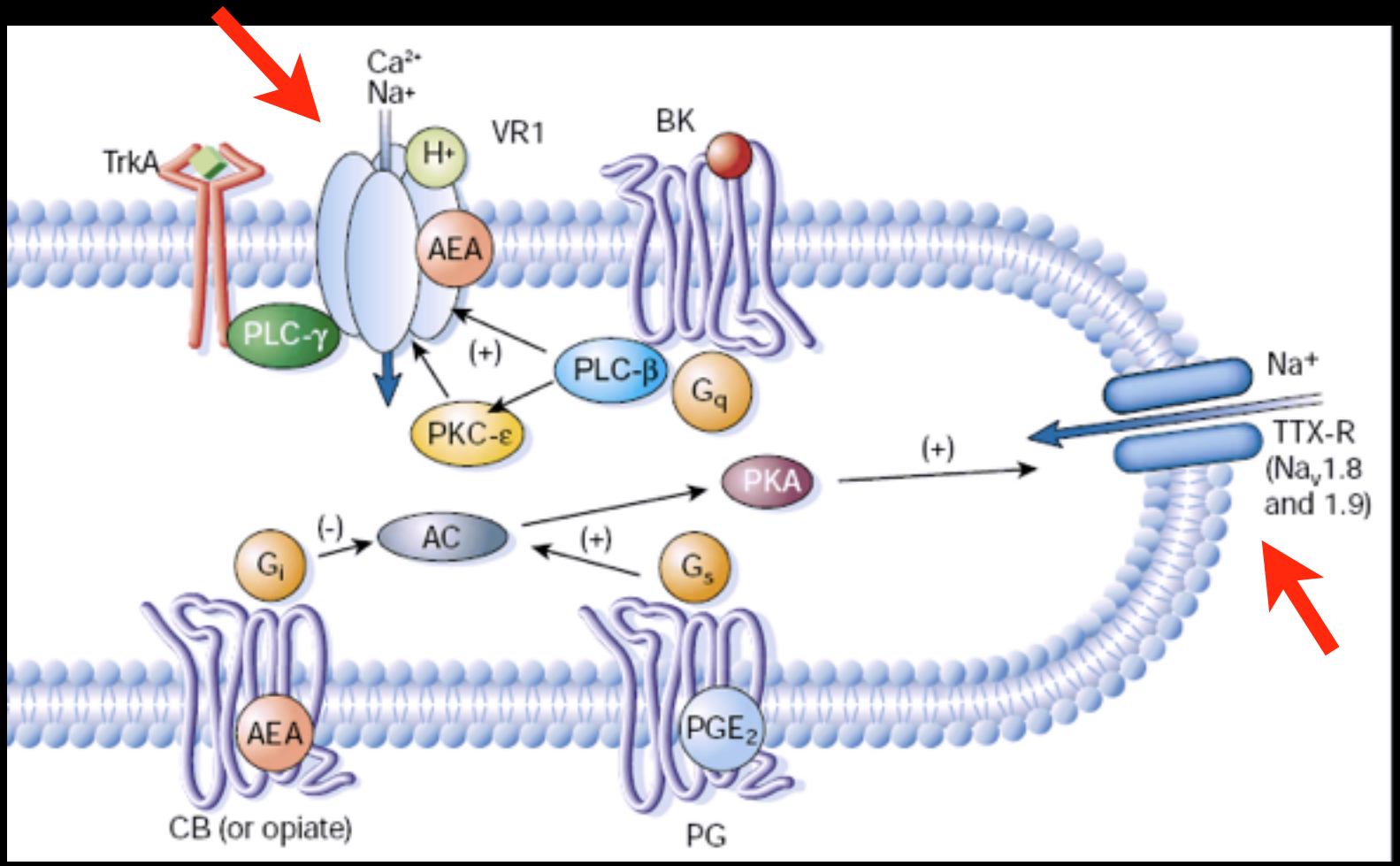


PAN Receptors Categories

- G-Protein Coupled
  - Bradykinins, 5HT, $PGE_{2,}$, cannabinoids, ATP (P2Y)
- Ligand-gates Ion Channels (VR1, TTX-R, ASIC)
  - ATP (P2X), H+, vanilloids
- Cytokine receptors / Receptor tyrosine kinases
  - IL-1, TNK-α, NGF, GDNF,BDNF

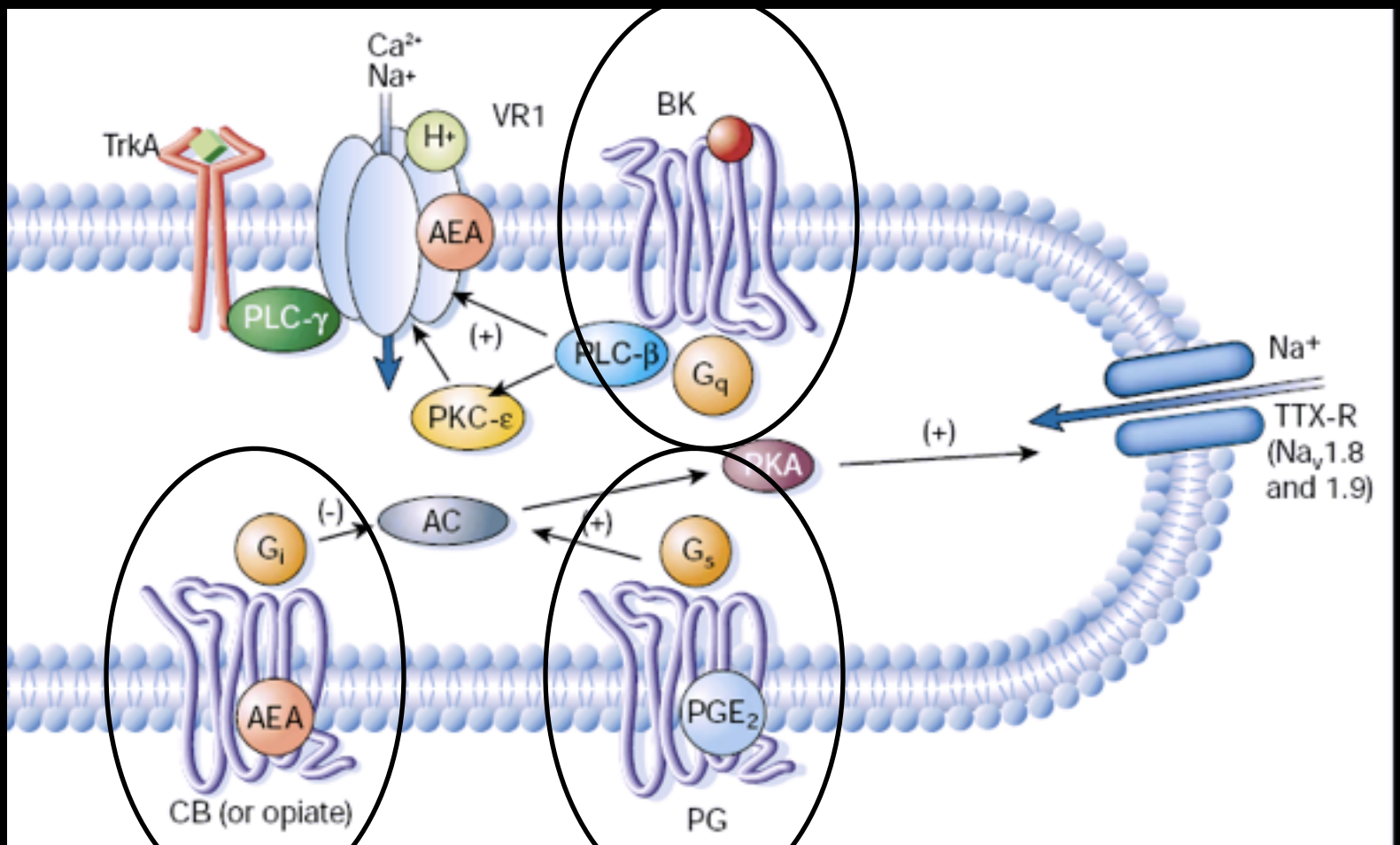
D. Julius and A. I. Basbaum. Molecular mechanisms of nociception. *Nature* 413 (6852):203-210, 2001.

Receptor Mechanisms



D. Julius and A. I. Basbaum. Molecular mechanisms of nociception. *Nature* 413 (6852):203-210, 2001.

G-Proteins



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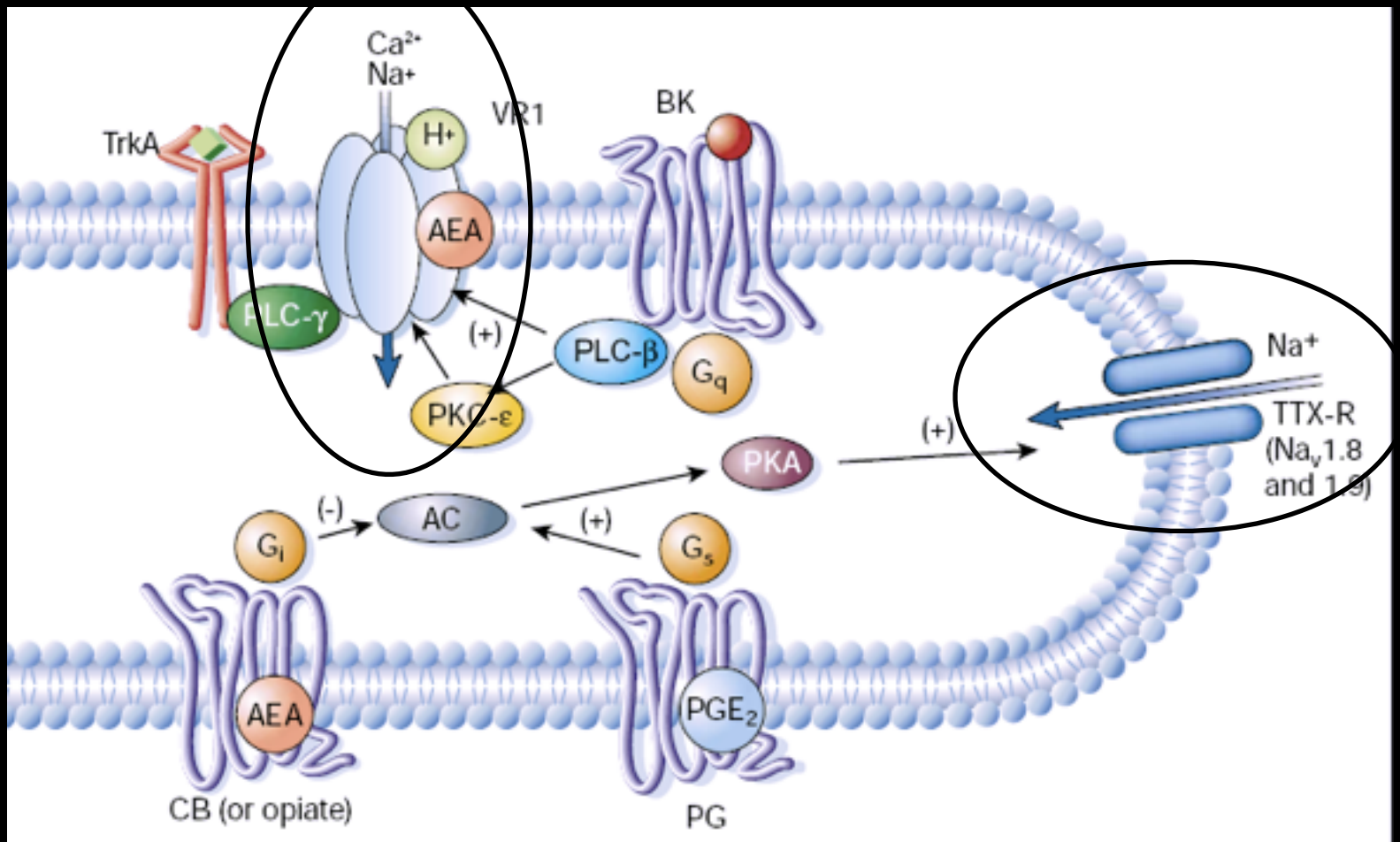
Ligand-Gate, Ion Channels



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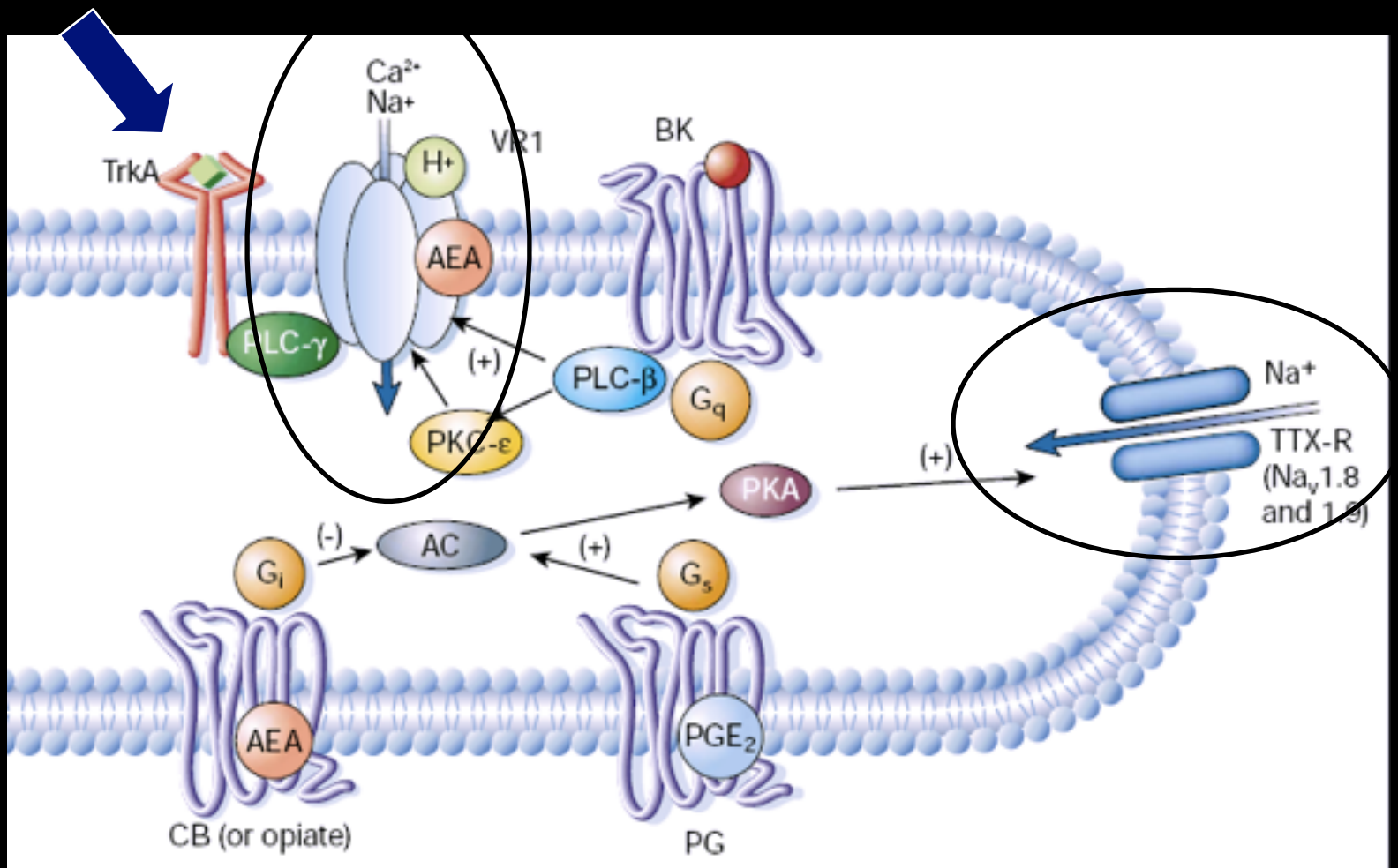
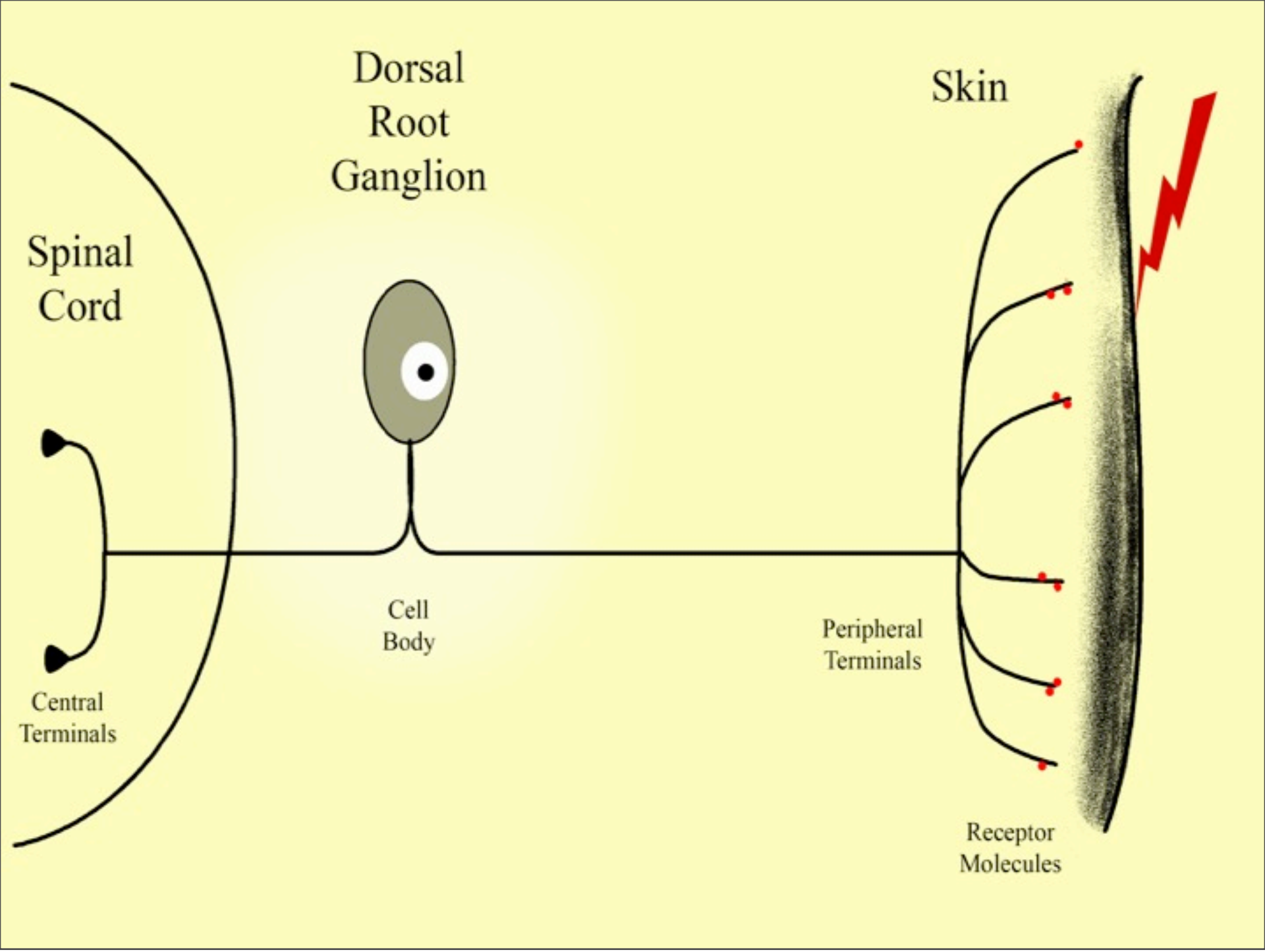
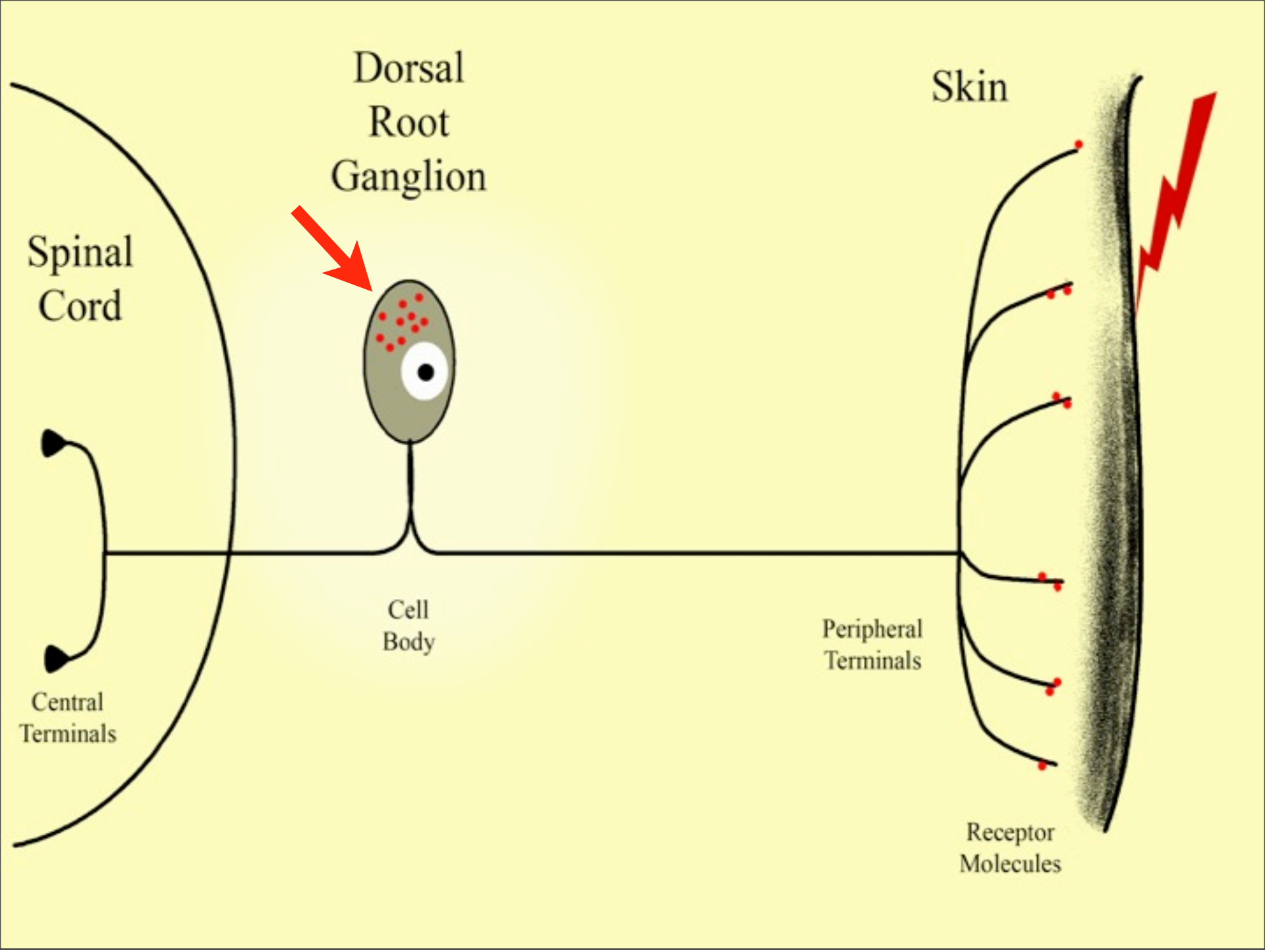
Ligand-Gate, Ion Channels




Dorsal
Root
Ganglion
Skin
Spinal
Cord
Cell
Body
Peripheral
Terminals
Central
Terminals
Receptor
Molecules


Dorsal
Root
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Body
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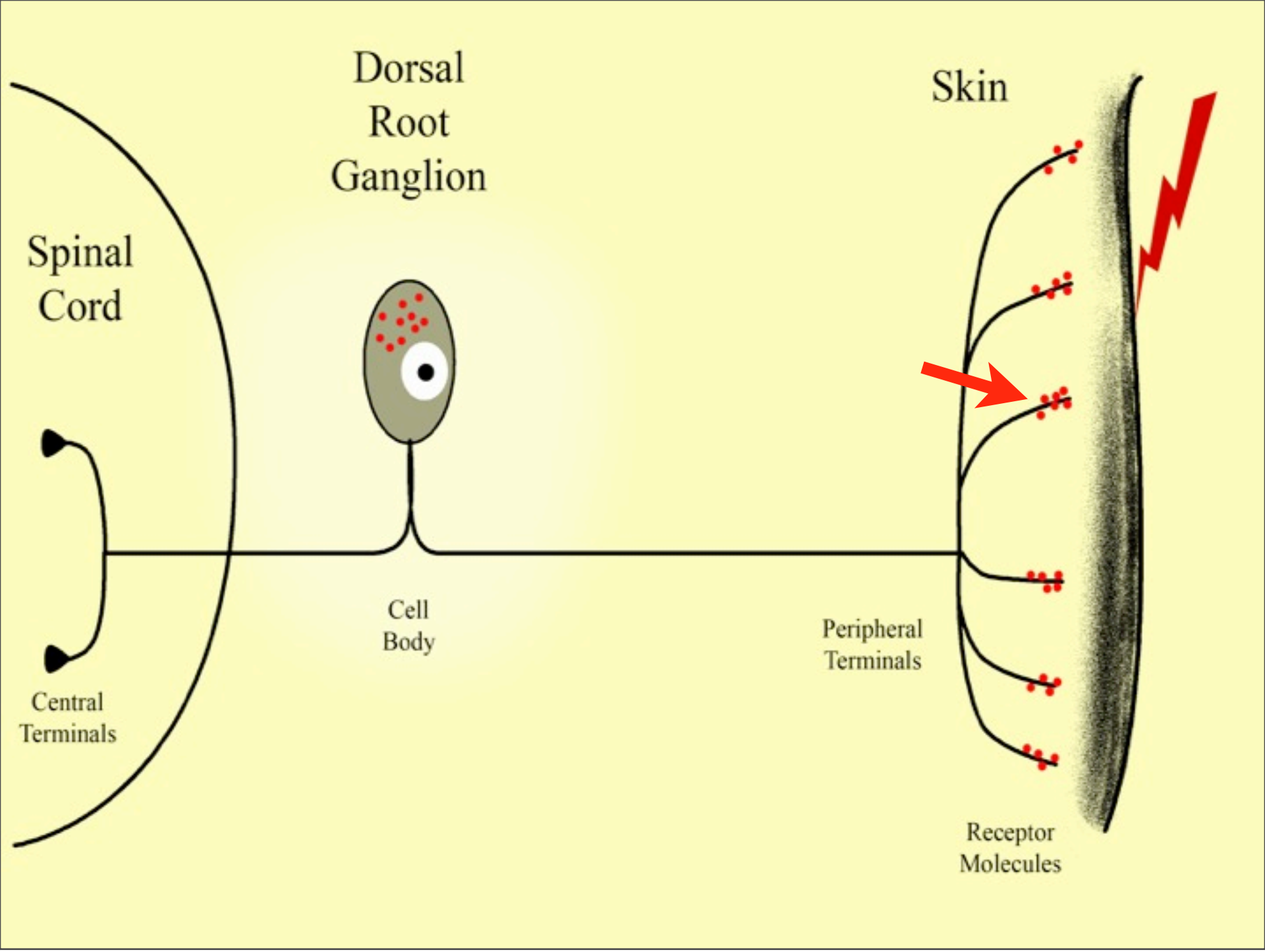

Dorsal
Root
Ganglion
Skin
Spinal
Cord
Cell
Body
Peripheral
Terminals
Central
Terminals
Receptor
Molecules

PAN Activation

- Activation of channel property modifiers
- Gene induction and altered channel properties

Results of PAN Activation

"Peripheral Sensitization"

Results of PAN Activation

- Lowering of thresholds

"Peripheral Sensitization"

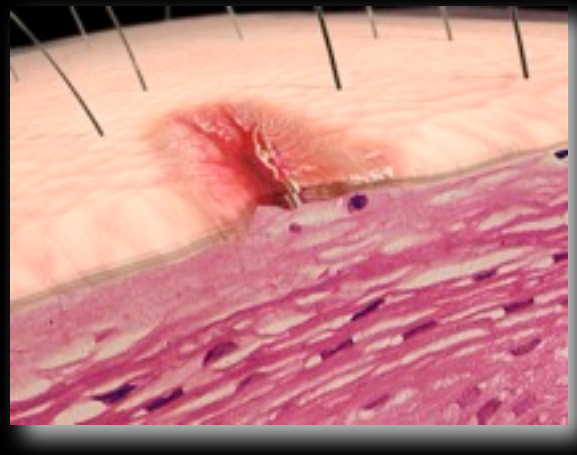
Results of PAN Activation

- Lowering of thresholds
- Development of hyperalgesia

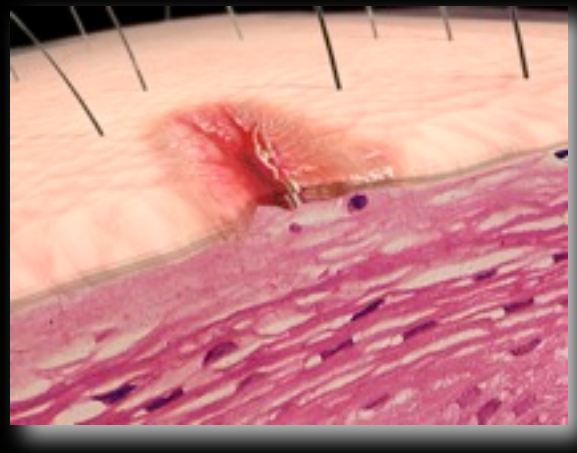
"Peripheral Sensitization"

Neurogenic Inflammatory Cycle

Tissue Inflammation



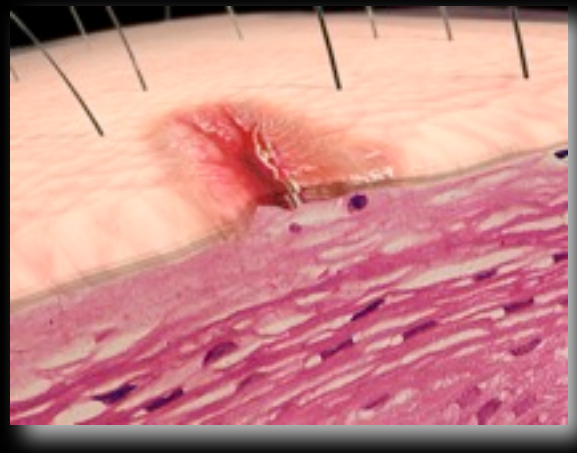
Neurogenic Inflammatory Cycle



Tissue Inflammation

Histamine Bradykinin Prostaglandins

Neurogenic Inflammatory Cycle



Tissue Inflammation

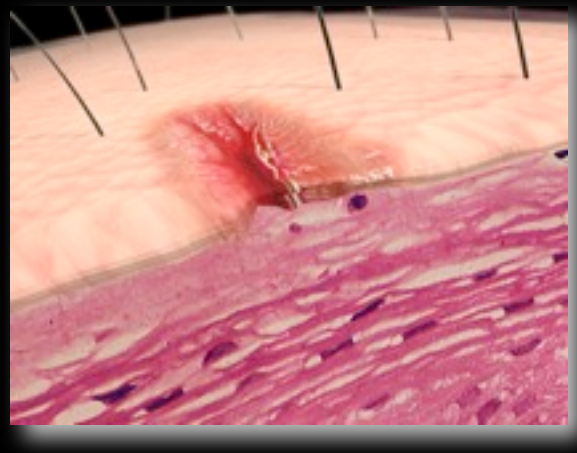
Histamine

Bradykinin

Prostaglandins

Primary Afferent Fibers

Neurogenic Inflammatory Cycle



Tissue Inflammation

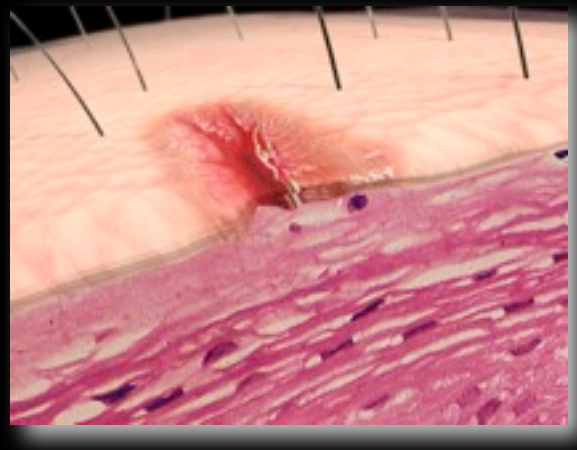
Histamine

Bradykinin

Prostaglandins

Primary Afferent Fibers → Spinal Cord

Neurogenic Inflammatory Cycle



Tissue Inflammation

\+

Neuropeptides

Histamine

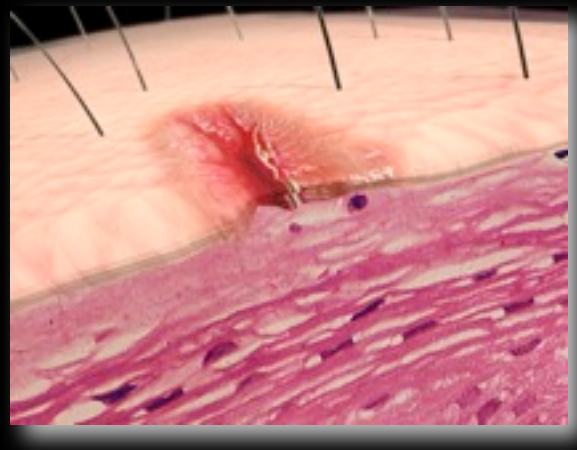
Bradykinin

Prostaglandins

Primary Afferent Fibers

Spinal Cord

Neurogenic Inflammatory Cycle



Tissue Inflammation

\+

Neuropeptides

Histamine

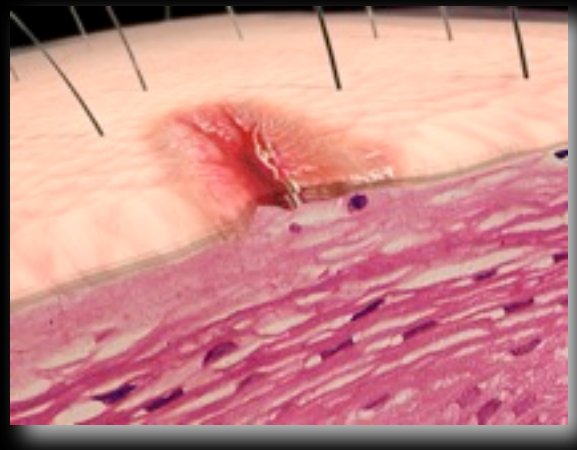
Bradykinin

Prostaglandins

Primary Afferent Fibers

Spinal Cord

Neurogenic Inflammatory Cycle



Tissue Inflammation

\+

Neuropeptides

Histamine

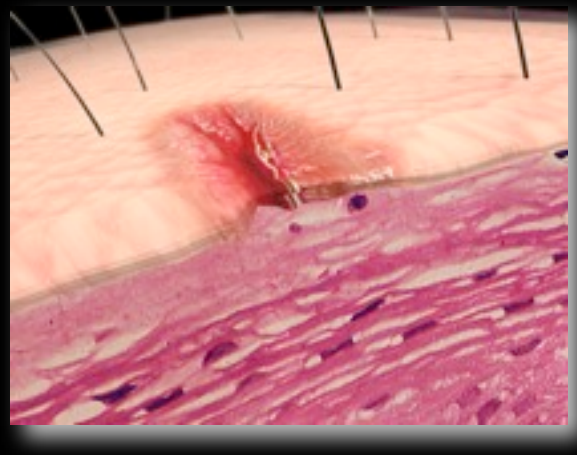
Bradykinin

Prostaglandins

Primary Afferent Fibers

Spinal Cord

Neurogenic Inflammatory Cycle



Tissue Inflammation

\+

Neuropeptides

Histamine

Bradykinin

Prostaglandins

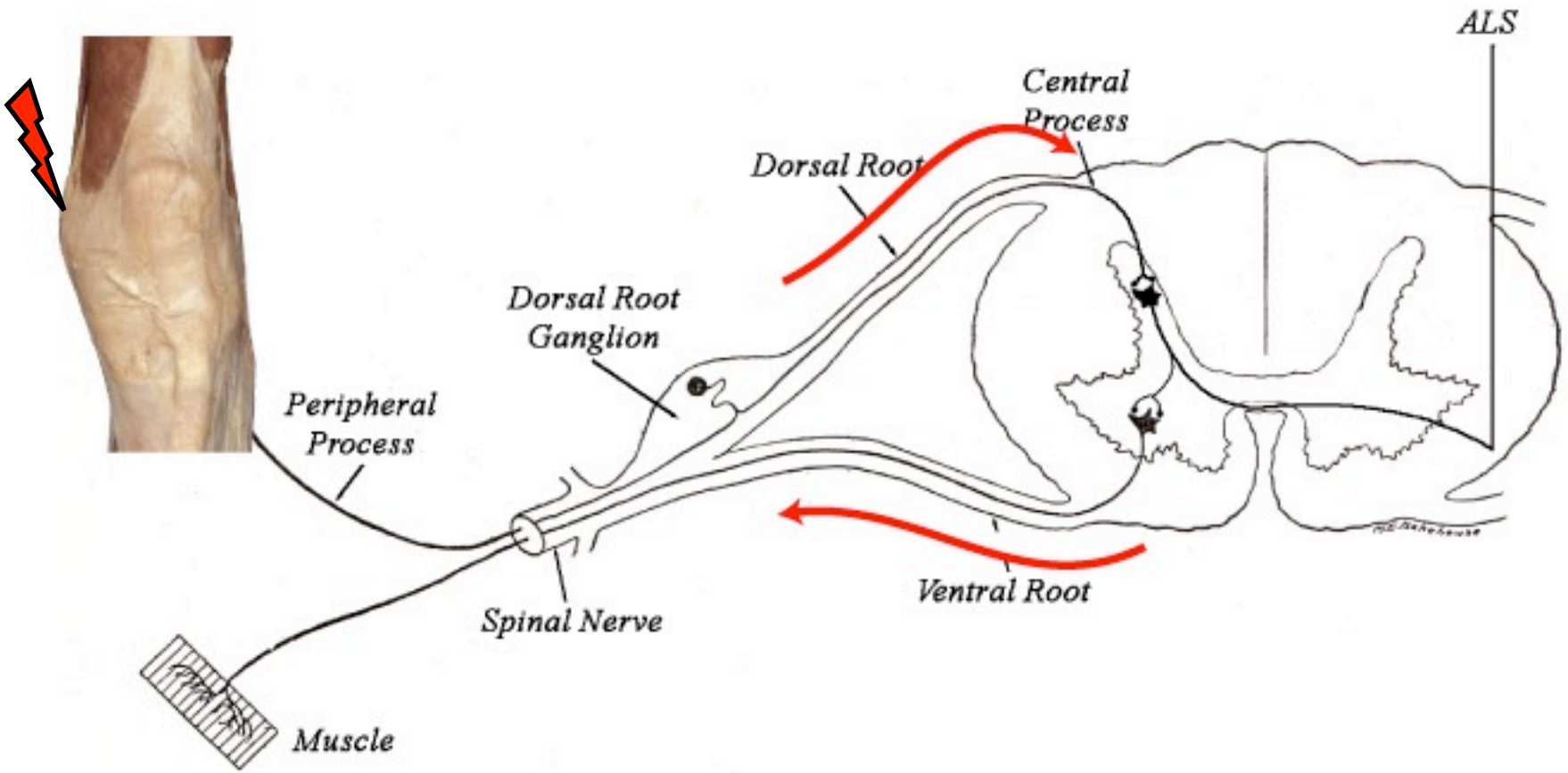
Sensitized Primary Afferent Fibers

Spinal Cord

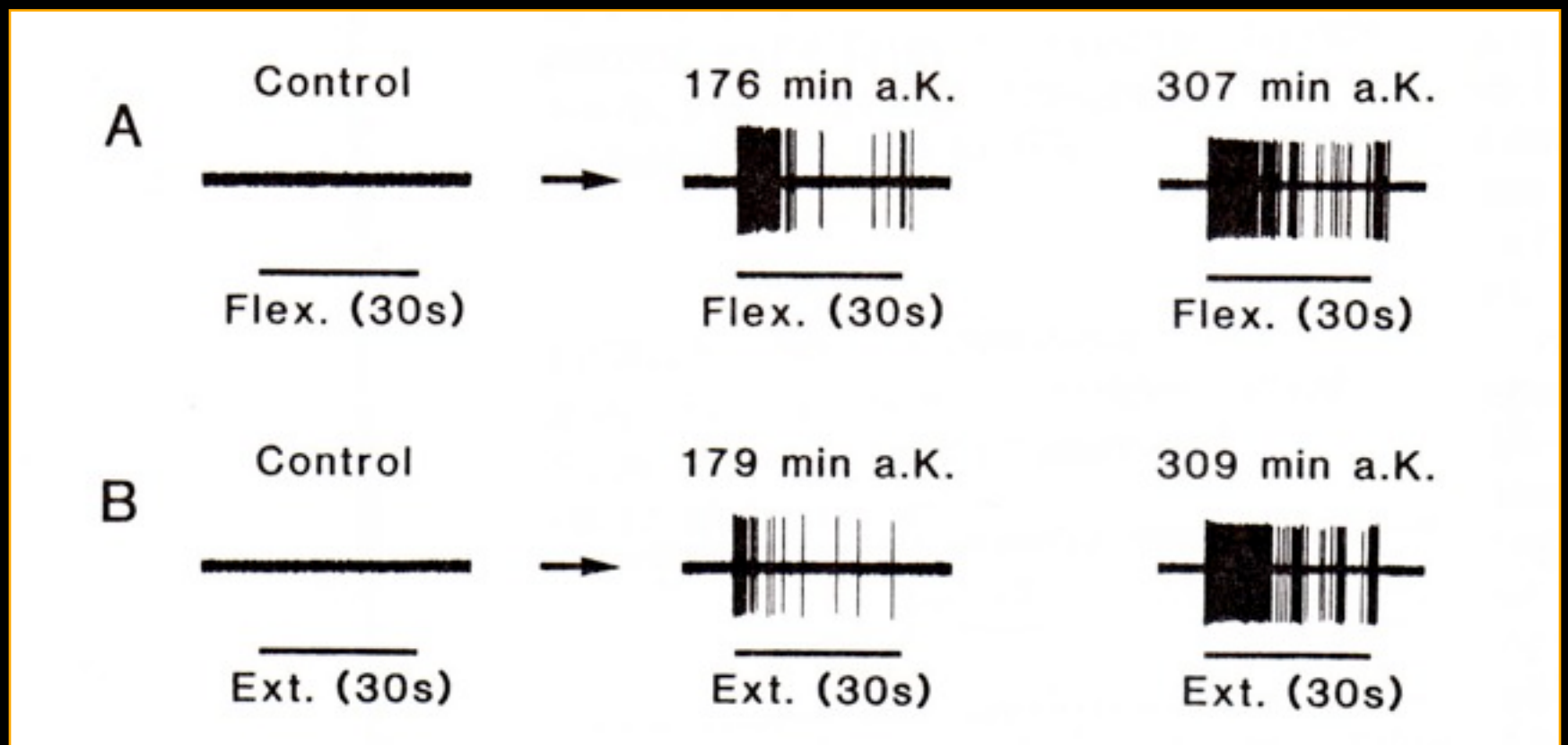
Results of Tissue Irritation

- Lowering of activation thresholds for small caliber, primary afferent fibers
- Peripheral sensitization
- Development of primary hyperalgesia

Motoneuron Facilitation



Motoneuron Facilitation



He *et al*., J. Neurophysiology 59:326-340, 1988

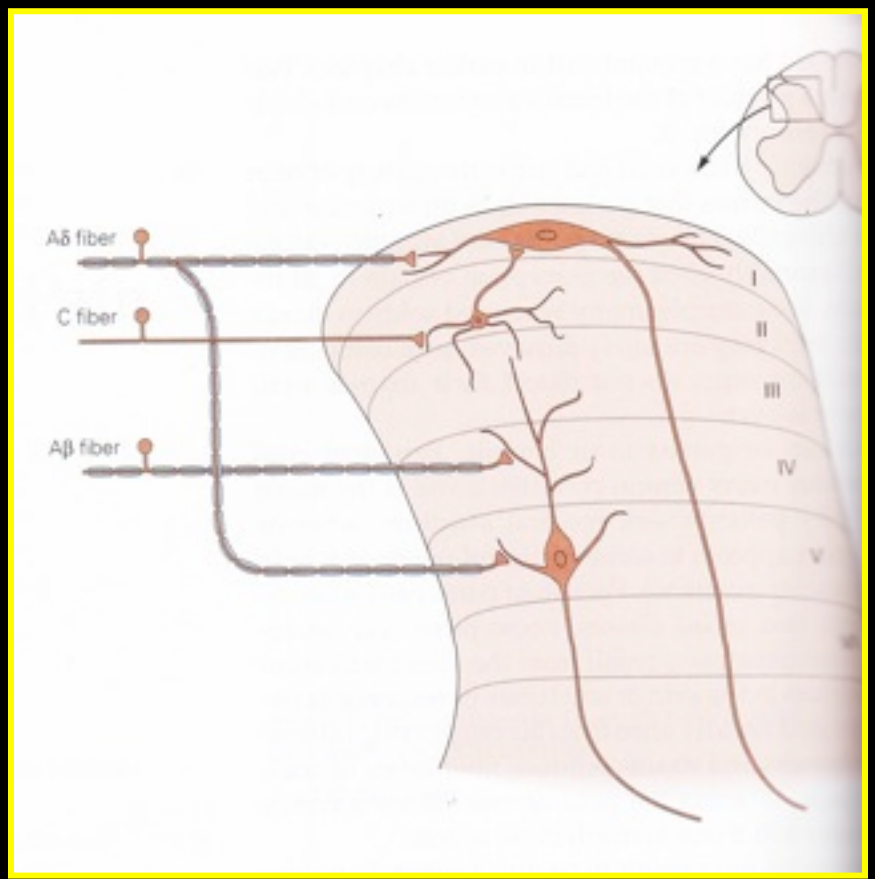
Facilitation:

- Clinical Observation
  - Objective - Somatic dysfunction
  - Subjective - Pain

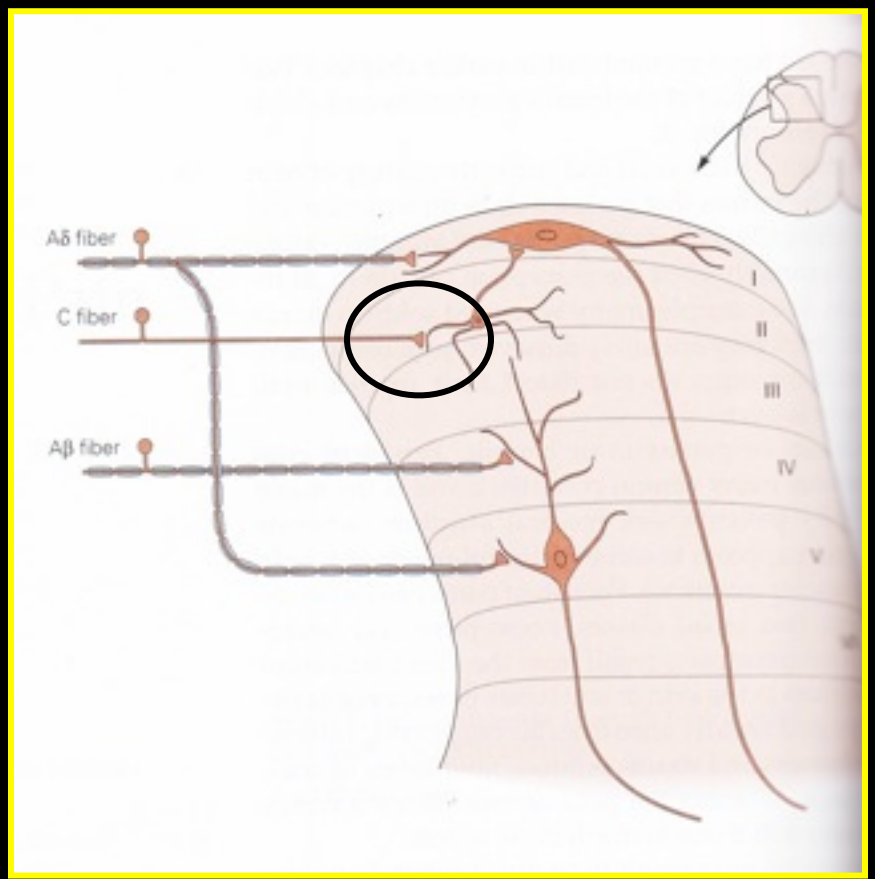
Sensitization:

- Physiological Event

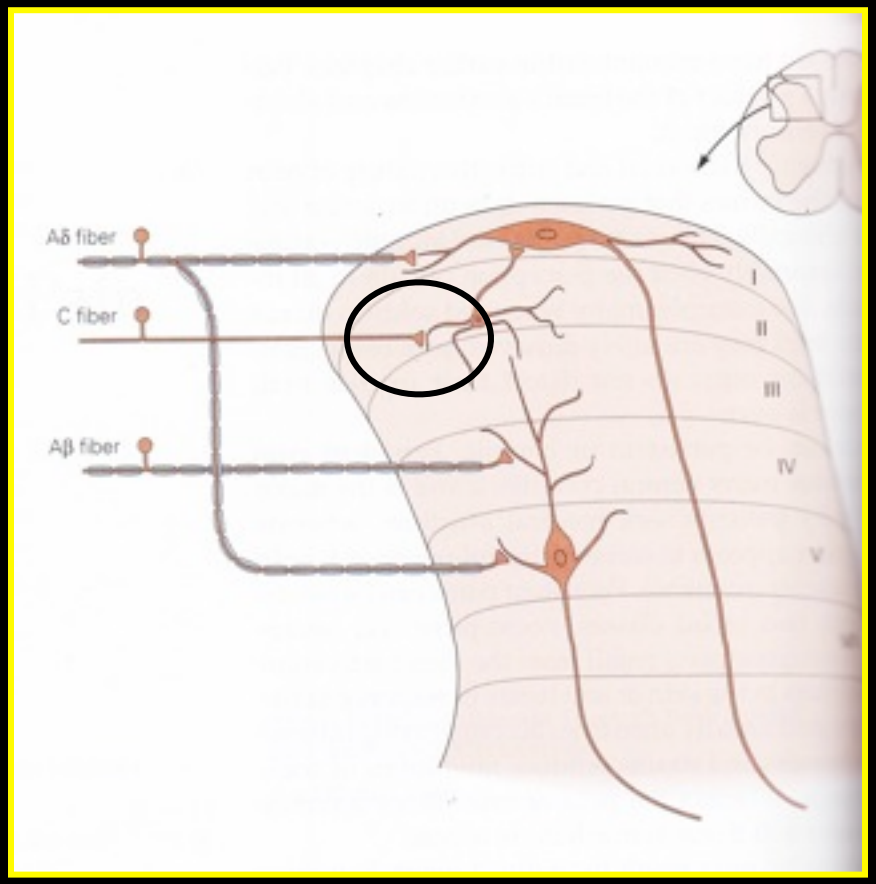
Dorsal Horn

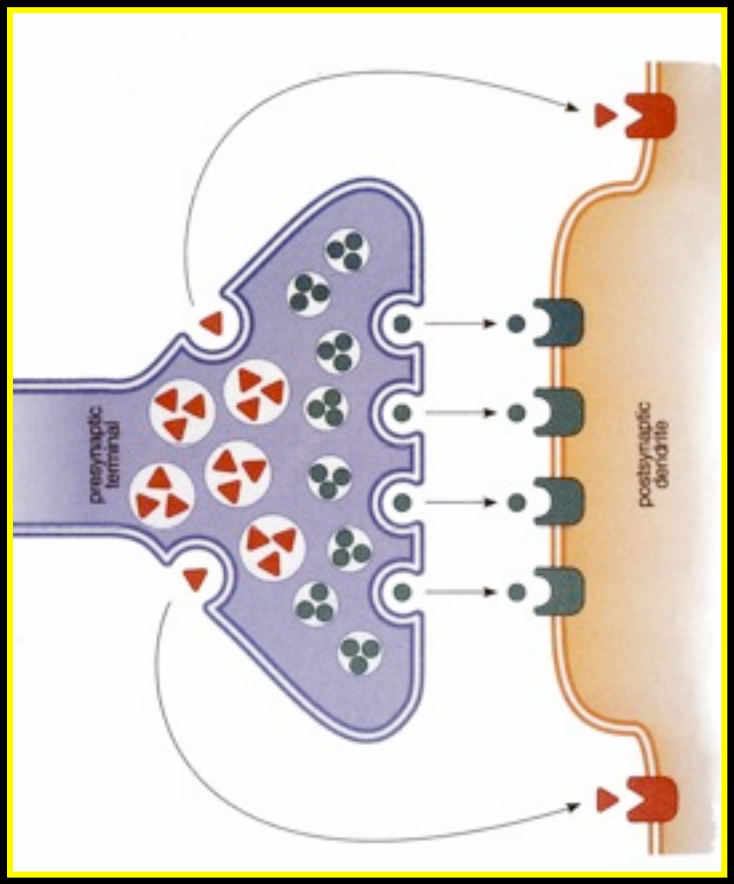


Dorsal Horn



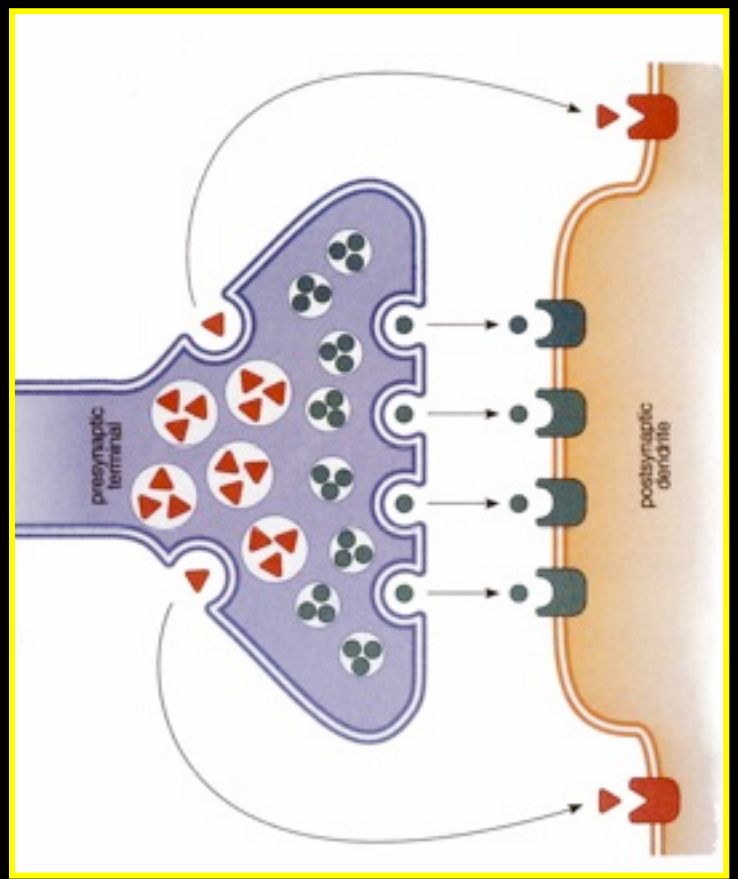
Dorsal Horn


Aδ fiber
C fiber
Aβ fiber
I
II
III
IV
V

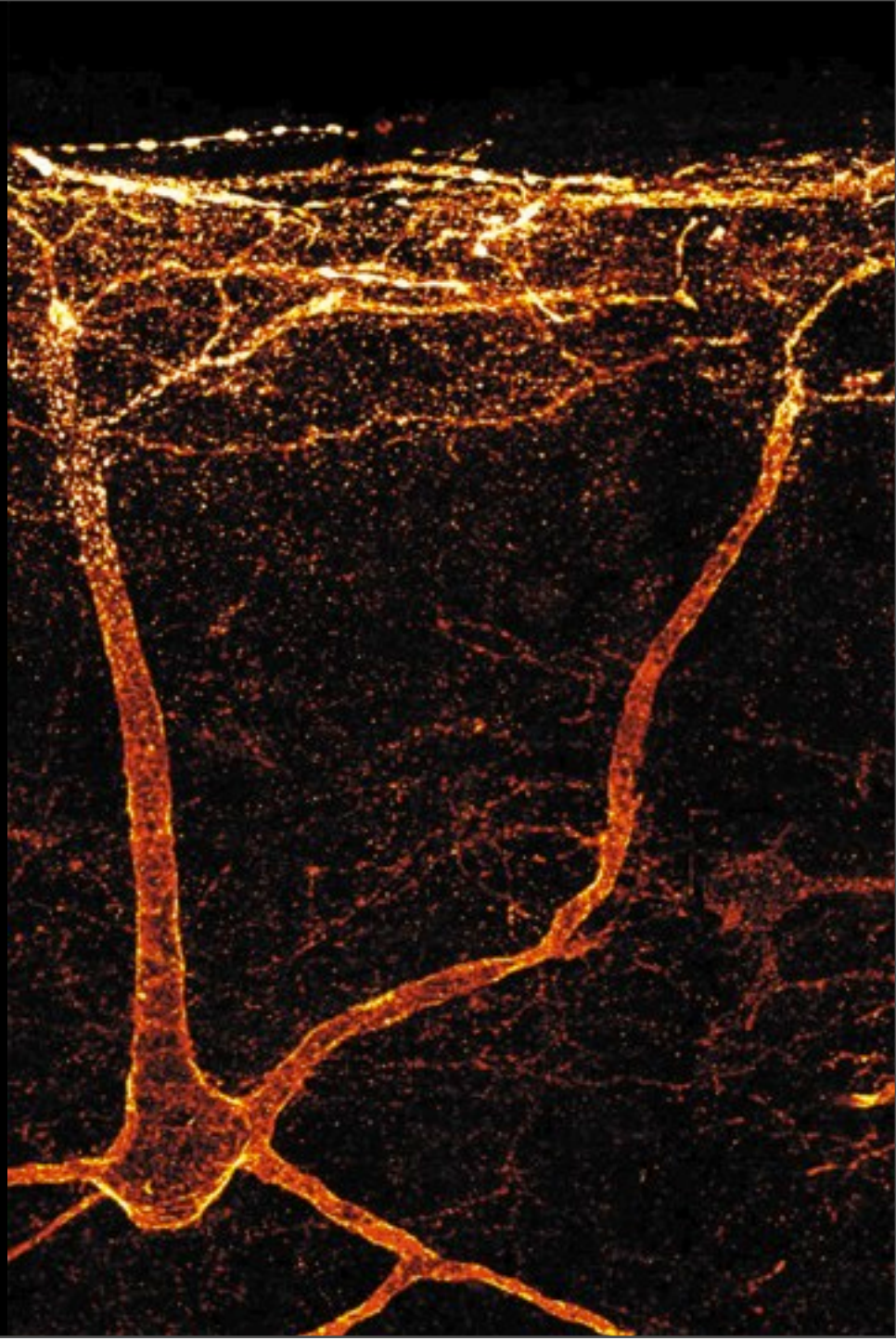

presynaptic terminal
postsynaptic dendrite

Release of Neurotransmitters

- Amino acids
  - Fast transmission
- Neuropeptides
  - Slow transmission



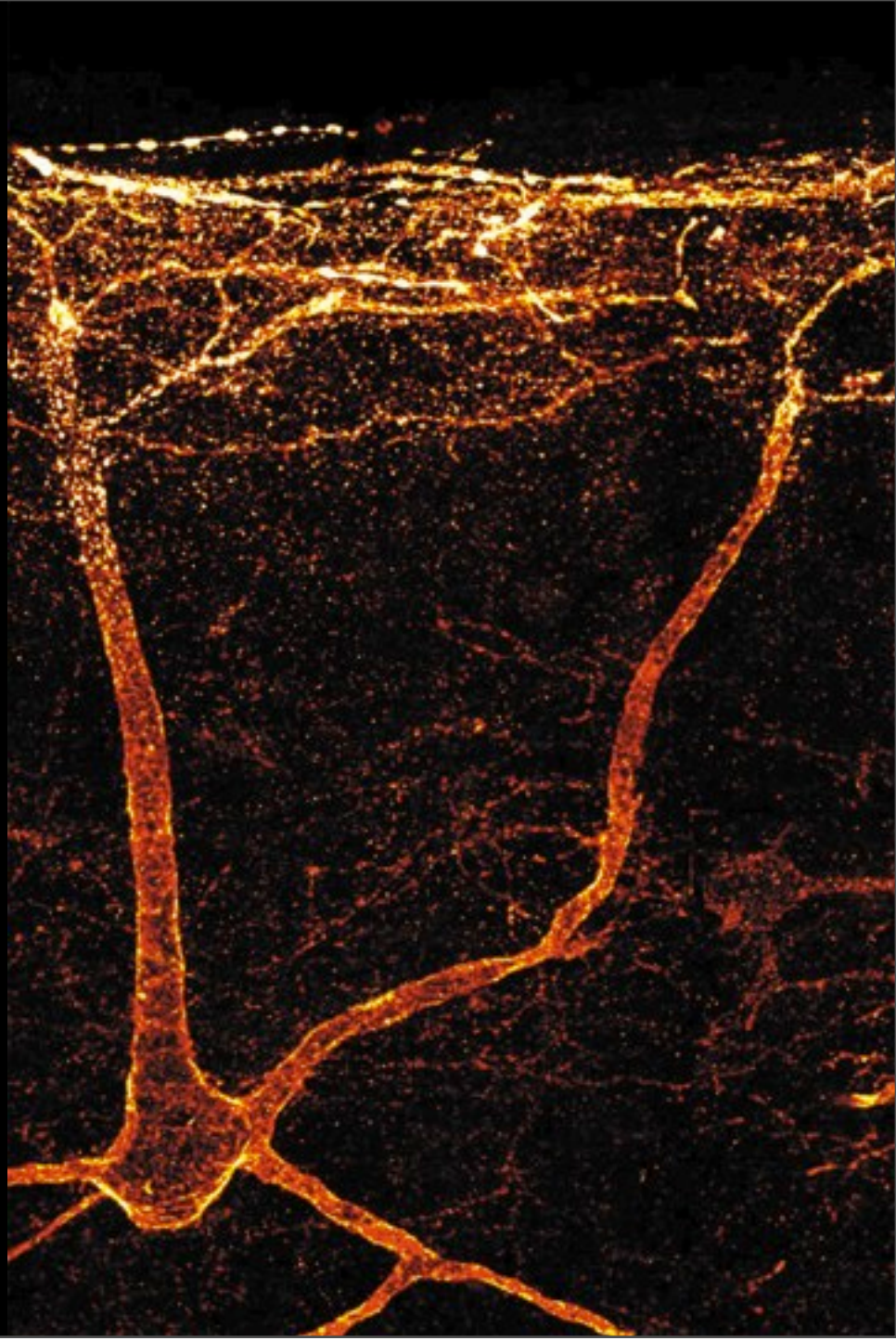
Spinal Facilitation - *Mechanisms*



Hunt SP, Mantyh PW (2001) The molecular dynamics of pain control. Nat Rev Neurosci 2: 83-91.

Spinal Facilitation - *Mechanisms*

- Neuropeptide release



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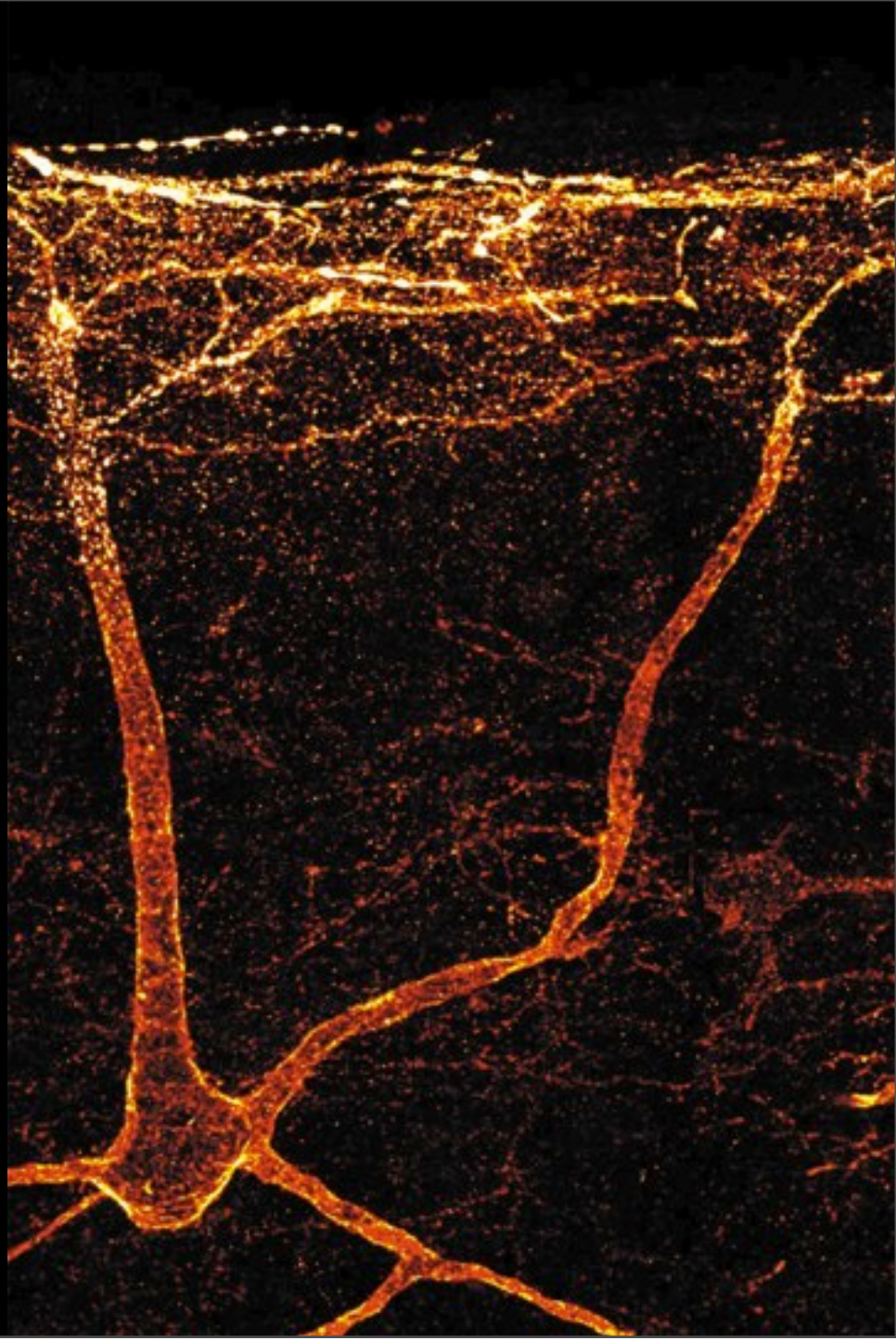
Spinal Facilitation - *Mechanisms*

- Neuropeptide release
- Internalization of neuropeptide receptor



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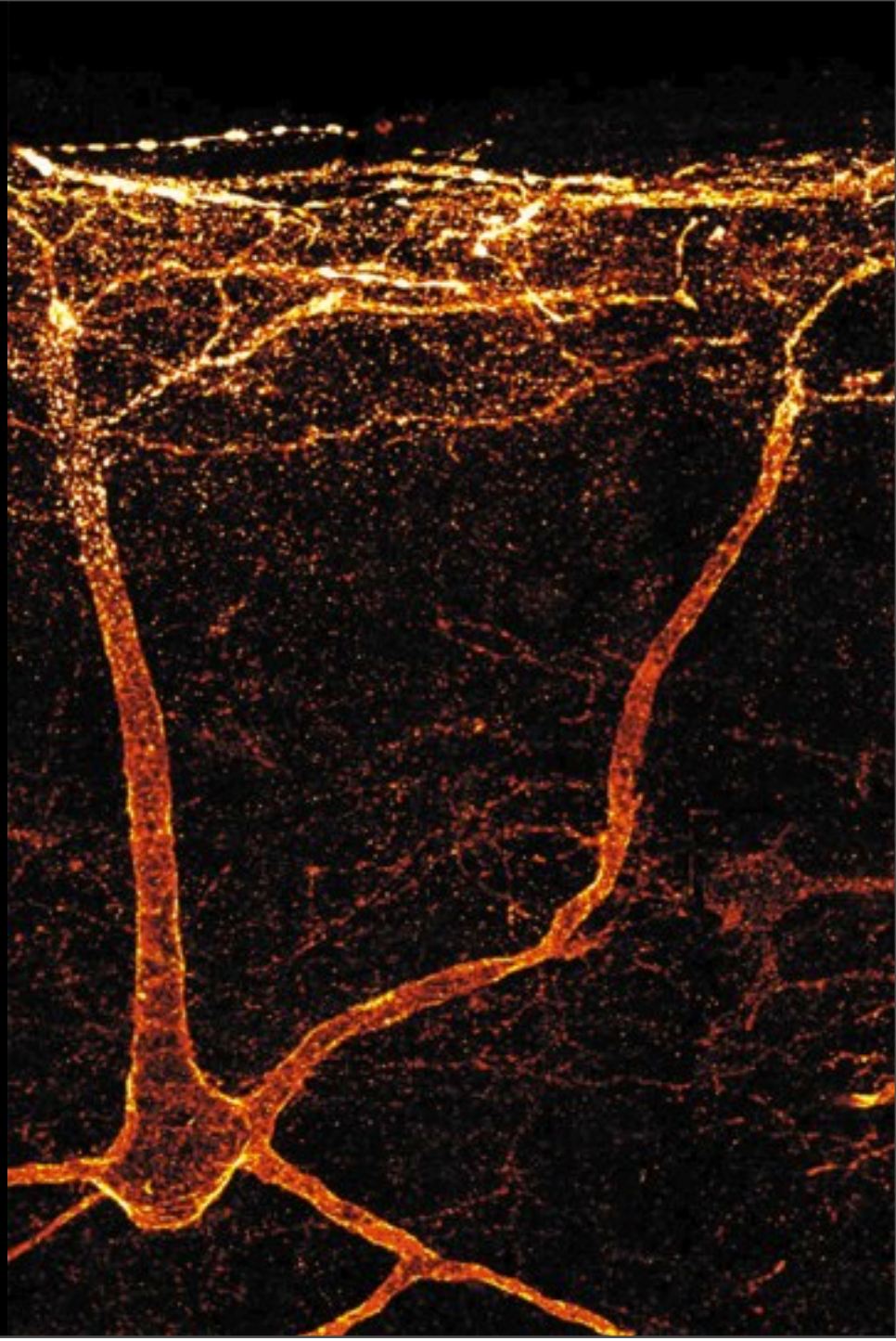
Spinal Facilitation - *Mechanisms*

- Neuropeptide release
- Internalization of neuropeptide receptor
- Hormone-like activity



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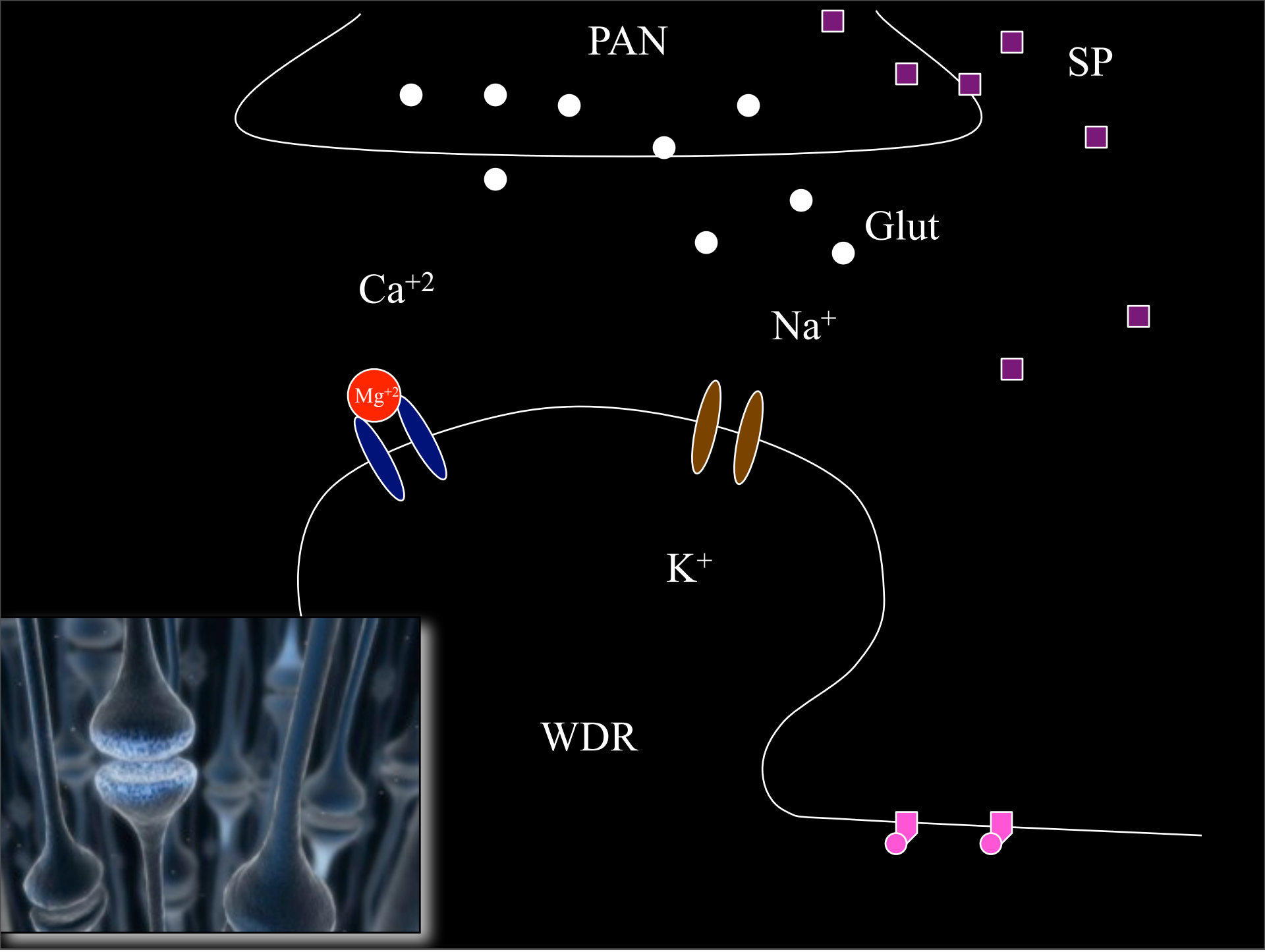
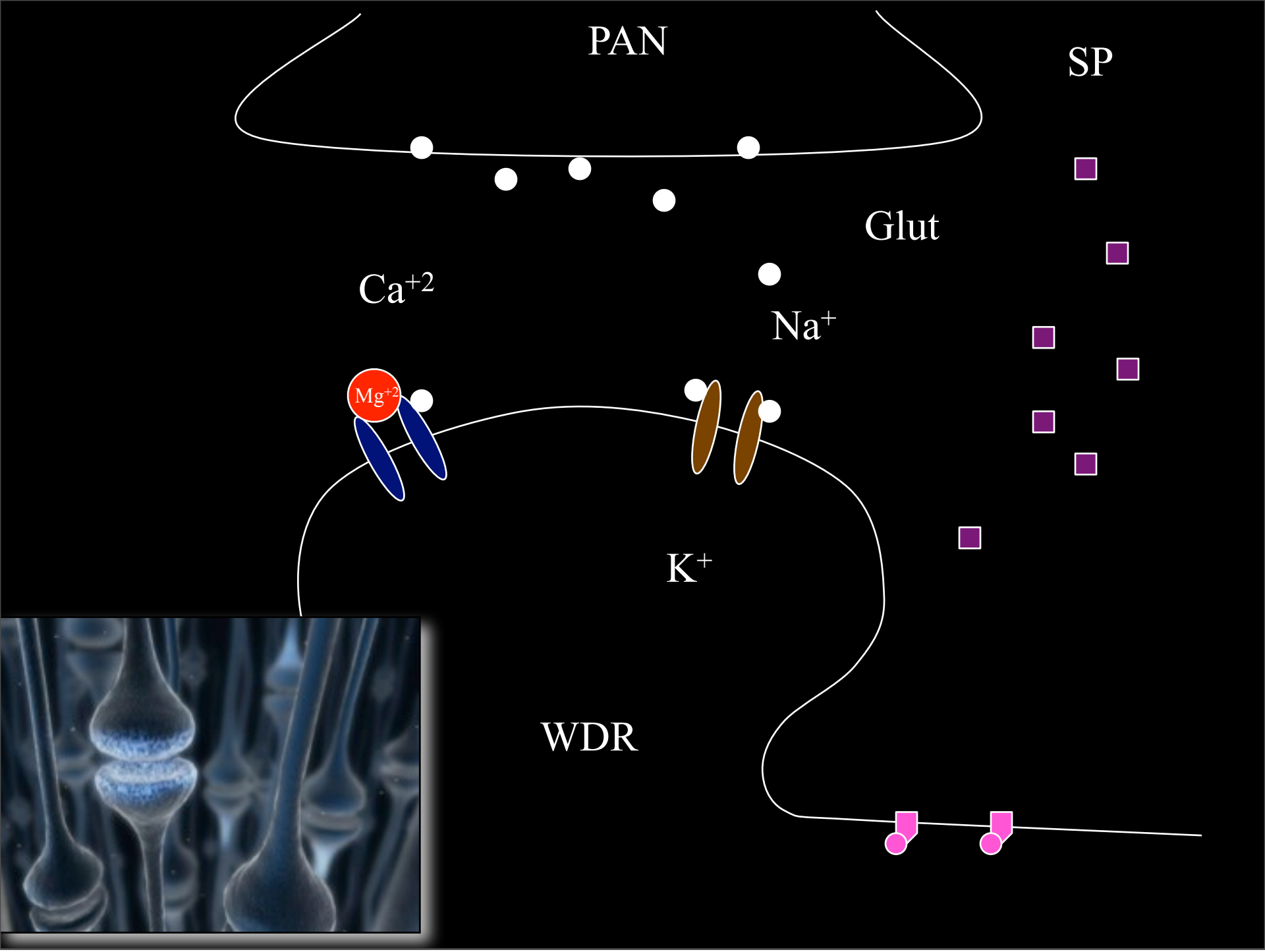
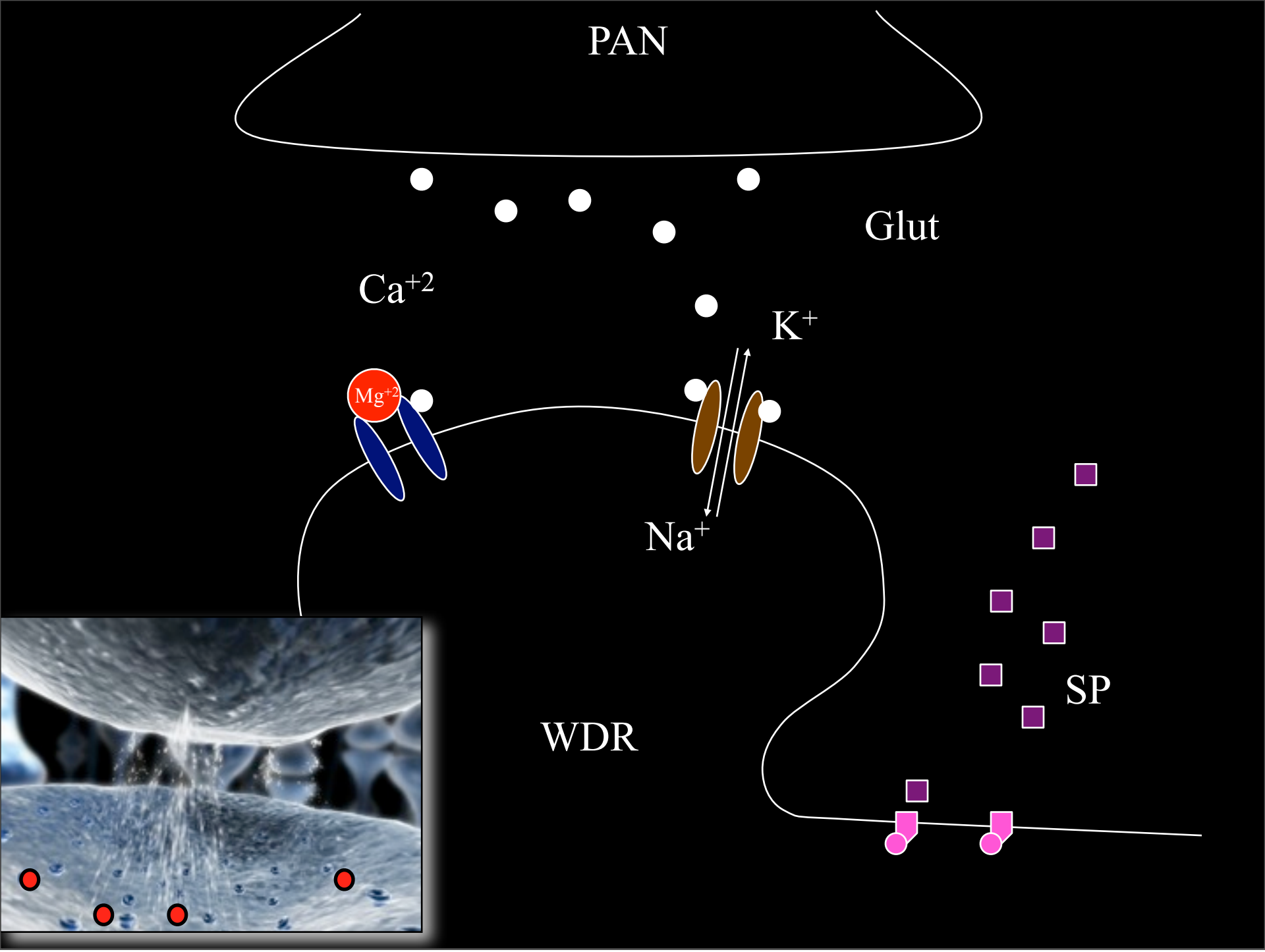
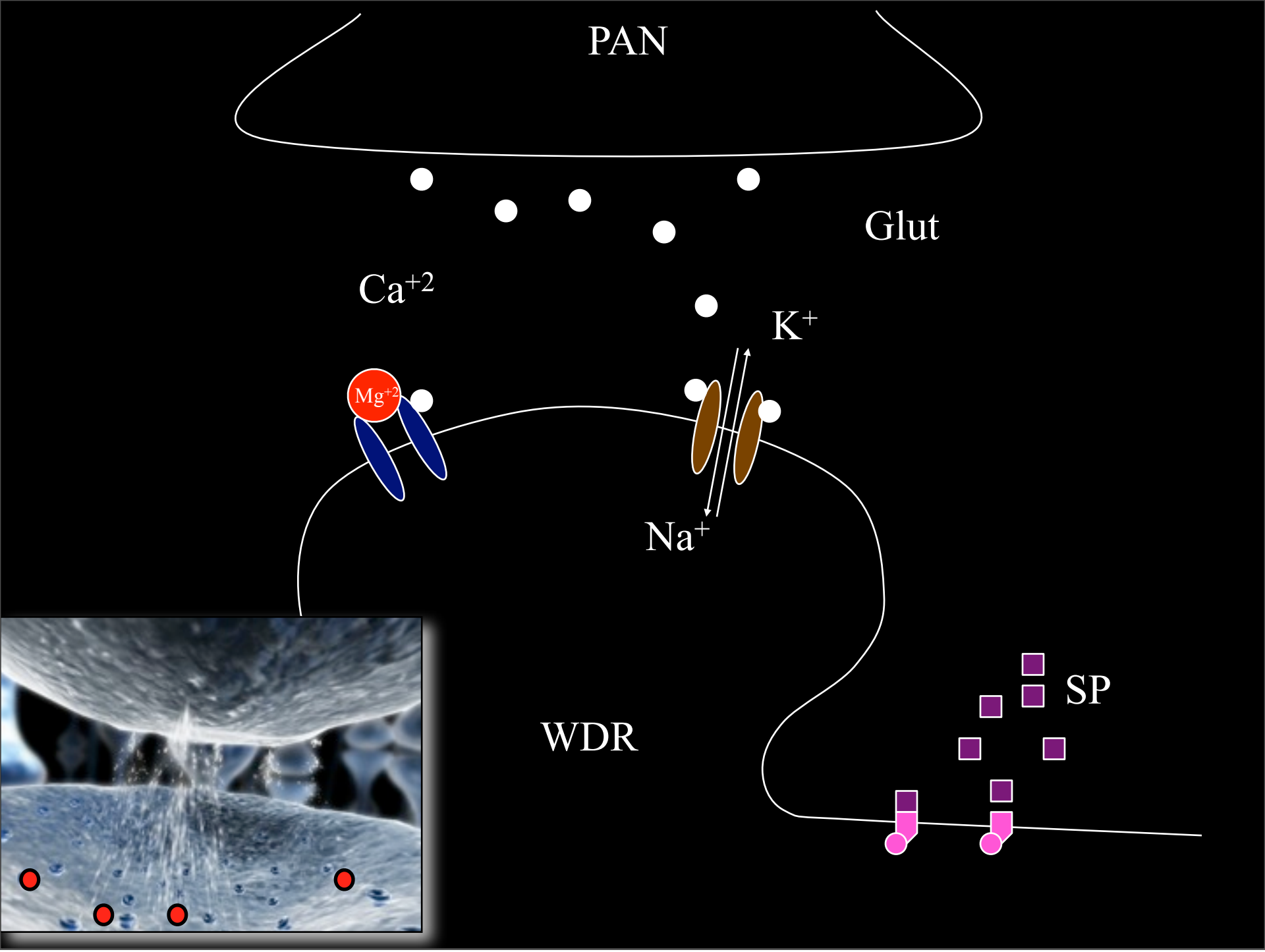
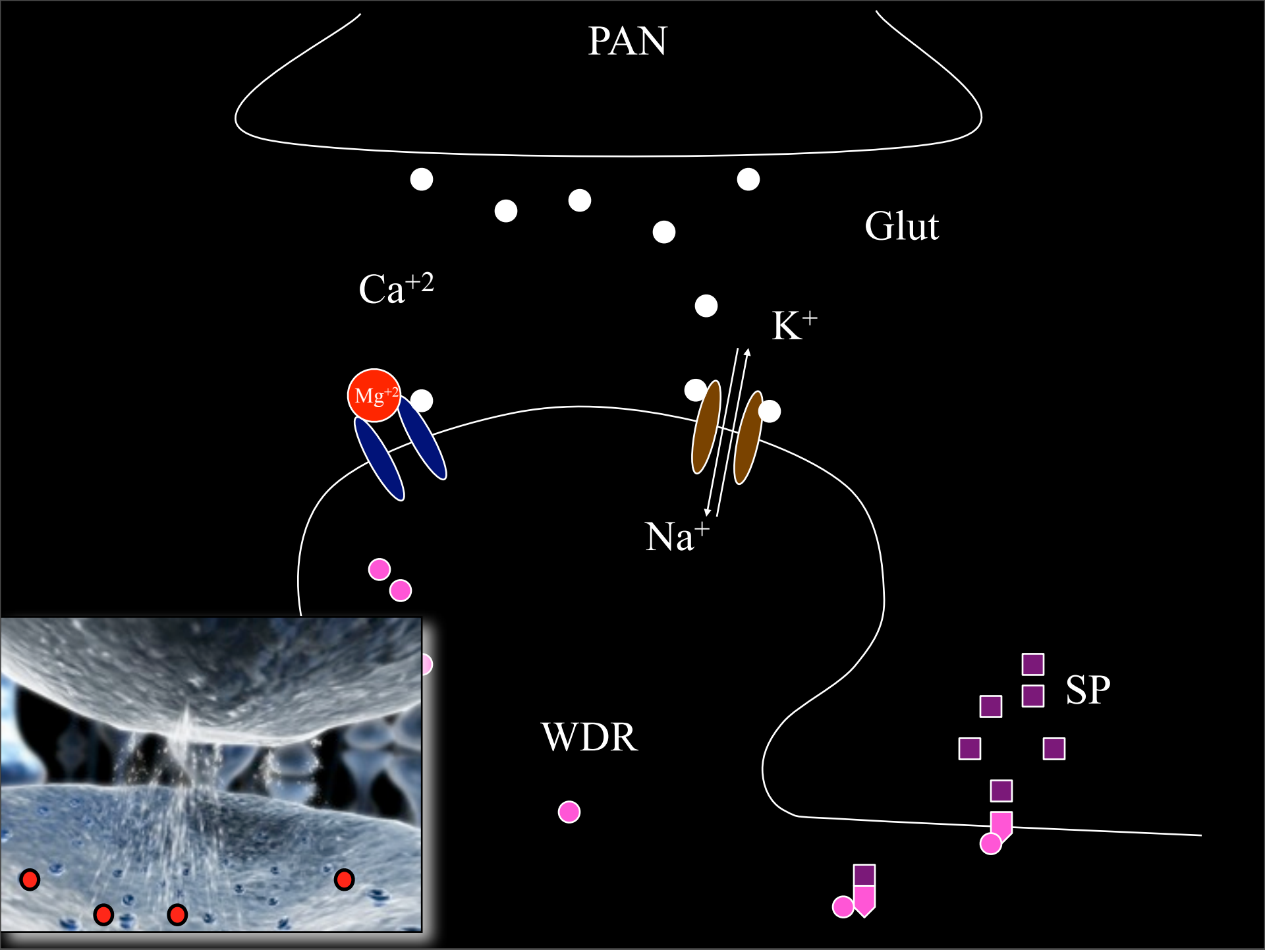
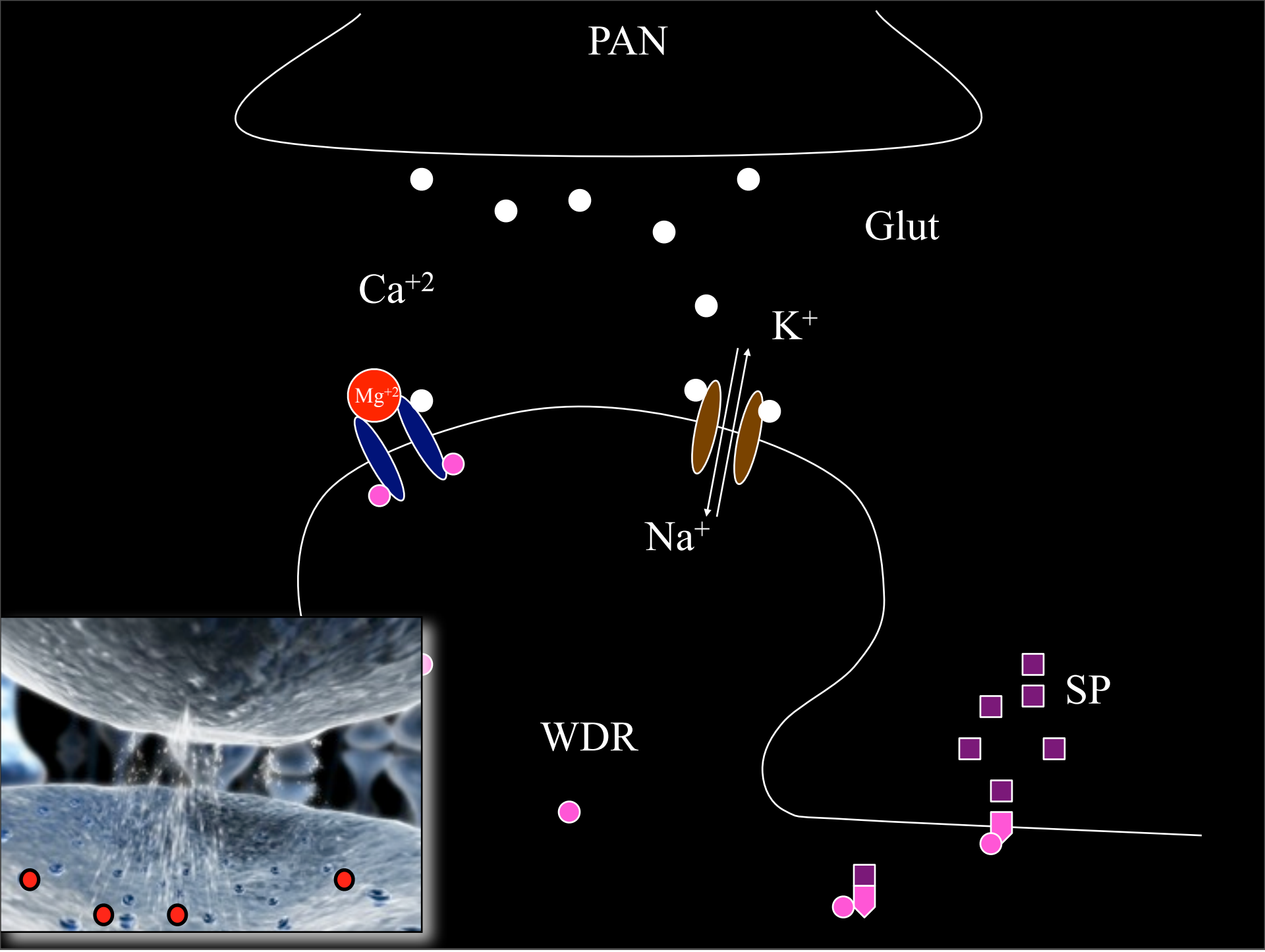

PAN
SP
Glut
Ca^{+2}
Na^{+}
Mg^{+2}
K^{+}
WDR

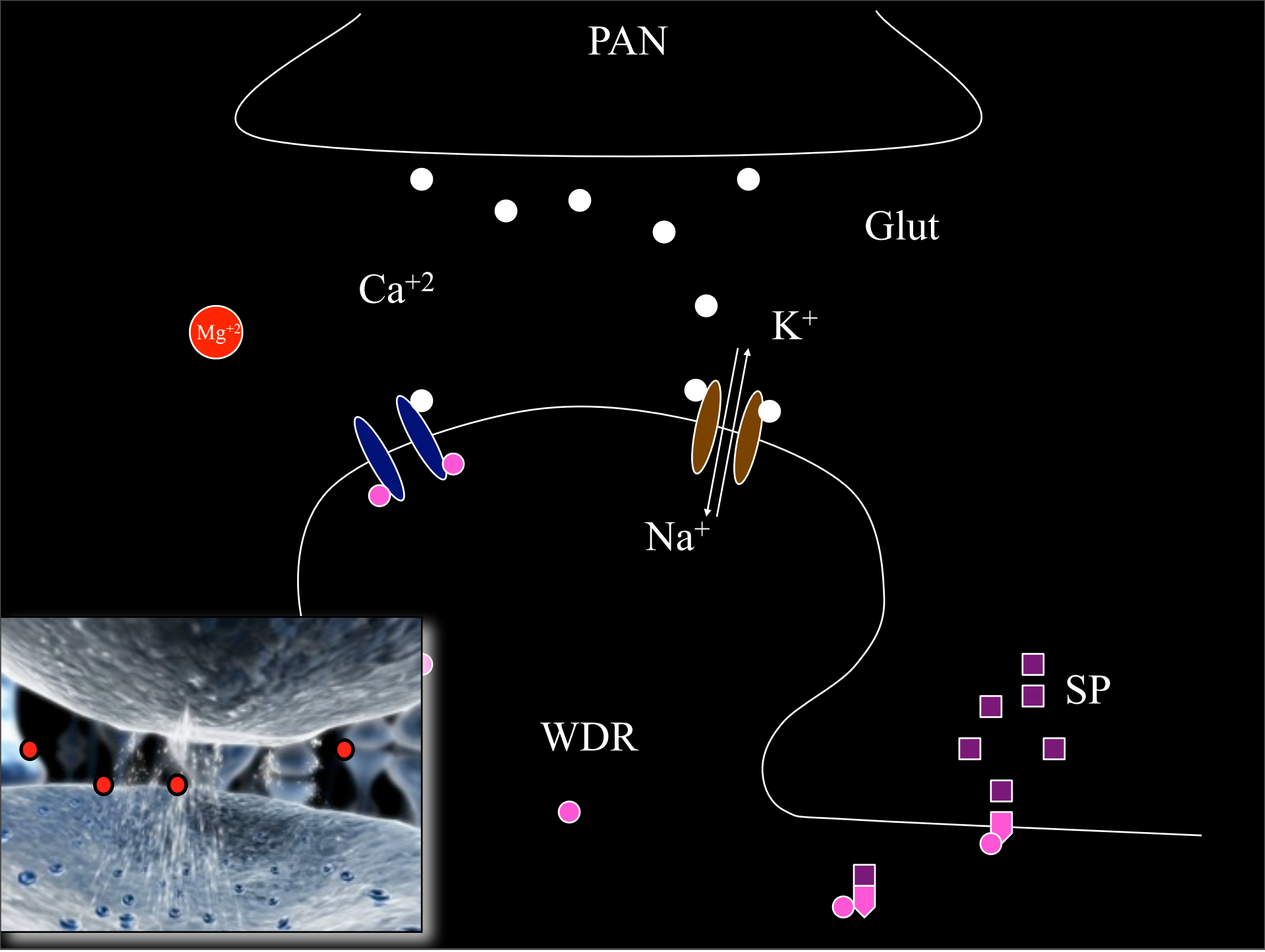

PAN
SP
Glut
Ca+2
Na+
Mg+2
K+
WDR

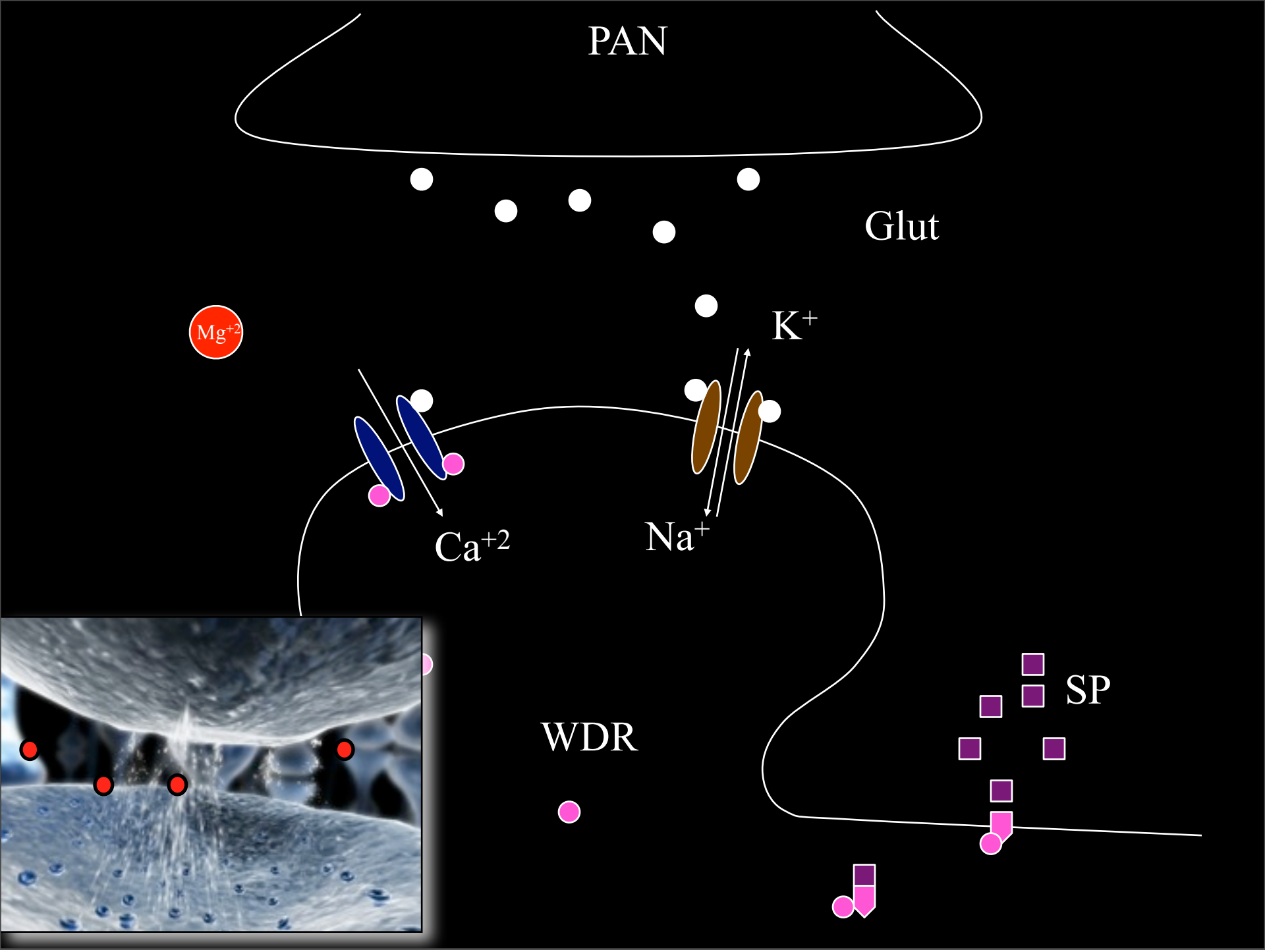

PAN
Glut
Ca+2
K+
Mg+2
Na+
SP
WDR

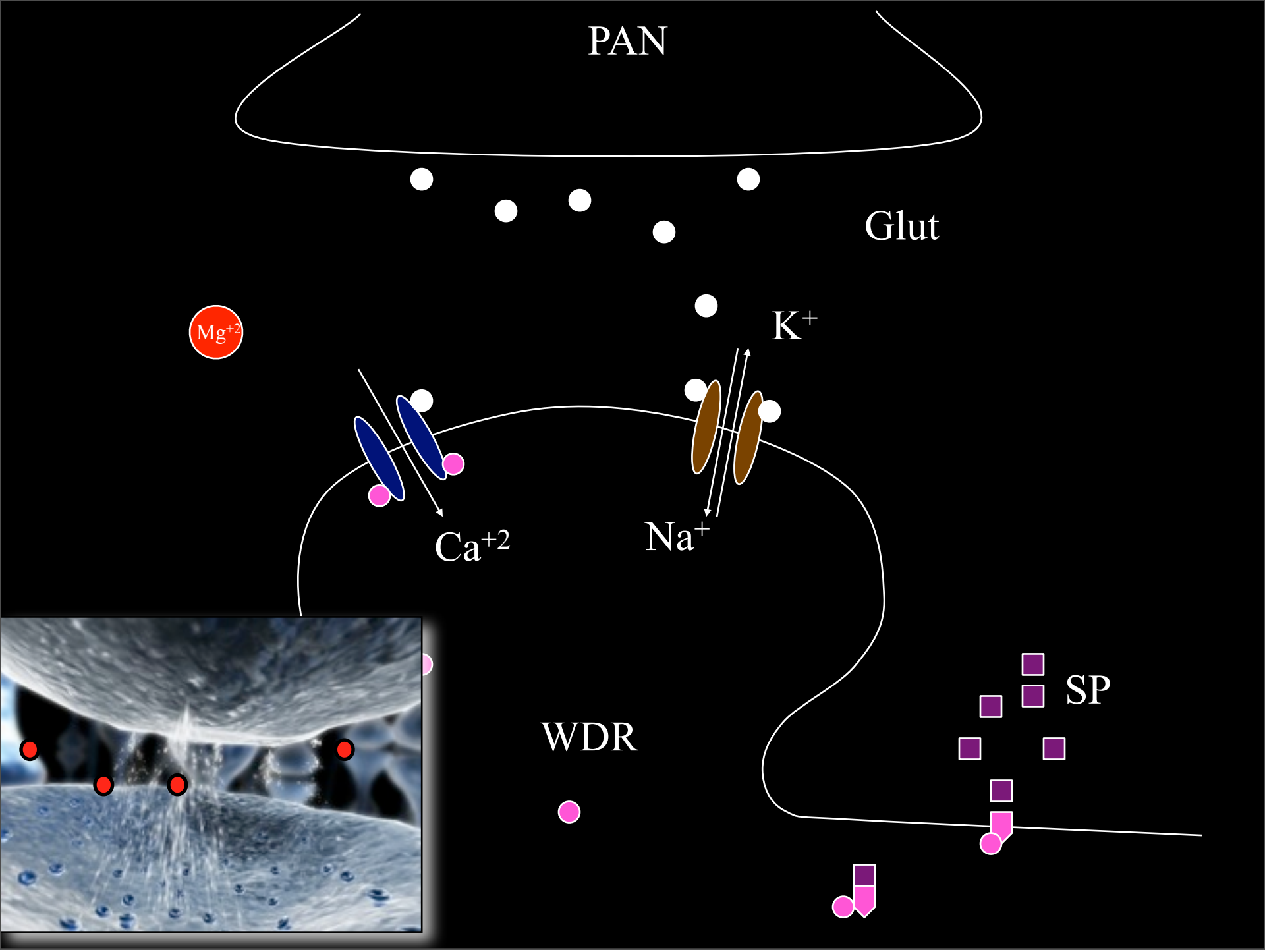

PAN
Glut
Ca+2
K+
Mg+2
Na+
WDR
SP


PAN
Glut
Ca+2
K+
Mg+2
Na+
WDR
SP


PAN
Glut
Ca+2
K+
Mg+2
Na+
WDR
SP


PAN
Glut
Ca^{+2}
Mg^{+2}
K^{+}
Na^{+}
WDR
SP

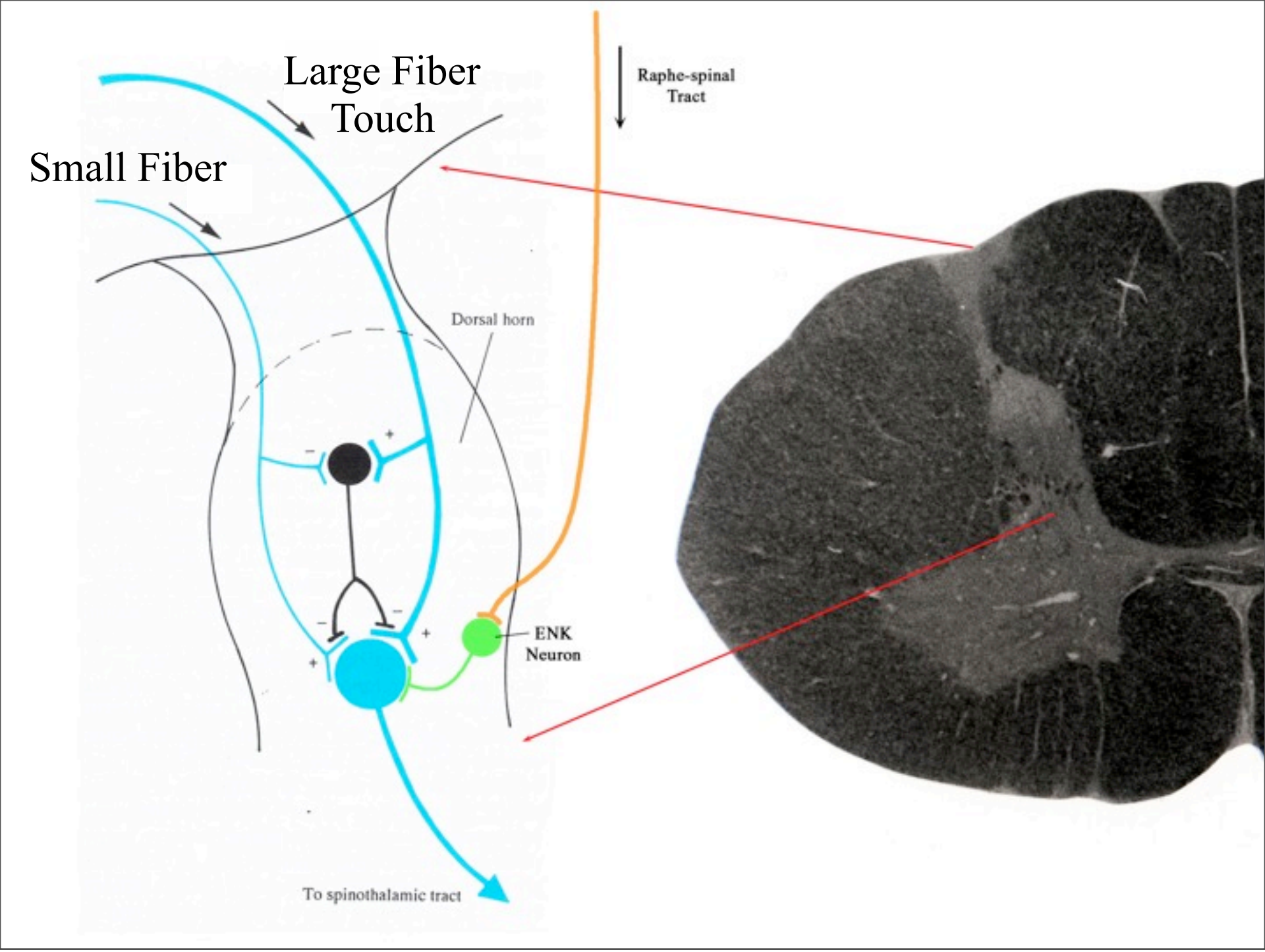

PAN
Glut
Mg^{+2}
K^{+}
Ca^{+2}
Na^{+}
WDR
SP

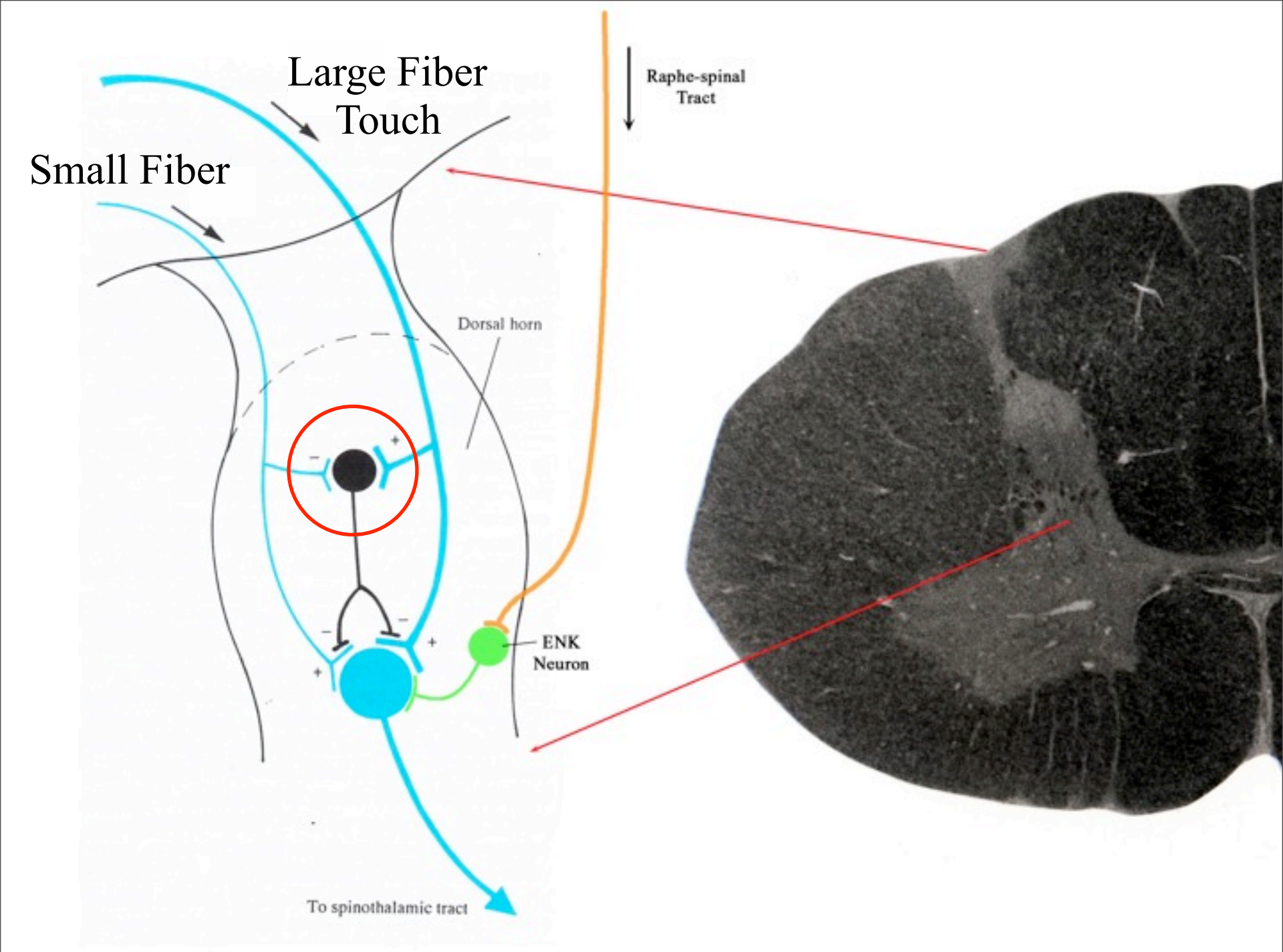

PAN
Glut
Mg^{+2}
K^{+}
Ca^{+2}
Na^{+}
WDR
SP

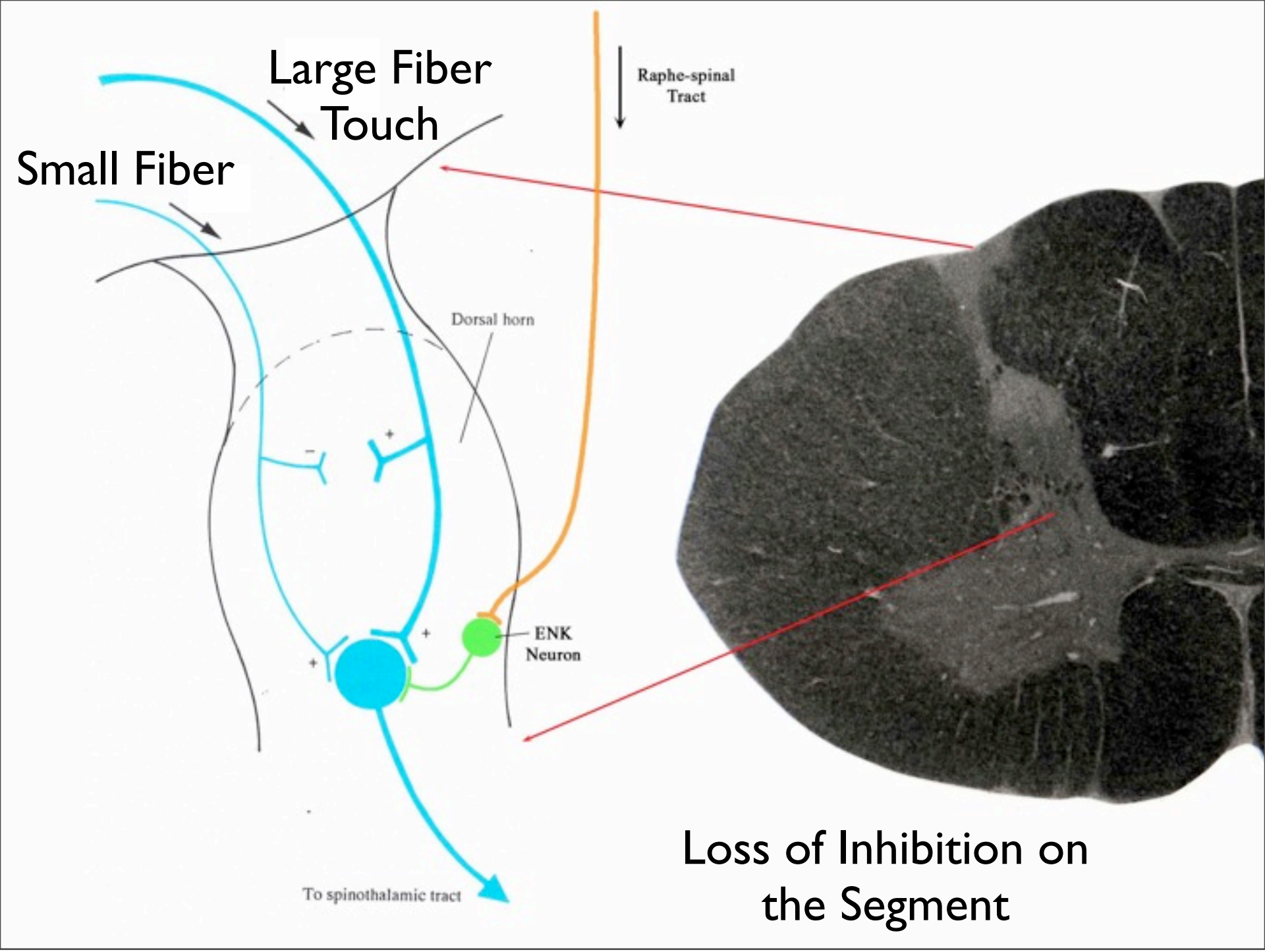
Spinal Memory System

- Transcription-independent:
  - Wind-up
  - Classic sensitization
  - Long-Term Potentiation

- Transcription-dependent:
  - New receptors
  - Membrane response enhancers


Large Fiber
Touch
Small Fiber
Raphe-spinal
Tract
Dorsal horn
ENK
Neuron
To spinothalamic tract


Large Fiber
Touch
Small Fiber
Raphe-spinal
Tract
Dorsal horn
ENK
Neuron
To spinothalamic tract



Loss of Inhibition on the Segment

Neuropeptide Actions

Neuropeptide Actions

- Triggering of second messenger cascades
  - Opening of voltage-dependent channels
  - Calcium influx

Neuropeptide Actions

- Triggering of second messenger cascades
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- Induction of immediate-early genes
  - Protein synthesis, e.g. Dynorphin

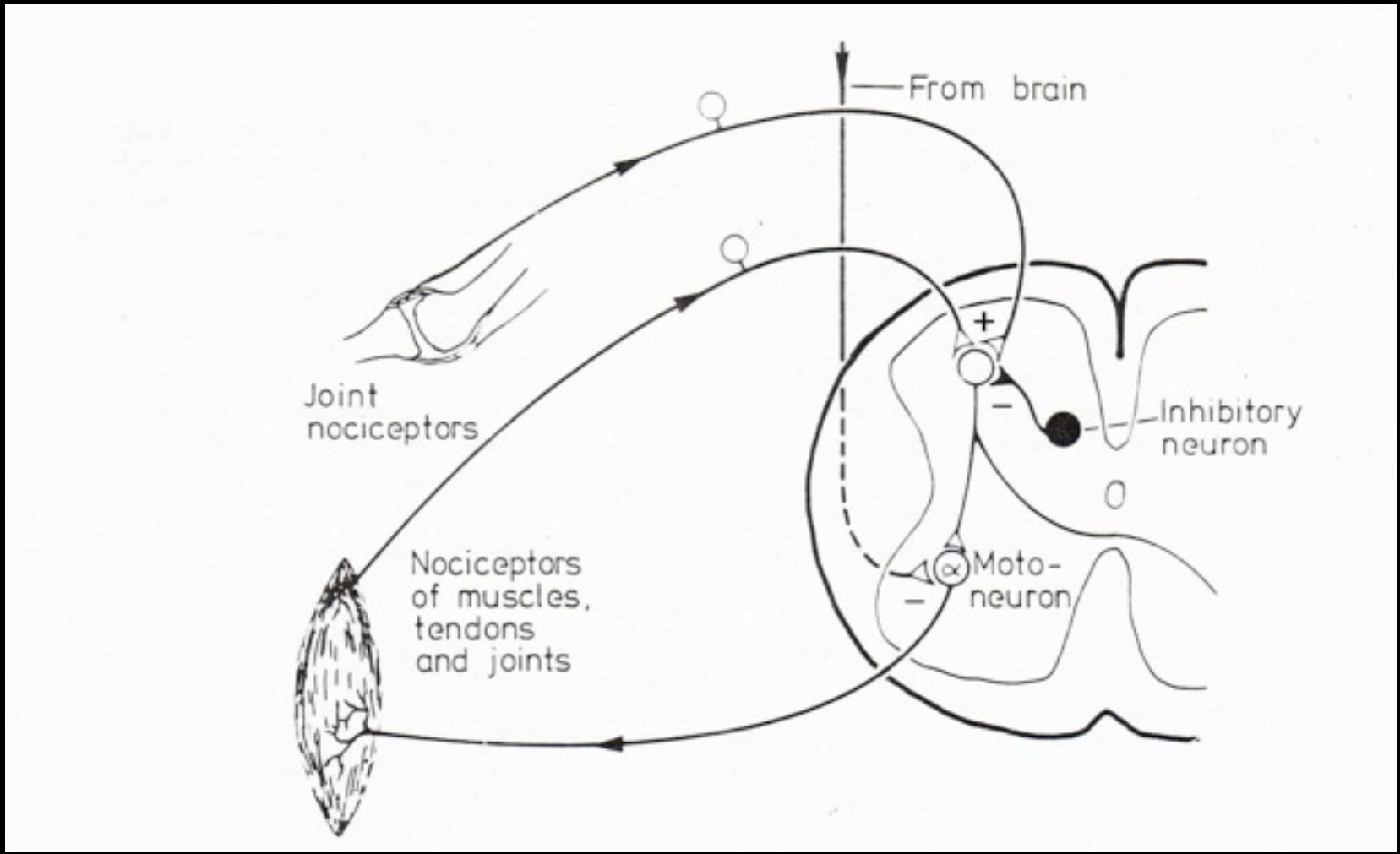
Neuropeptide Actions

- Triggering of second messenger cascades
  - Opening of voltage-dependent channels
  - Calcium influx

- Induction of immediate-early genes
  - Protein synthesis, e.g. Dynorphin

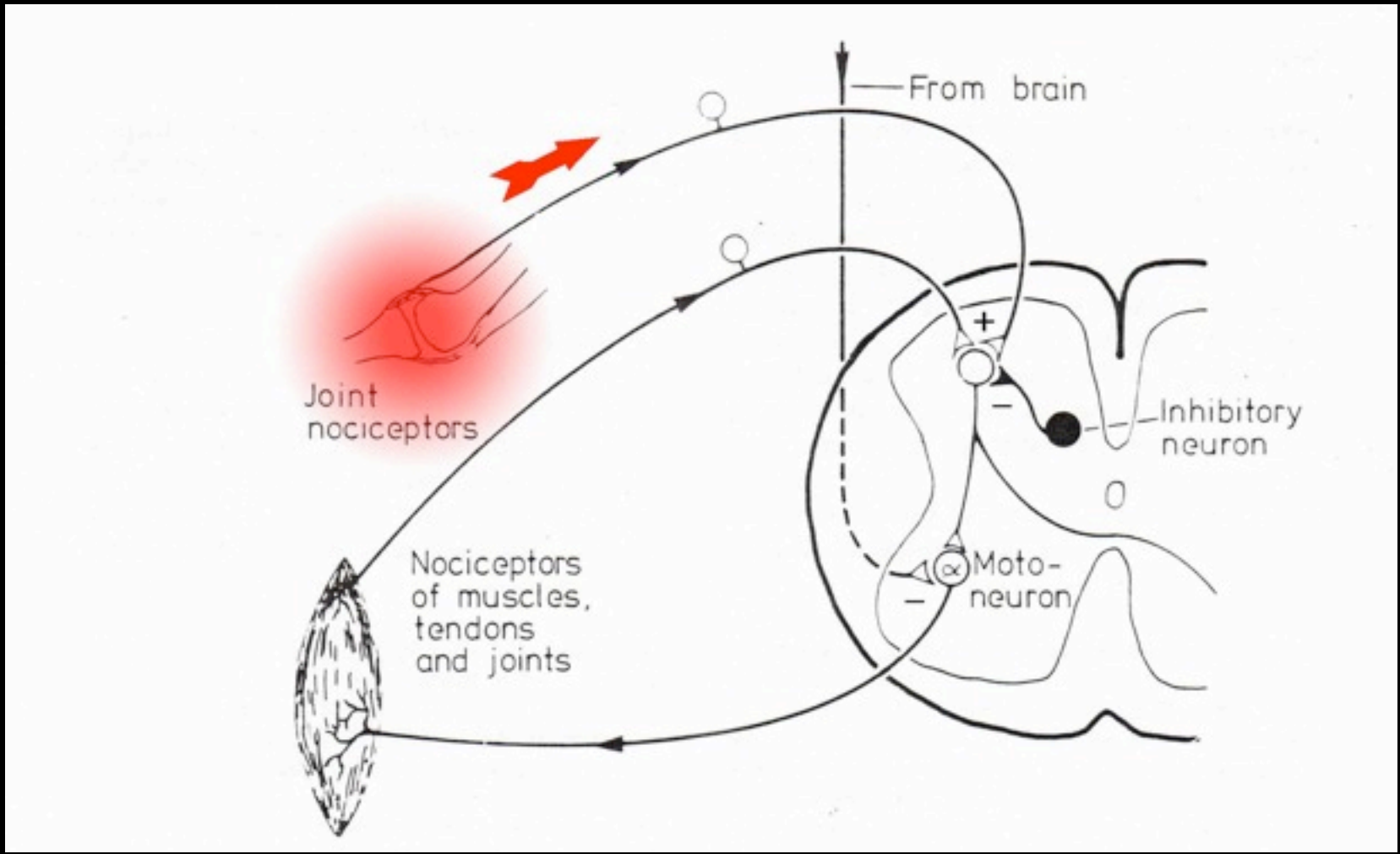
- Excitotoxicity and Cell Death
  - Apoptosis of inhibitory neurons

Spinal Facilitation



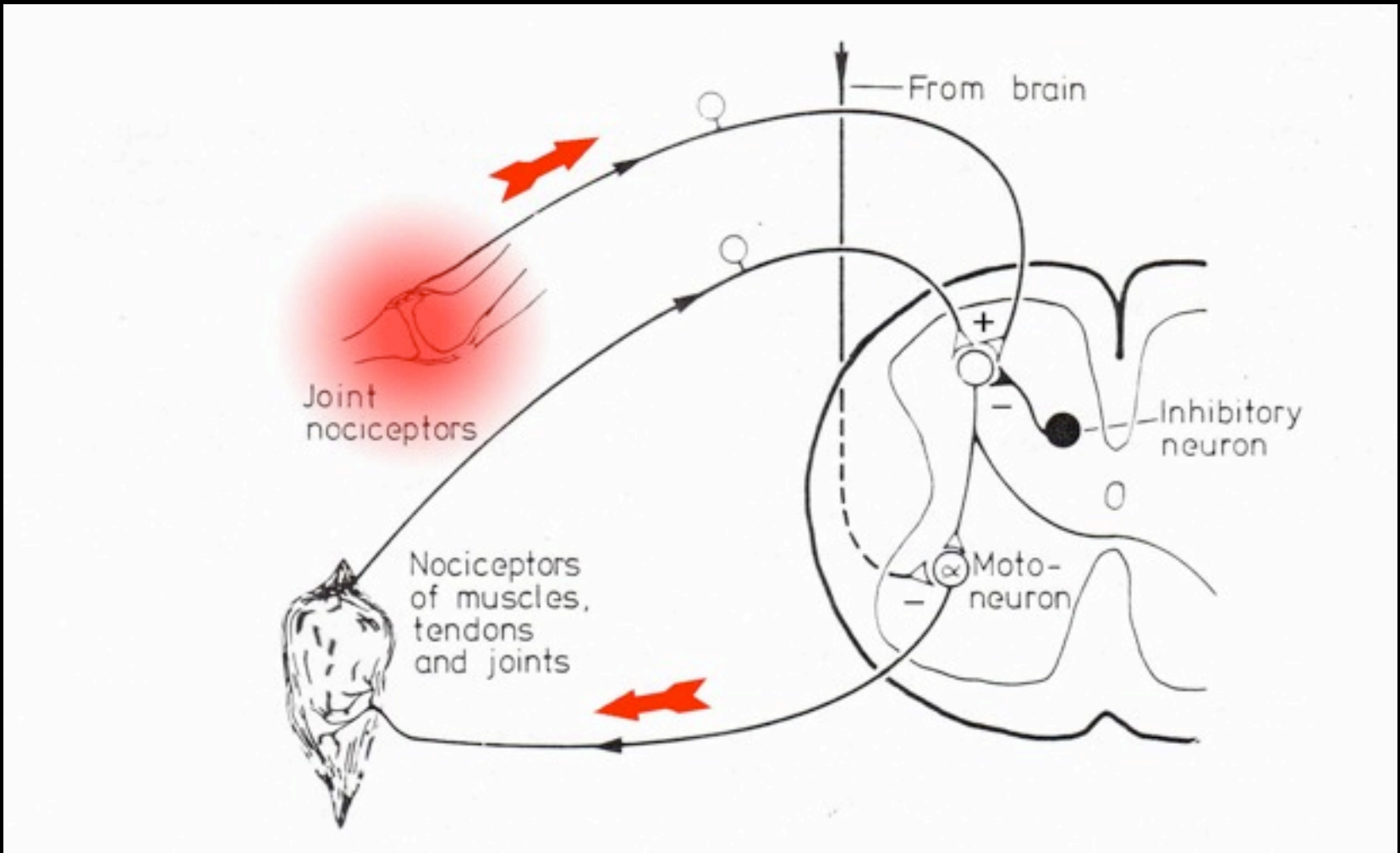
Zimmermann, Sem Arth. Rheu. 18:22, 1989

Spinal Facilitation



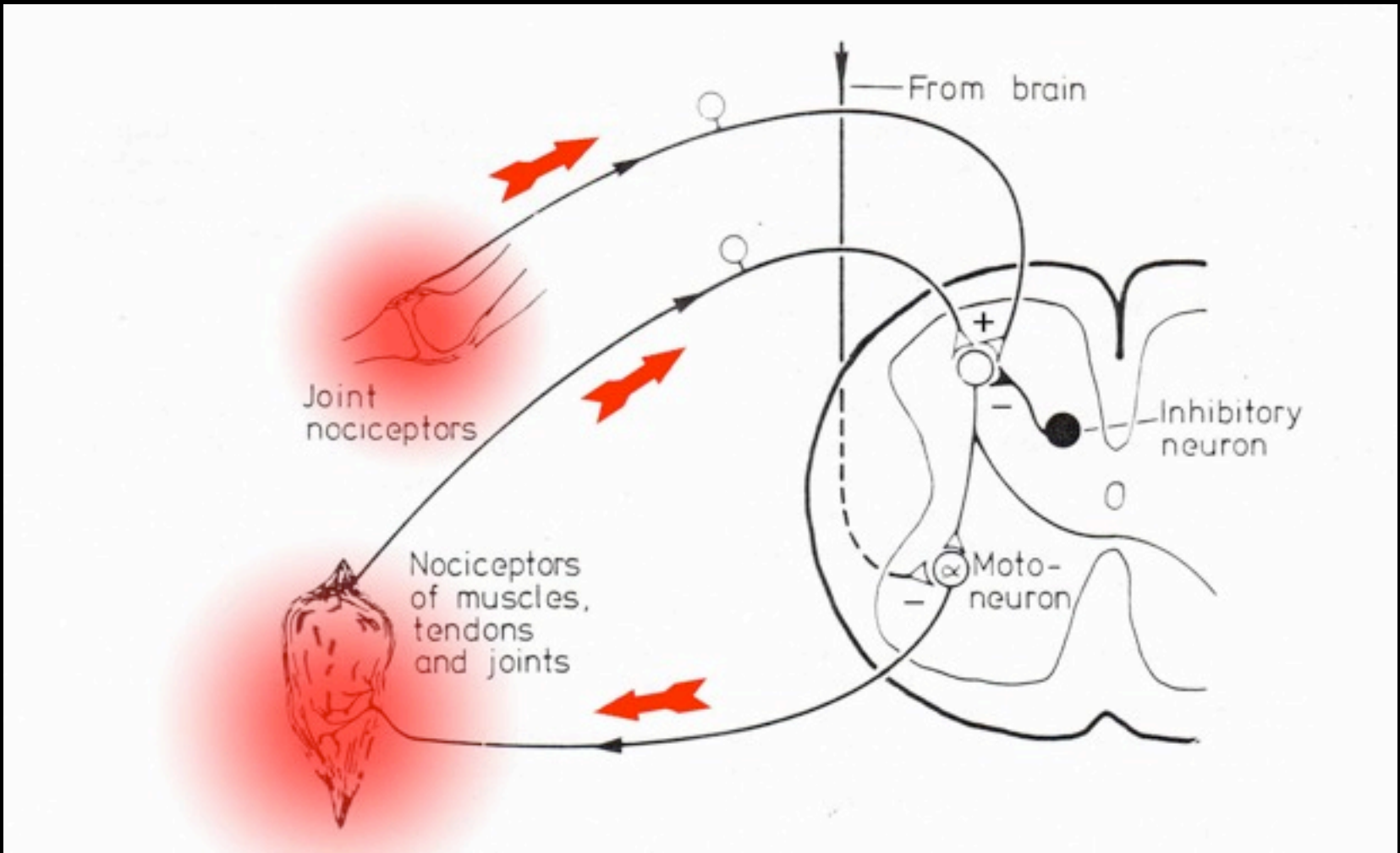
Zimmermann, Sem Arth. Rheu. 18:22, 1989

Spinal Facilitation



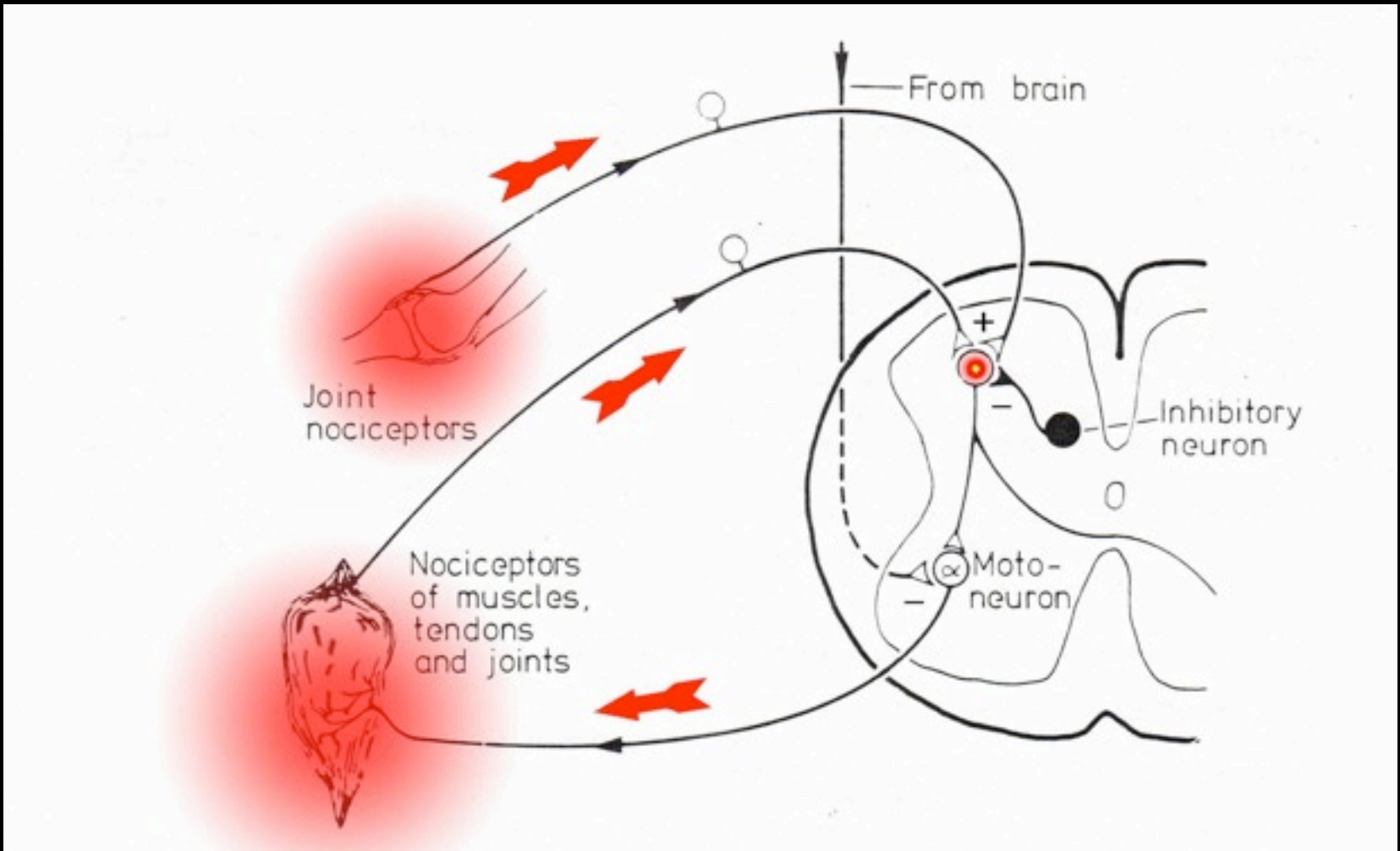
Zimmermann, Sem Arth. Rheu. 18:22, 1989

Spinal Facilitation



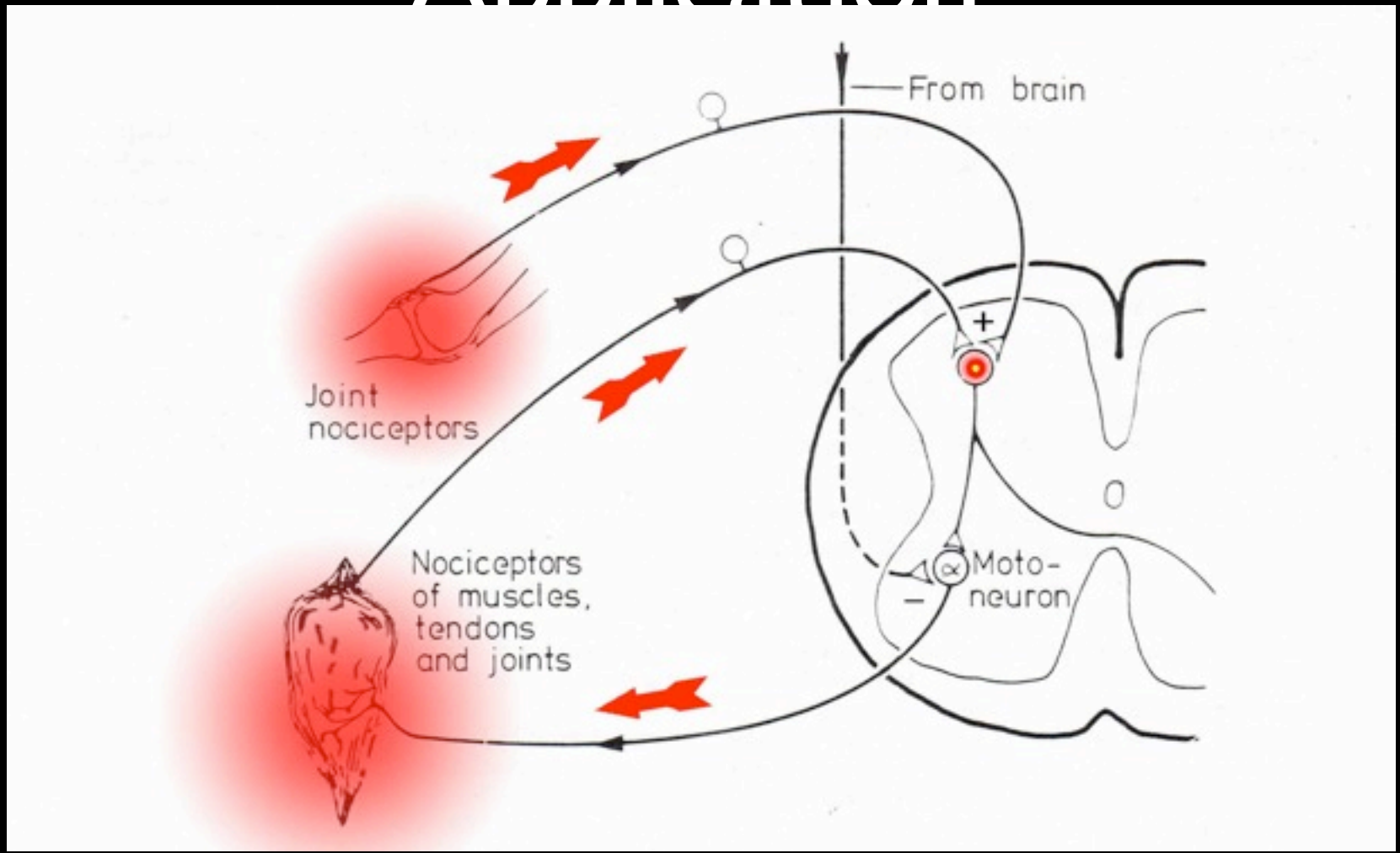
Zimmermann, Sem Arth. Rheu. 18:22, 1989

Spinal Facilitation



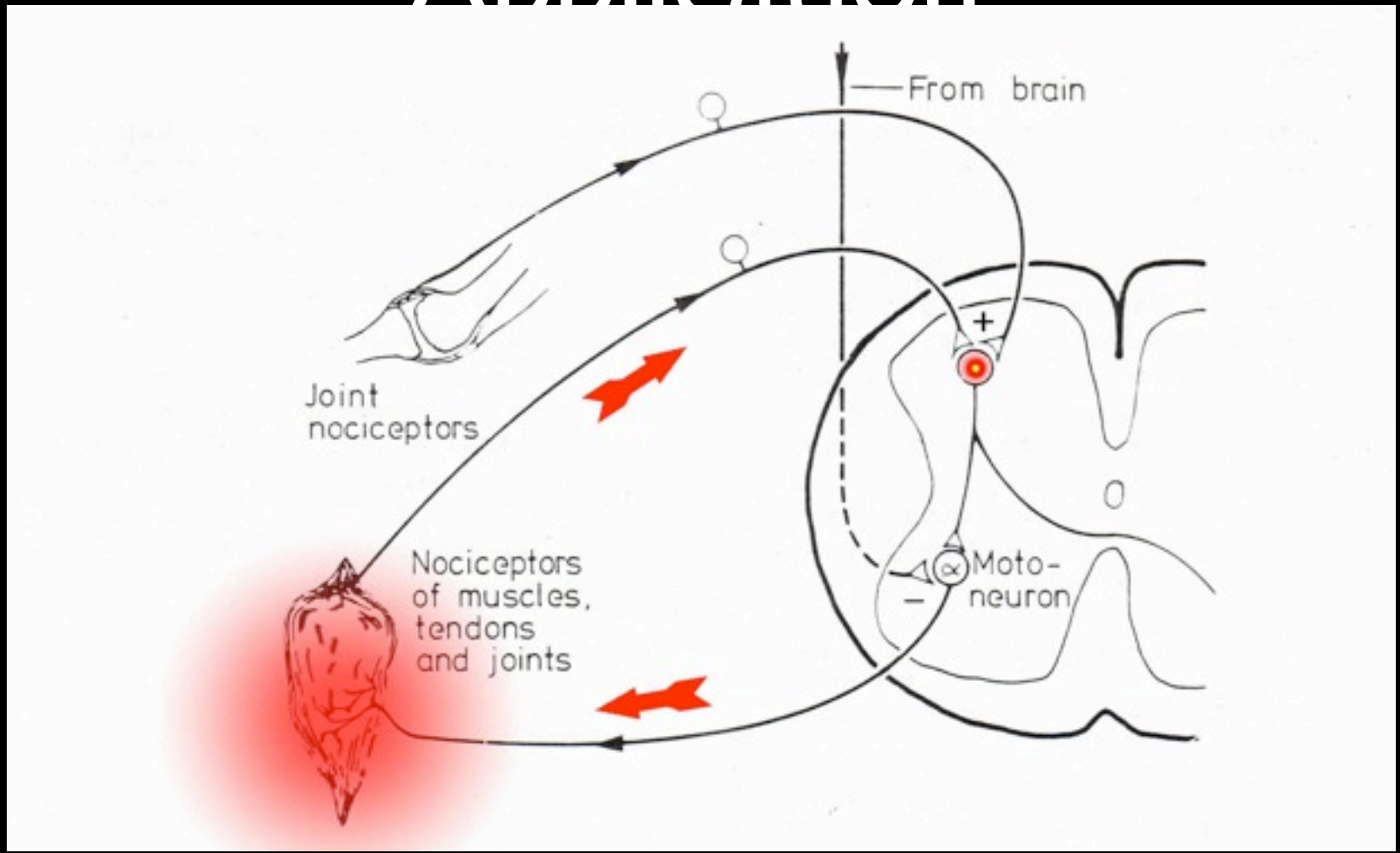
Zimmermann, Sem Arth. Rheu. 18:22, 1989

Spinal Facilitation - Application



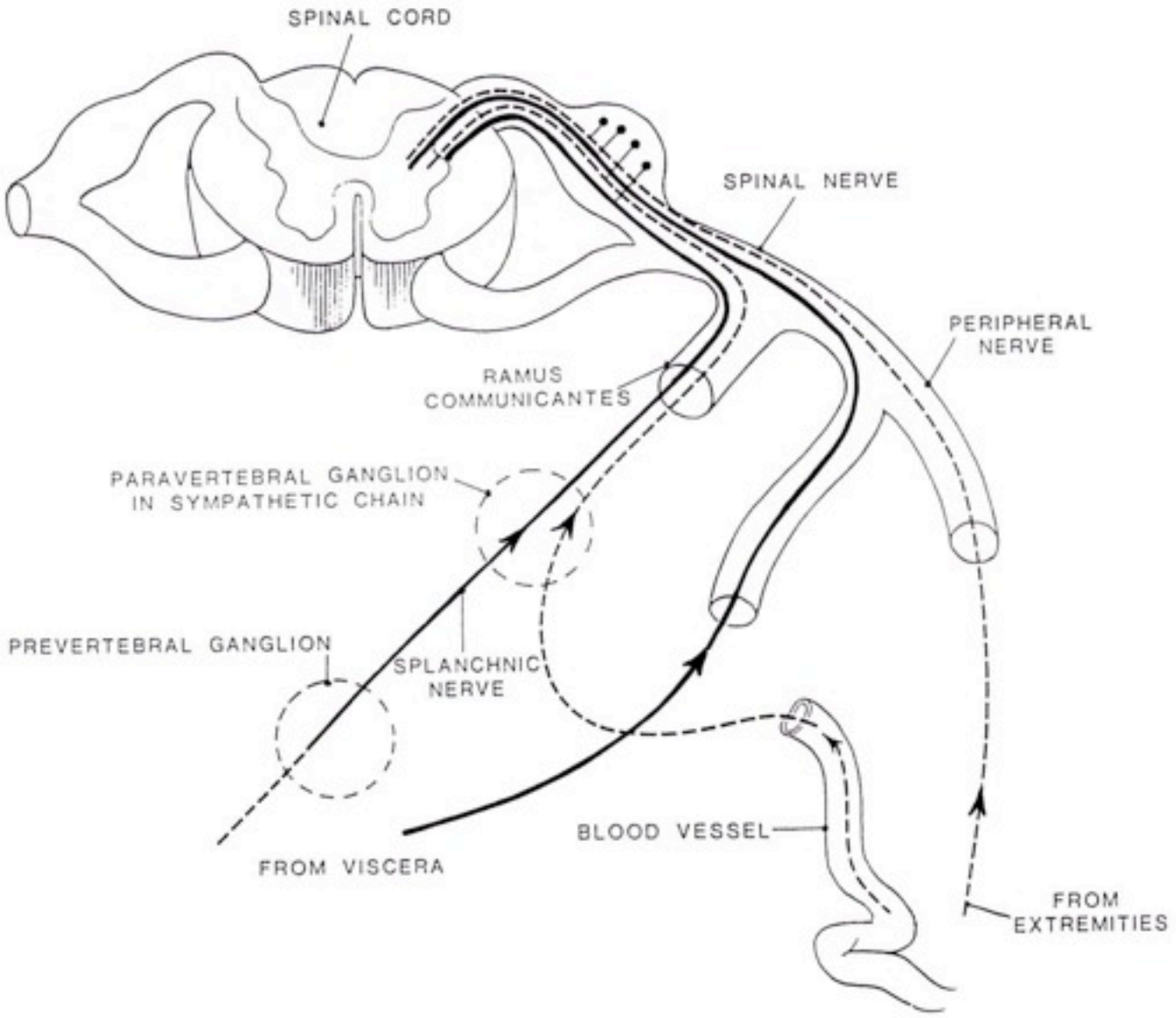
Zimmermann, Sem Arth. Rheu. 18:22, 1989

Spinal Facilitation - Application



Zimmermann, Sem Arth. Rheu. 18:22, 1989

Viscerosomatic Integration



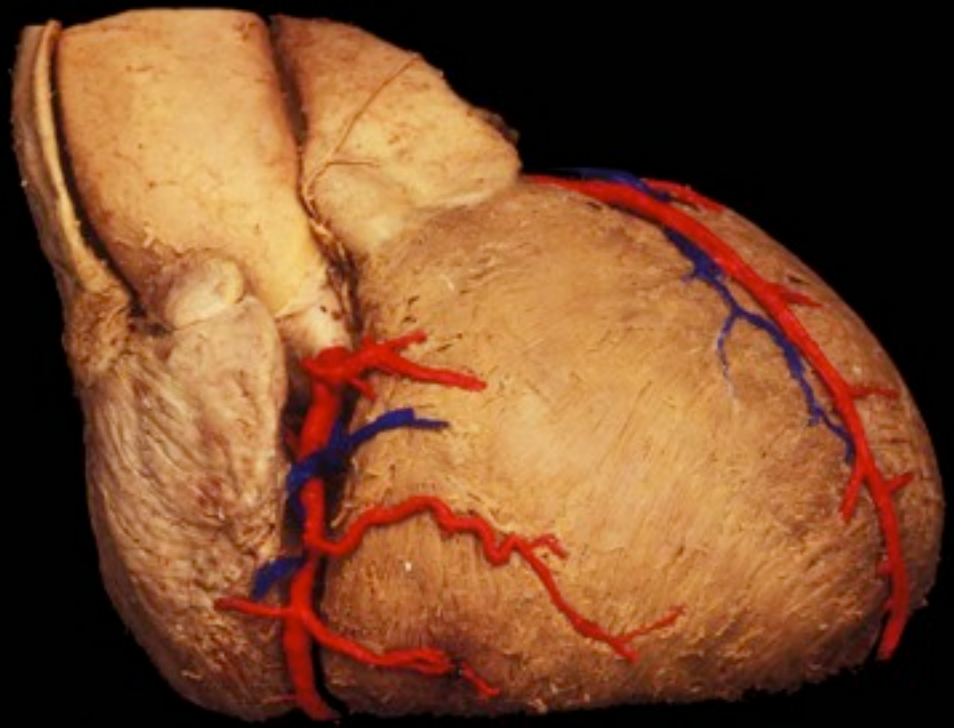
E. E. Benarroch, B. F. Westmoreland, J. R. Daube, T. J. Reagan, and B. A. Sandock. *Medical Neurosciences*, Philadelphia:Lippincott Williams & Wilkins, 1999.

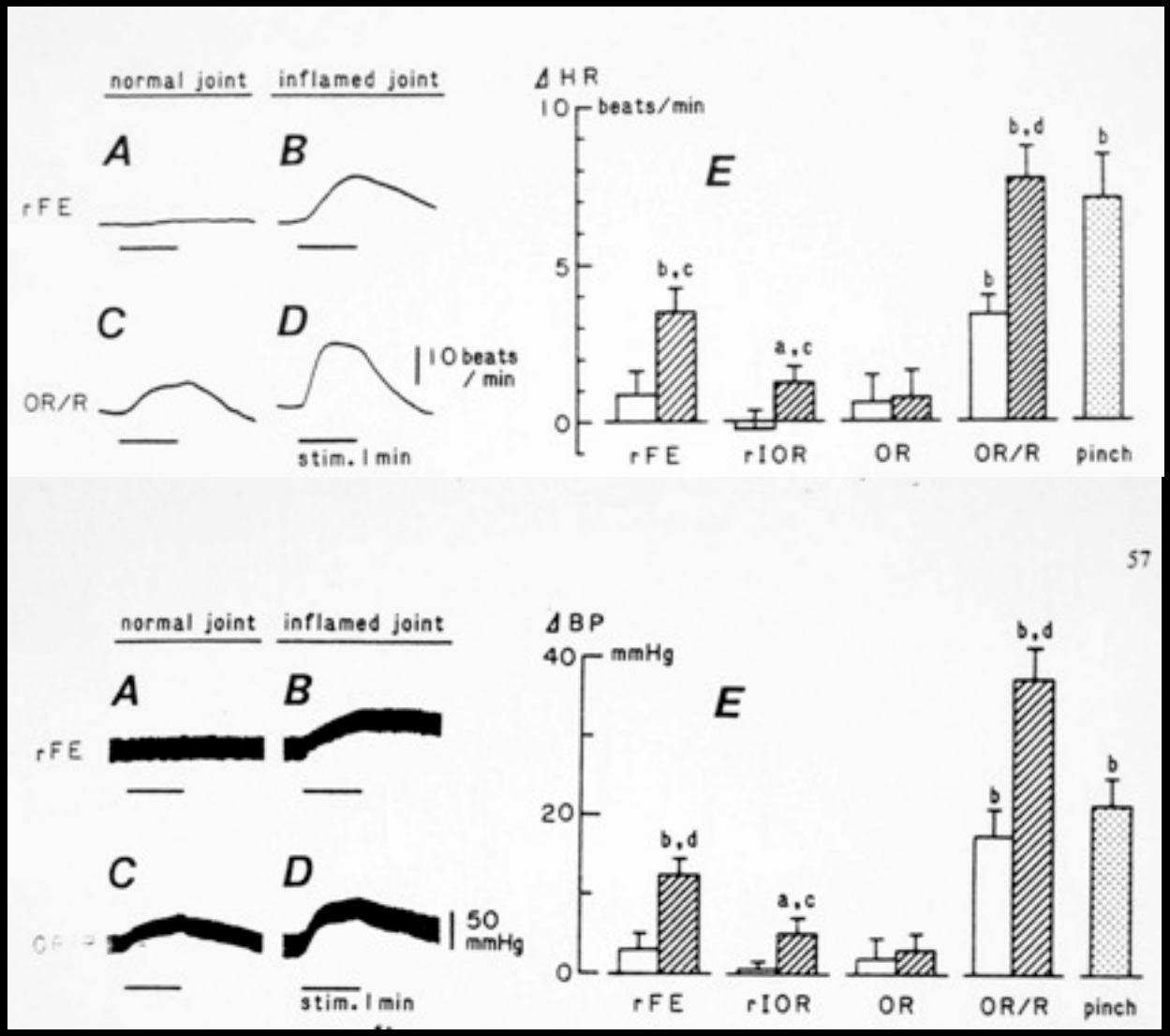
Clinical Presentation

- Viscerosomatic reflexes are **objective** findings mediated through the spinal cord.
- Referred pain is a **subjective** complaint representing nociceptive mapping in the spinal cord, thalamus, or cortex.

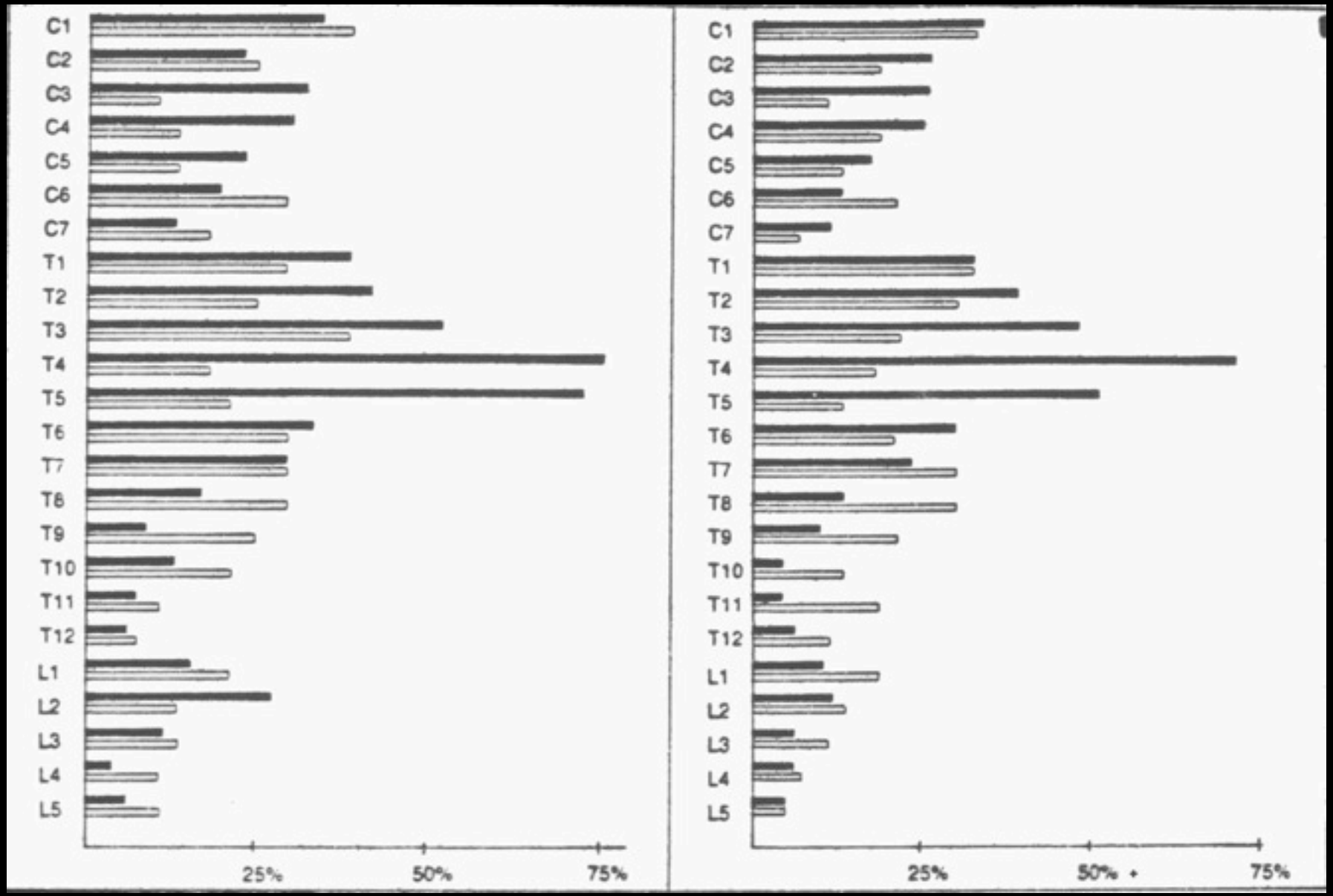
Somatocardiac Reflex

- Nociceptive somatic stimuli
- Elevation of heart rate and blood pressure

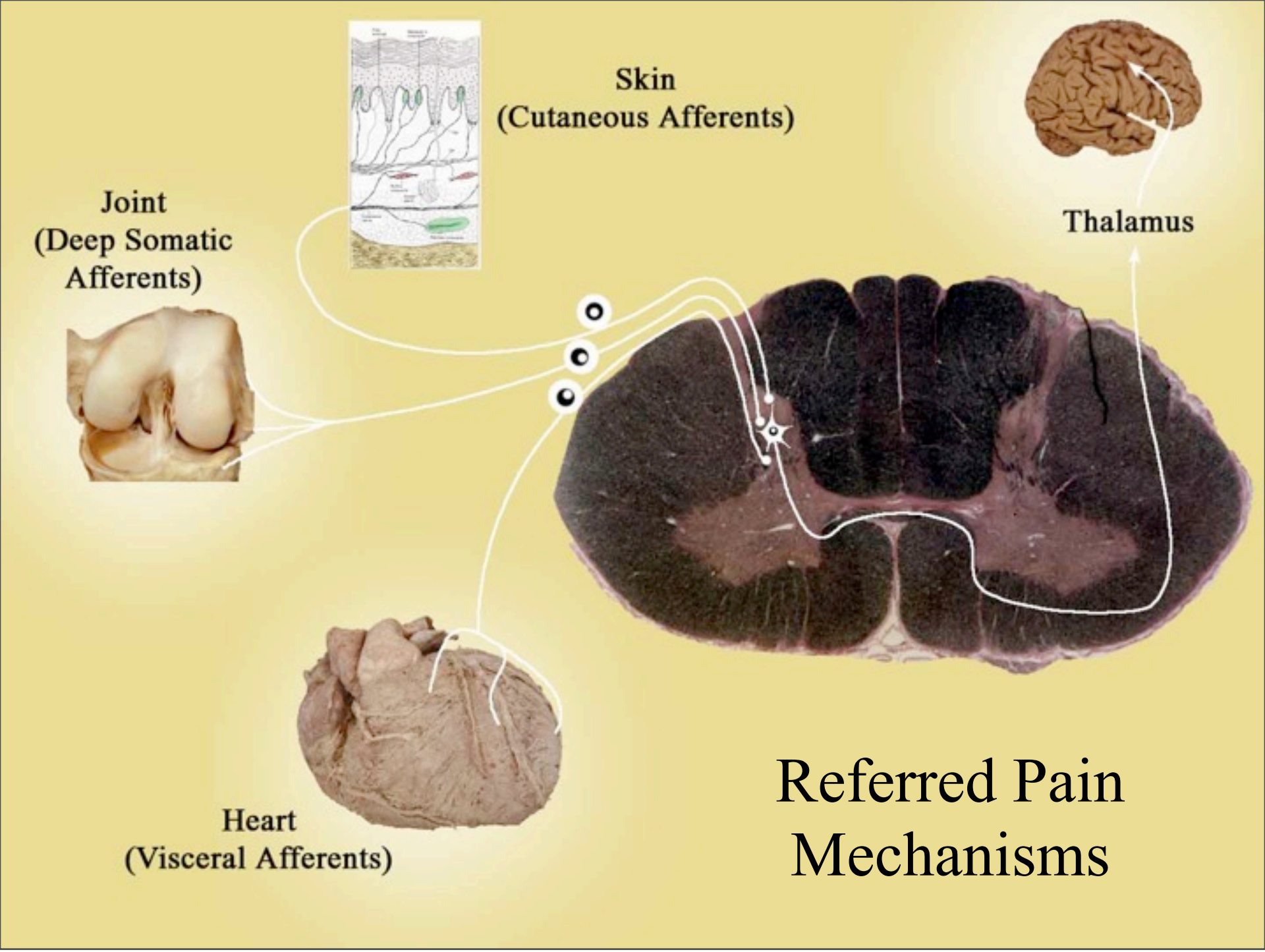




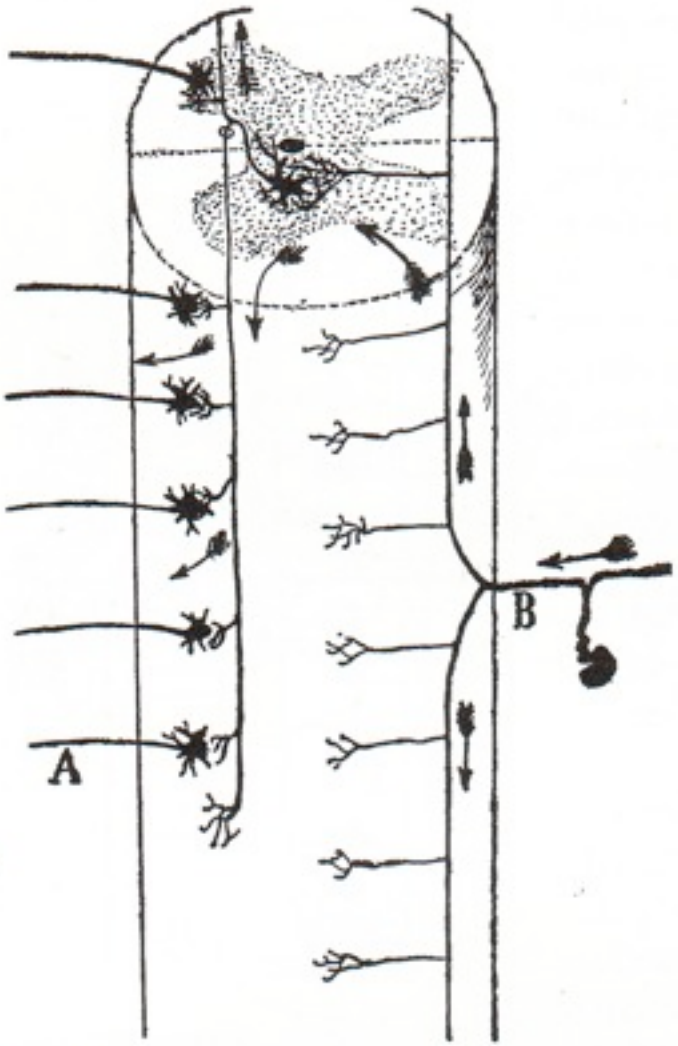
A. Sato, Y. Sato, and R. F. Schmidt. Changes in blood pressure and heart rate induced by movements of normal and inflamed knee joints. *Neurosci.Lett.* 52:55-60, 1984



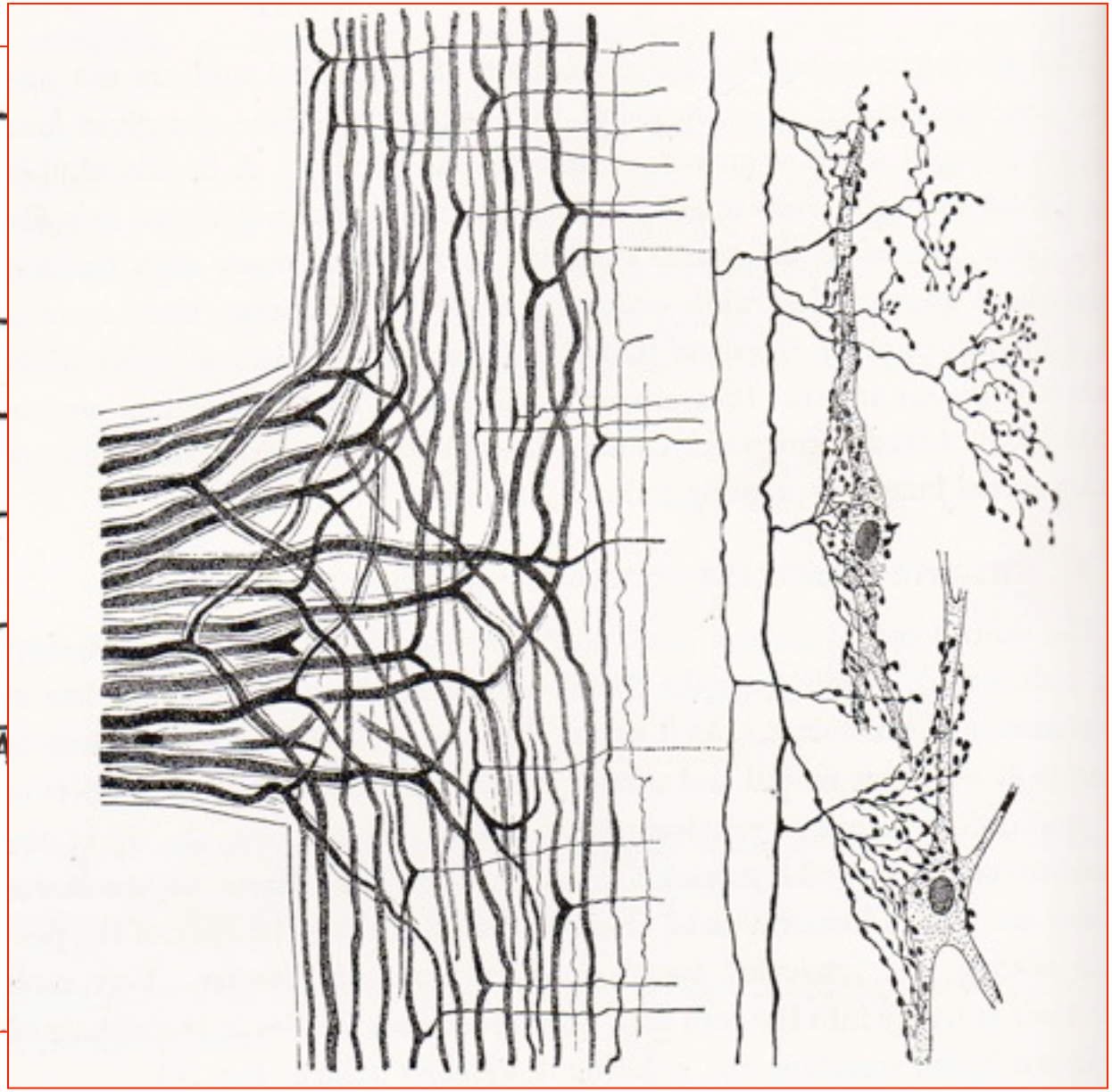
J. M. Cox, S. Gorbis, L. M. Dick, J. C. Rogers, and F. J. Rogers. Palpable musculoskeletal findings in coronary artery disease: results of a double-blind study. *J.A.O.A.* 82:832-836, 1983

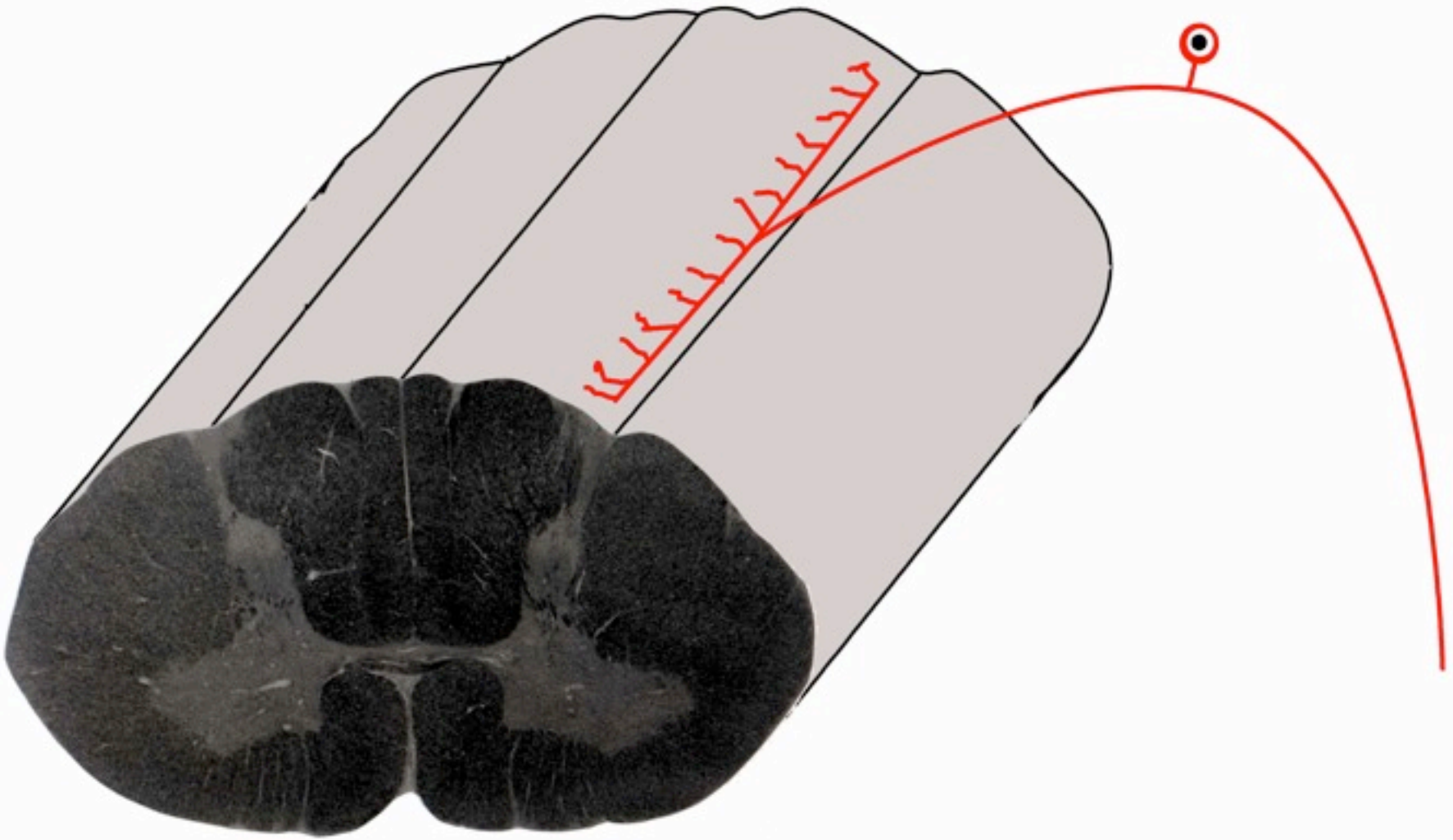

Skin
(Cutaneous Afferents)
Thalamus
Joint
(Deep Somatic
Afferents)
Heart
(Visceral Afferents)
Referred Pain
Mechanisms

Primary
Afferent
Branching



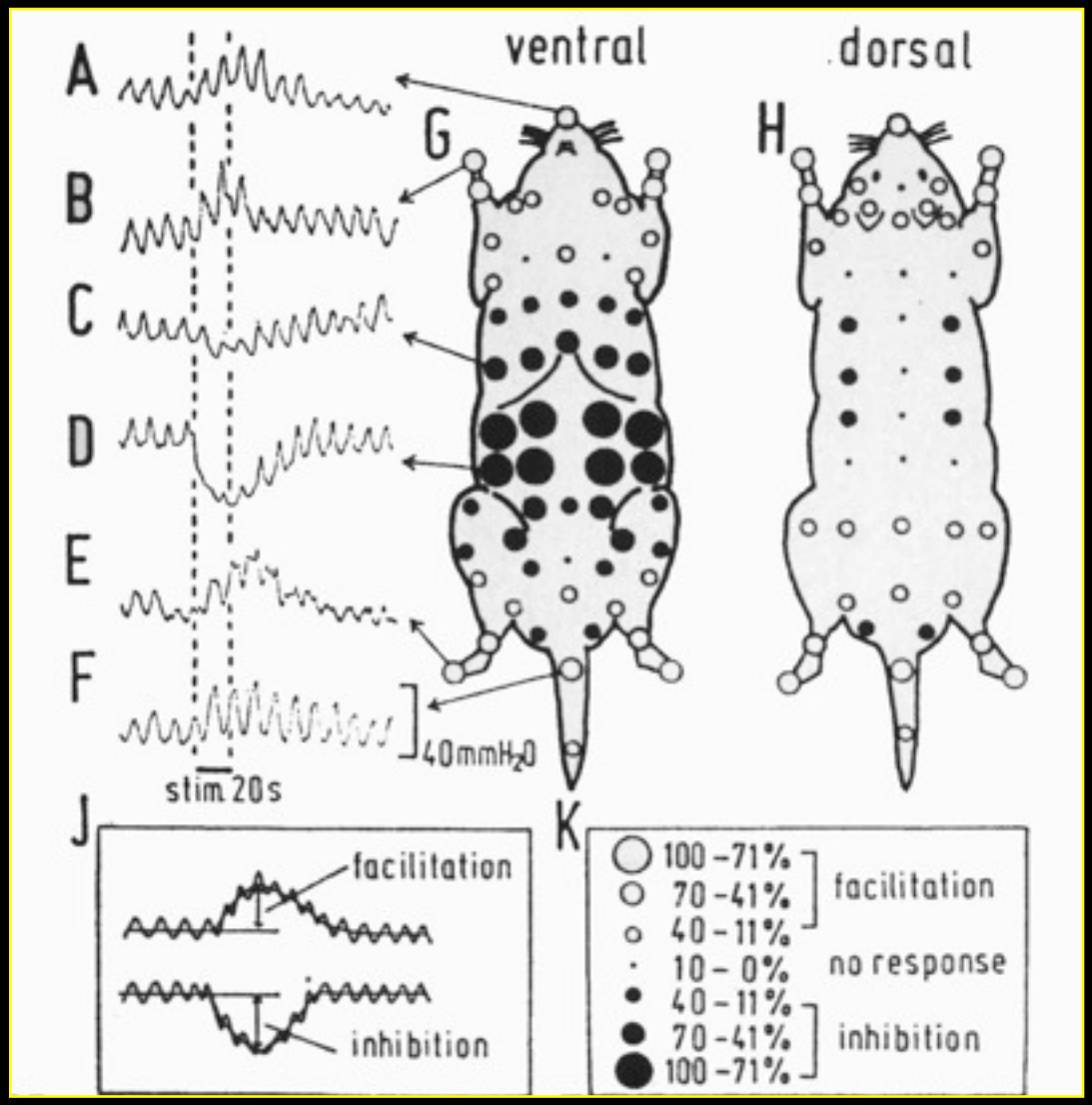
Primary
Afferent
Branching





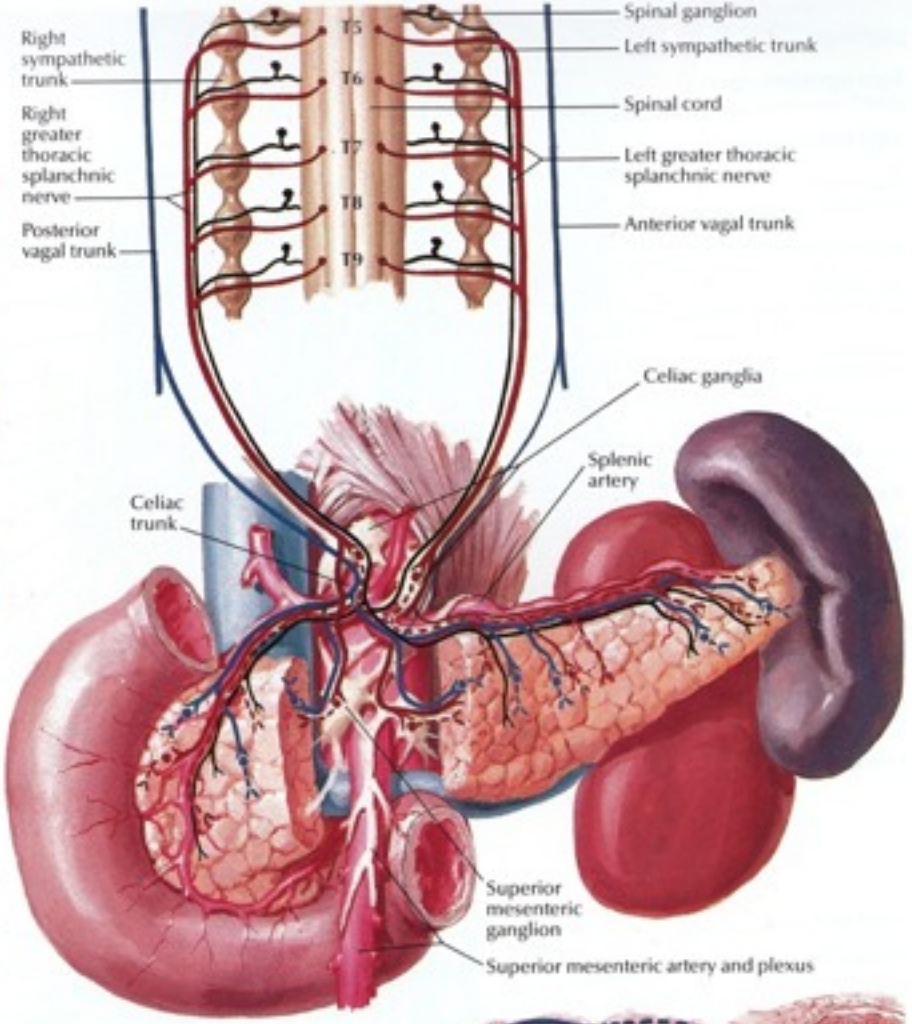
Somatogastric Reflex

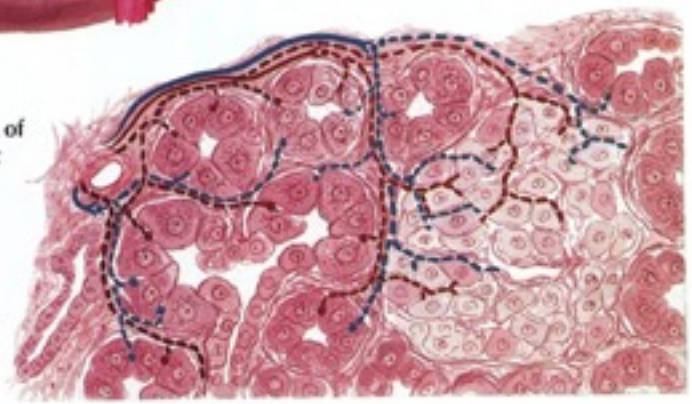
- Nociceptive somatic stimuli
- Inhibition of peristalsis in the stomach



Y. Aihara, H. Nakamura, A. Sato, and A. Simpson. Neural control of gastric motility with special reference to cutaneo-gastric reflexes. In: *Integrative functions of the Autonomic Nervous System*, edited by C. Brooks, New York:Elsevier, 1979, p. 38-49.

Common areas of pancreatic pain





Schema of intrinsic nerve supply

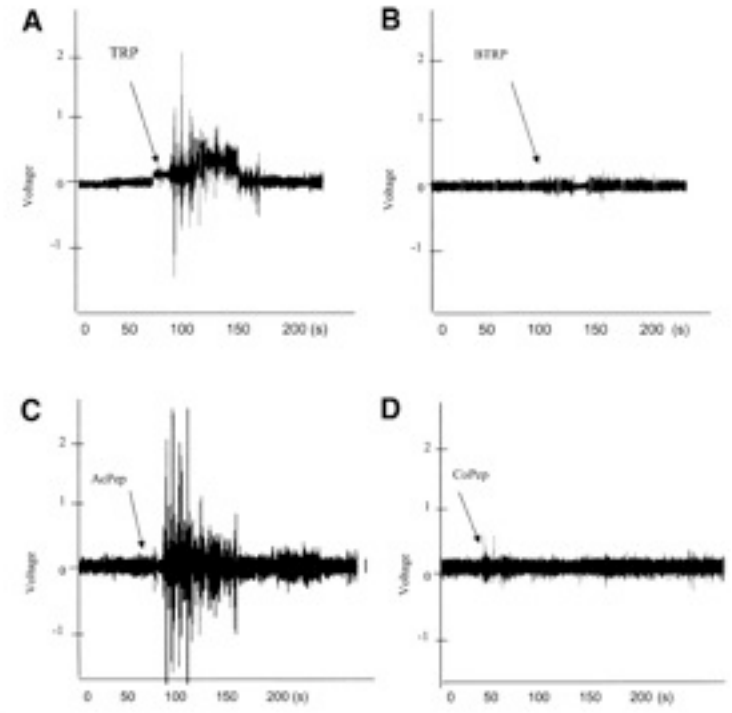
Sympathetic fibers
- Preganglionic
- Postganglionic

Parasympathetic fibers
- Preganglionic
- Postganglionic

Afferent fibers

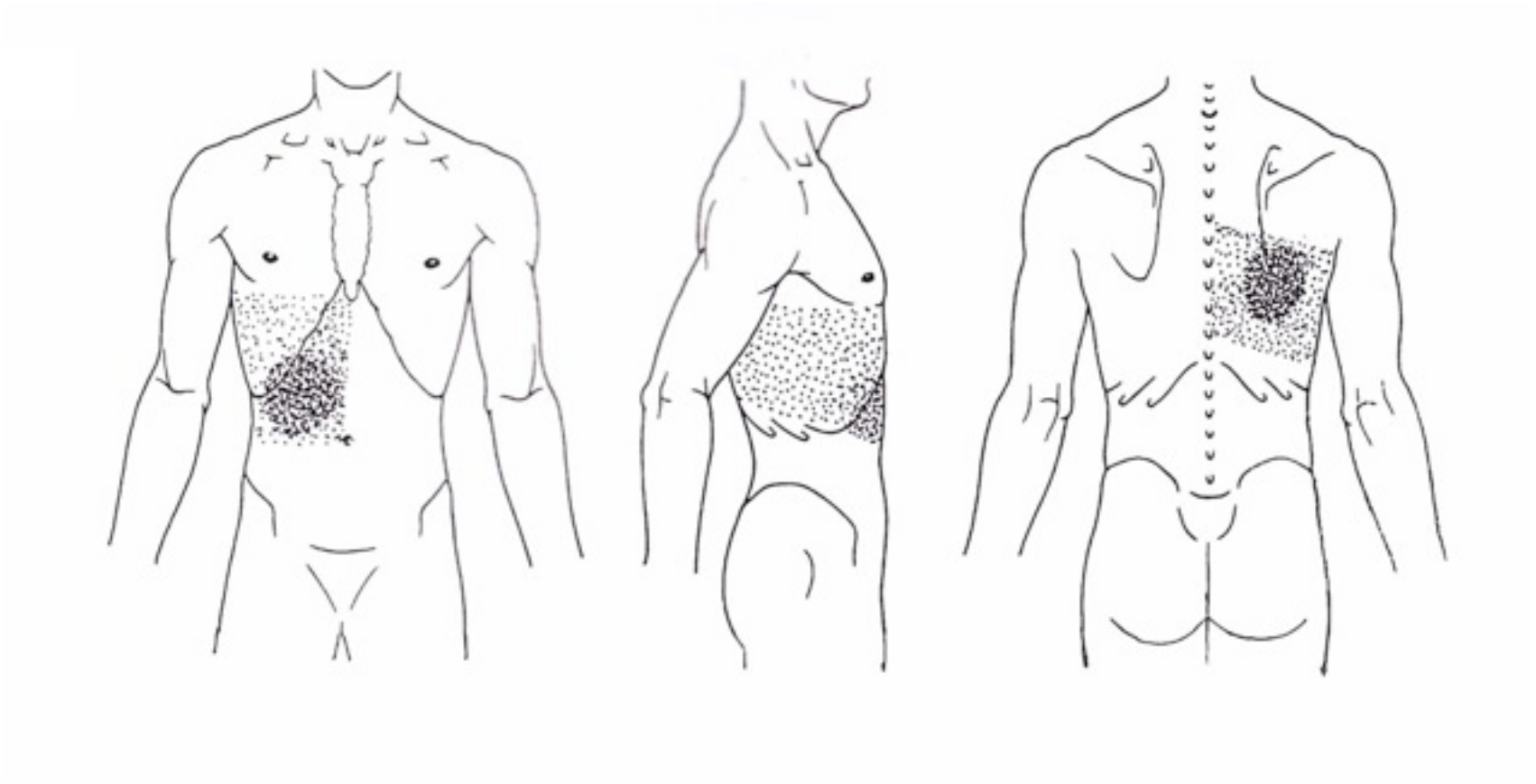
Pancreaticosomatic Reflexes

- Stimulation of the pancreatic duct with trypsin
- Enhance EMG activity in the acromiotrapezius muscle of the back



Hoogerwerf *et al*,. Trypsin mediates nociception via the proteinase-activated receptor 2: a potentially novel role in pancreatic pain. *Gastroenterol.* 127 (3): 883-891, 2004.

Referred Gall Bladder Pain

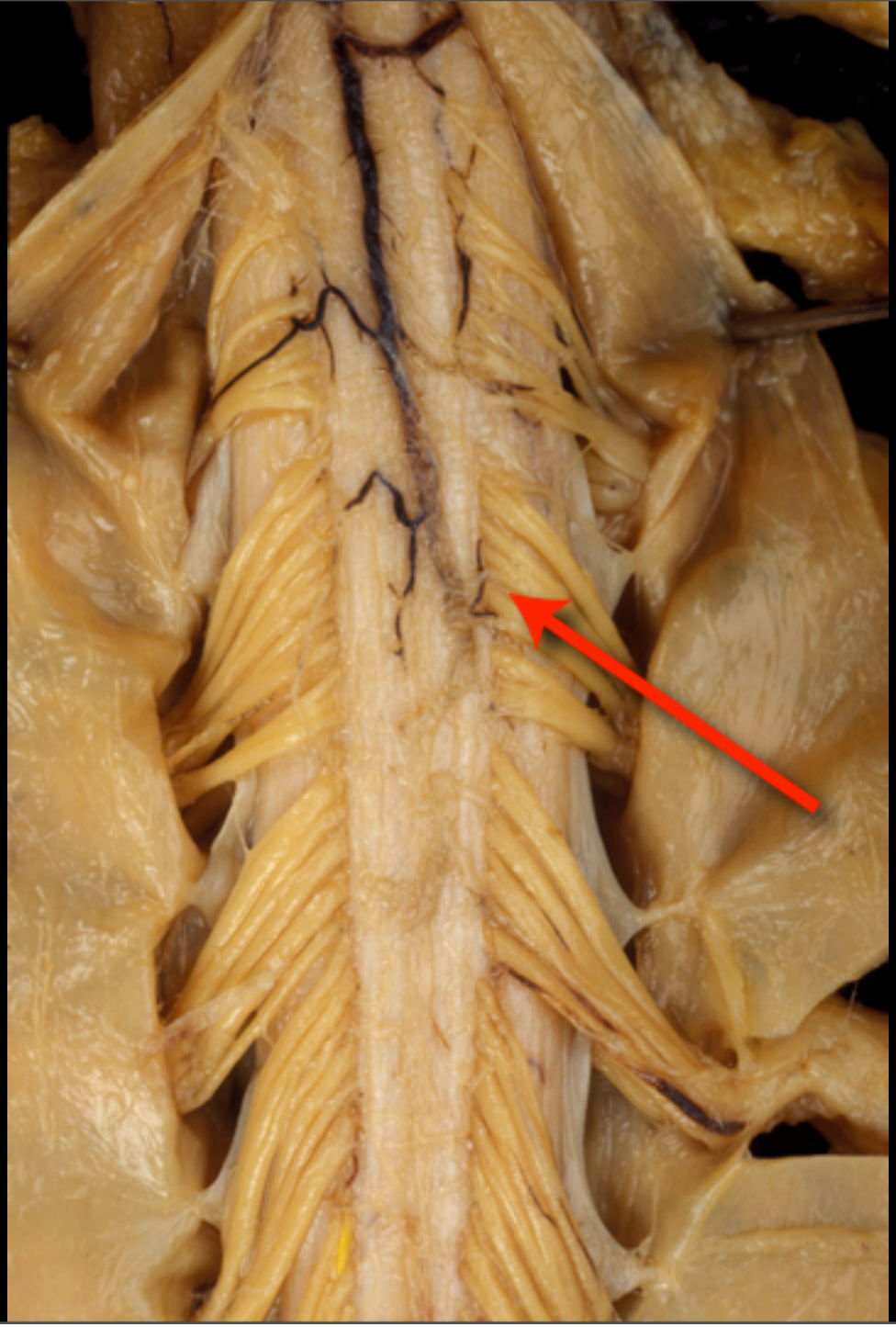


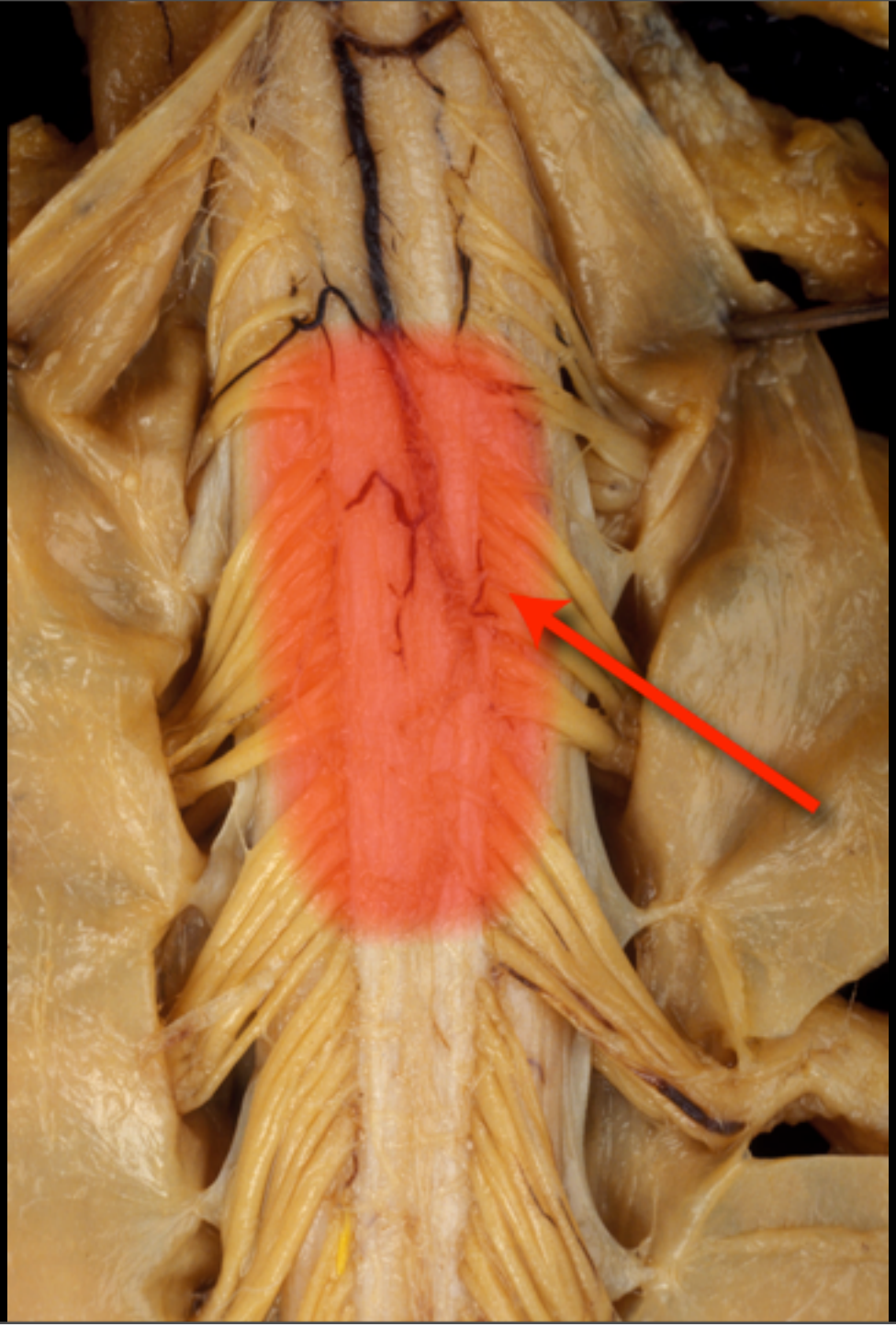
M. A. Giamberardino, G. Affaitati, and R. Costantini. Referred pain from internal organs. *Hdbk Clin.Neurol.* 81 (3rd Series):343-361, 2006

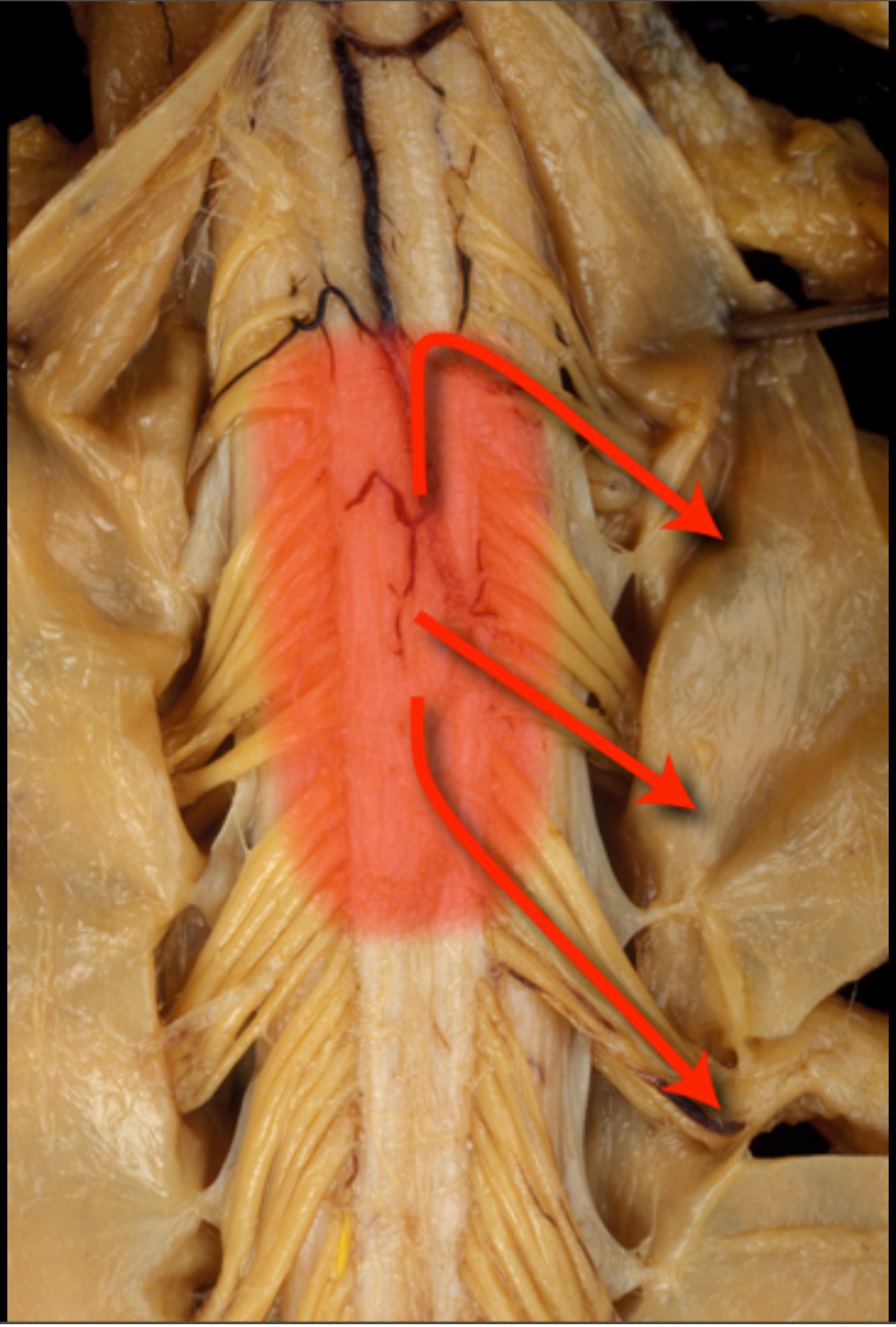
Trophic Changes

- Increased thickness of the subcutaneous tissue
  - Firmness not related to edema
- Decreased thickness in the associated muscle layers
  - Muscle atrophy
- Degree of change related to duration of painful episodes

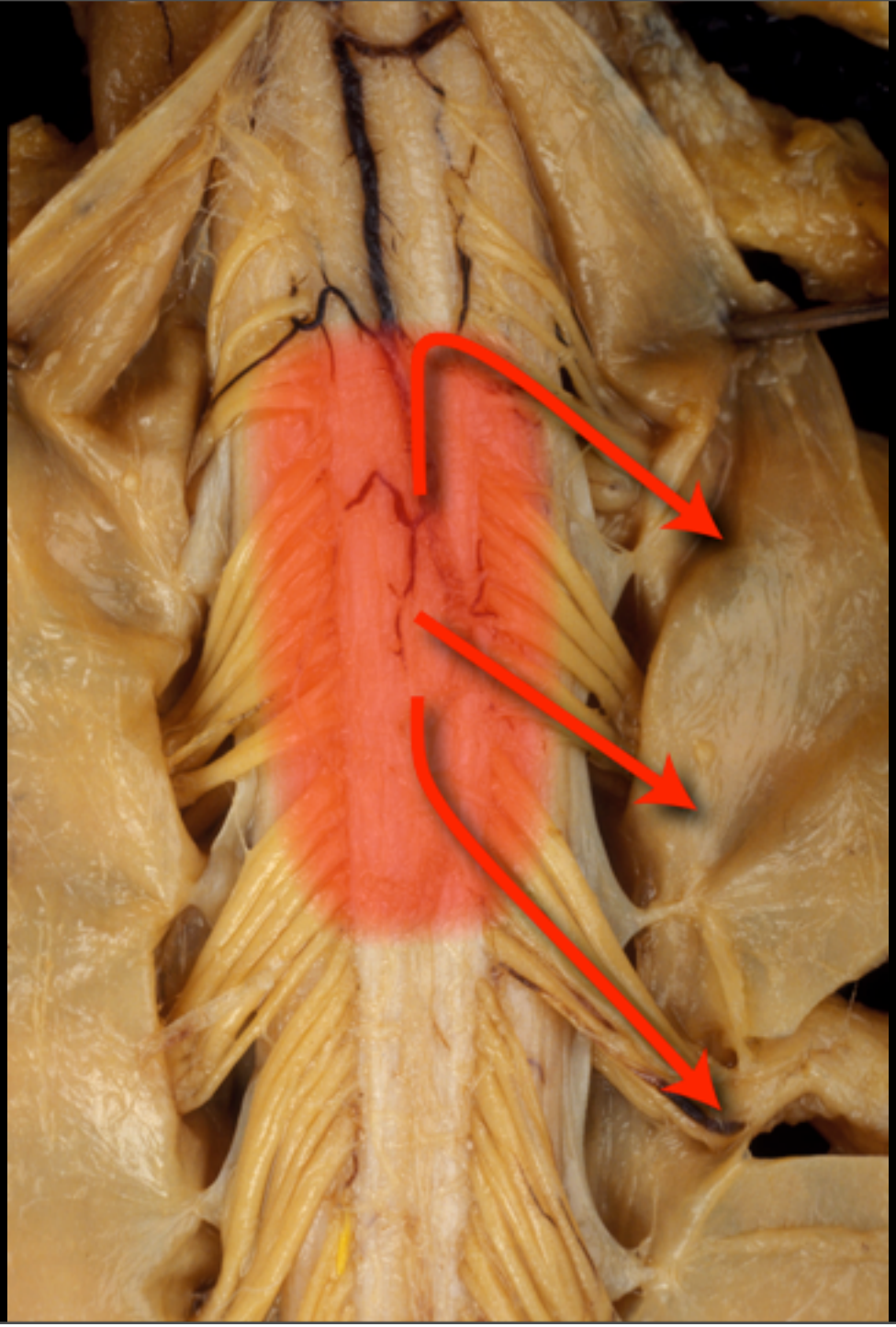
M. A. Giamberardino, G. Affaitati, and R. Costantini. Referred pain from internal organs. *Hdbk Clin.Neurol.* 81 (3rd Series):343-361, 2006



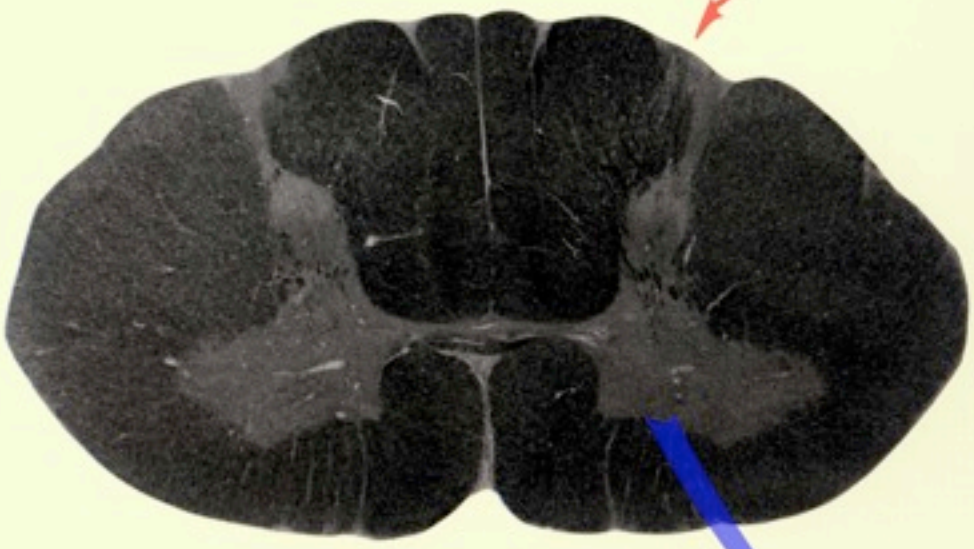




Dorsal Root Reflexes



Spinal Facilitation



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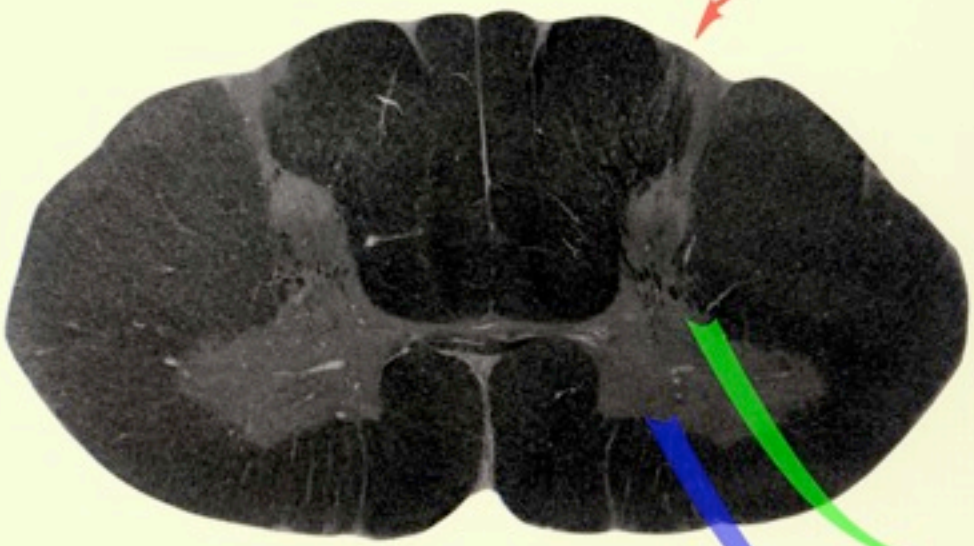
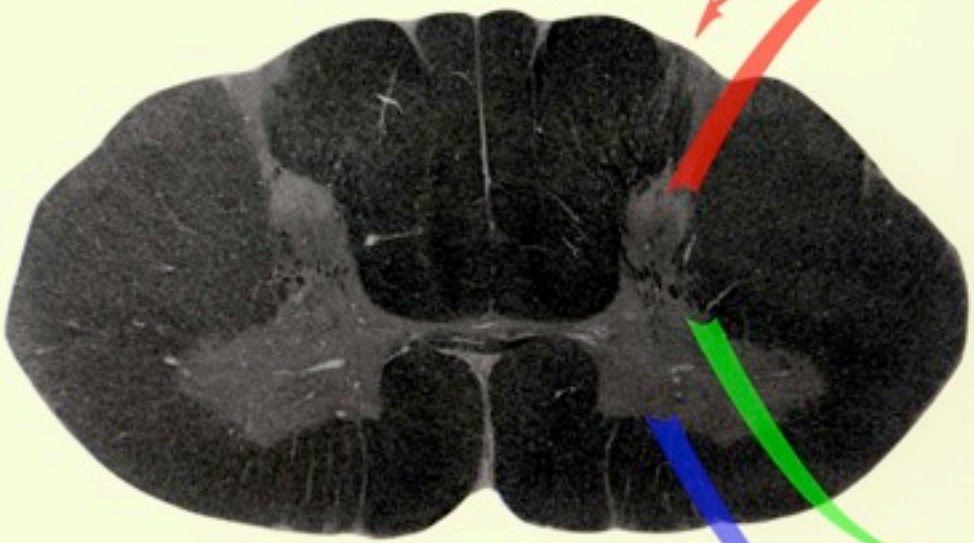


Spinal Facilitation

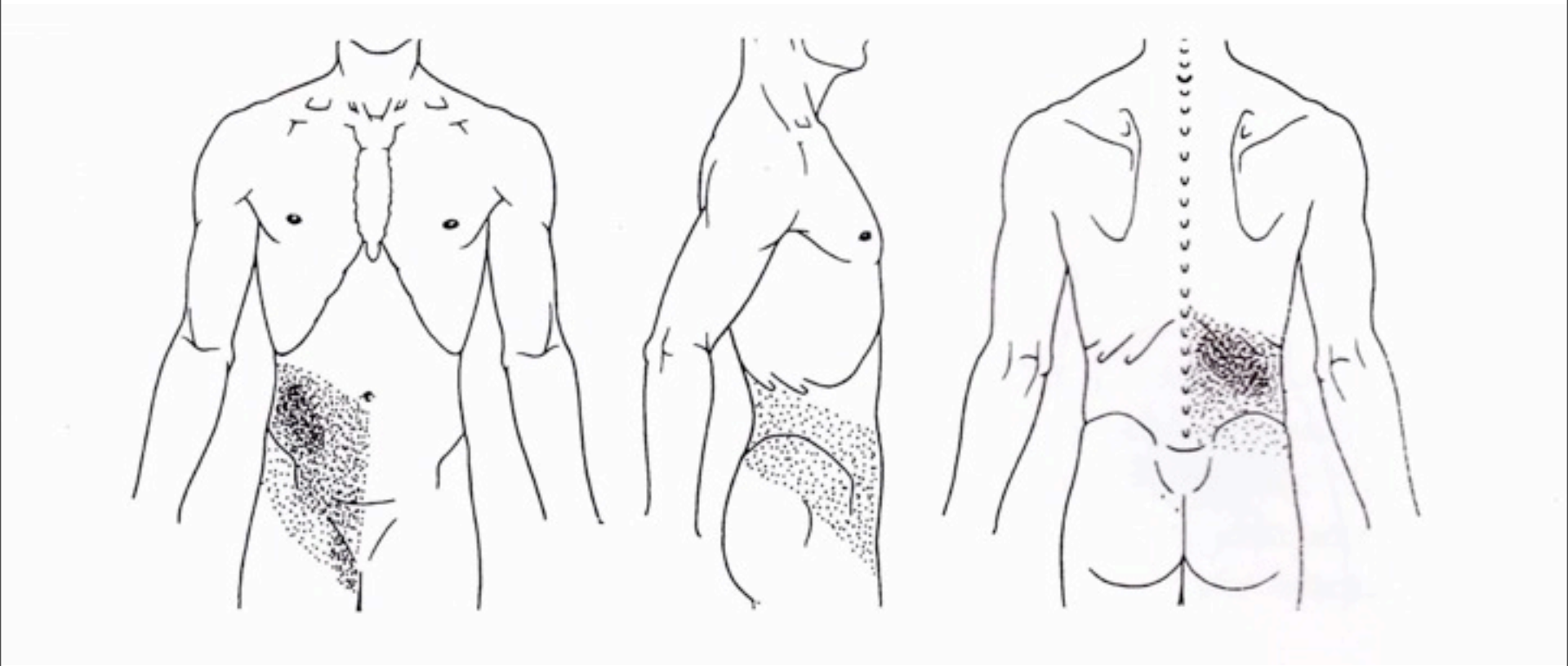


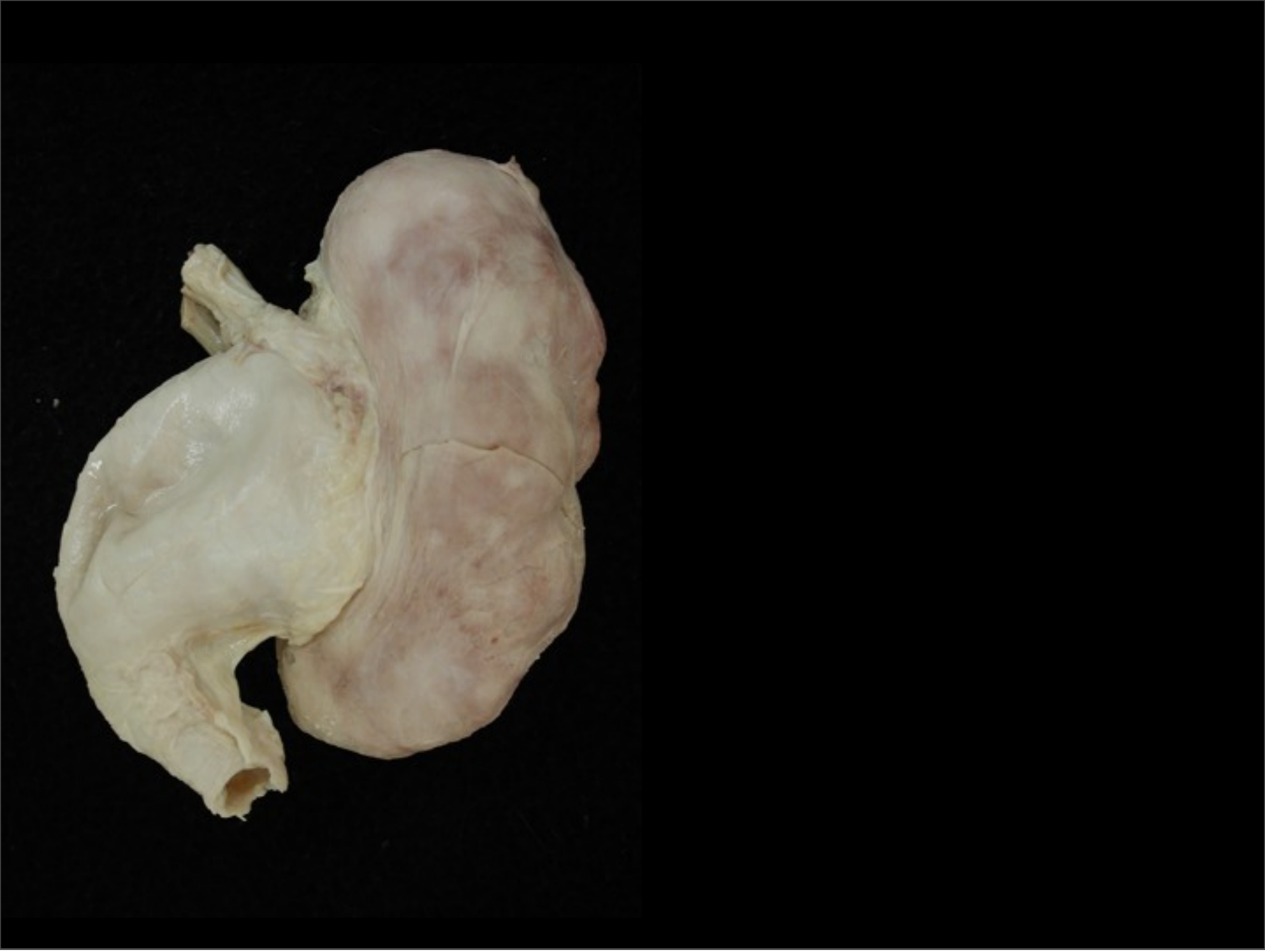
Nephrosomatic Reflexes

- Paraspinal muscle spasms
  - Low back region L1-L2

- Referred pain
  - Flank pain, L1-L2 distribution
  - Testicular pain in a male

Referred Urinary Tract Pain

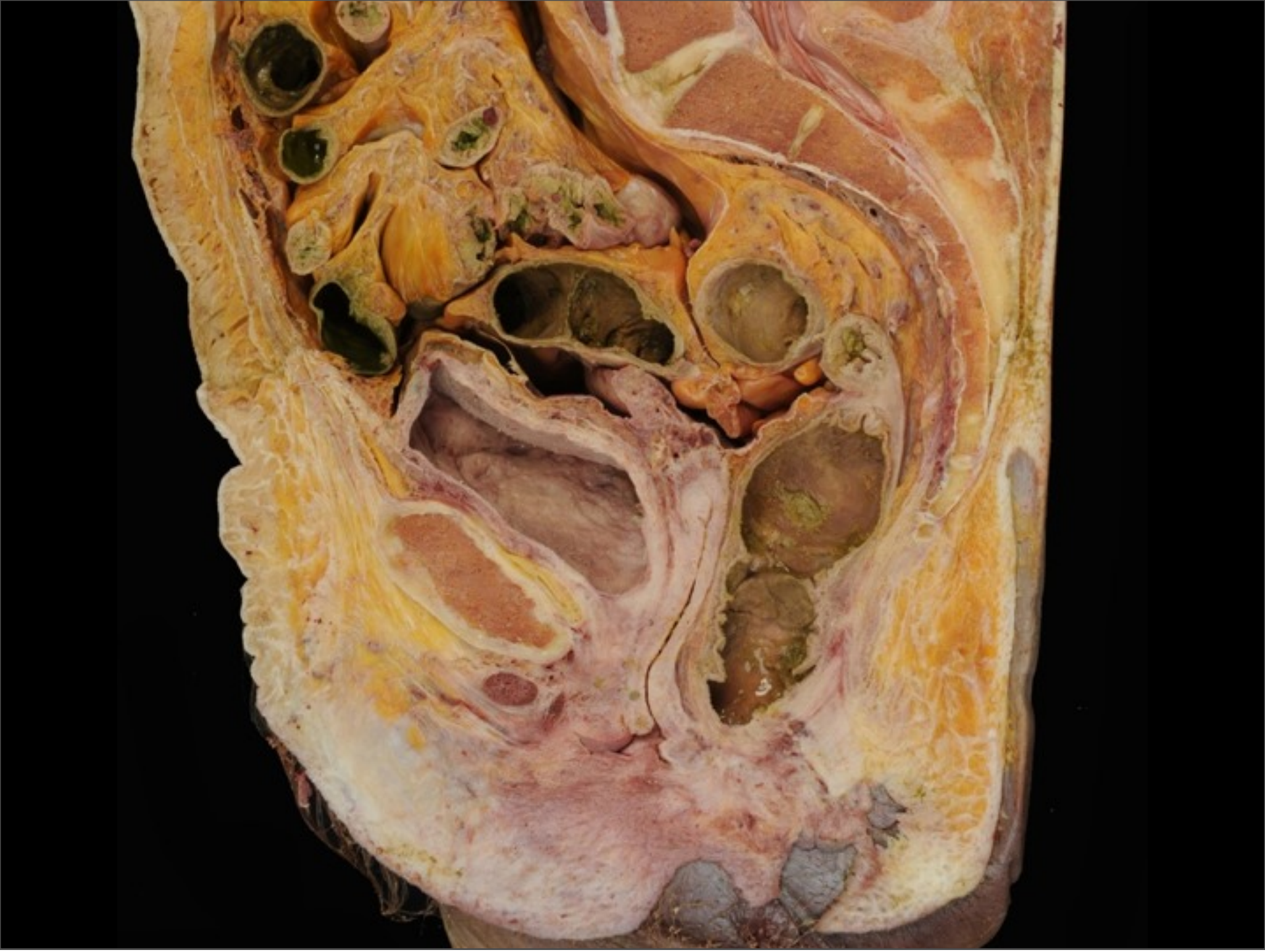


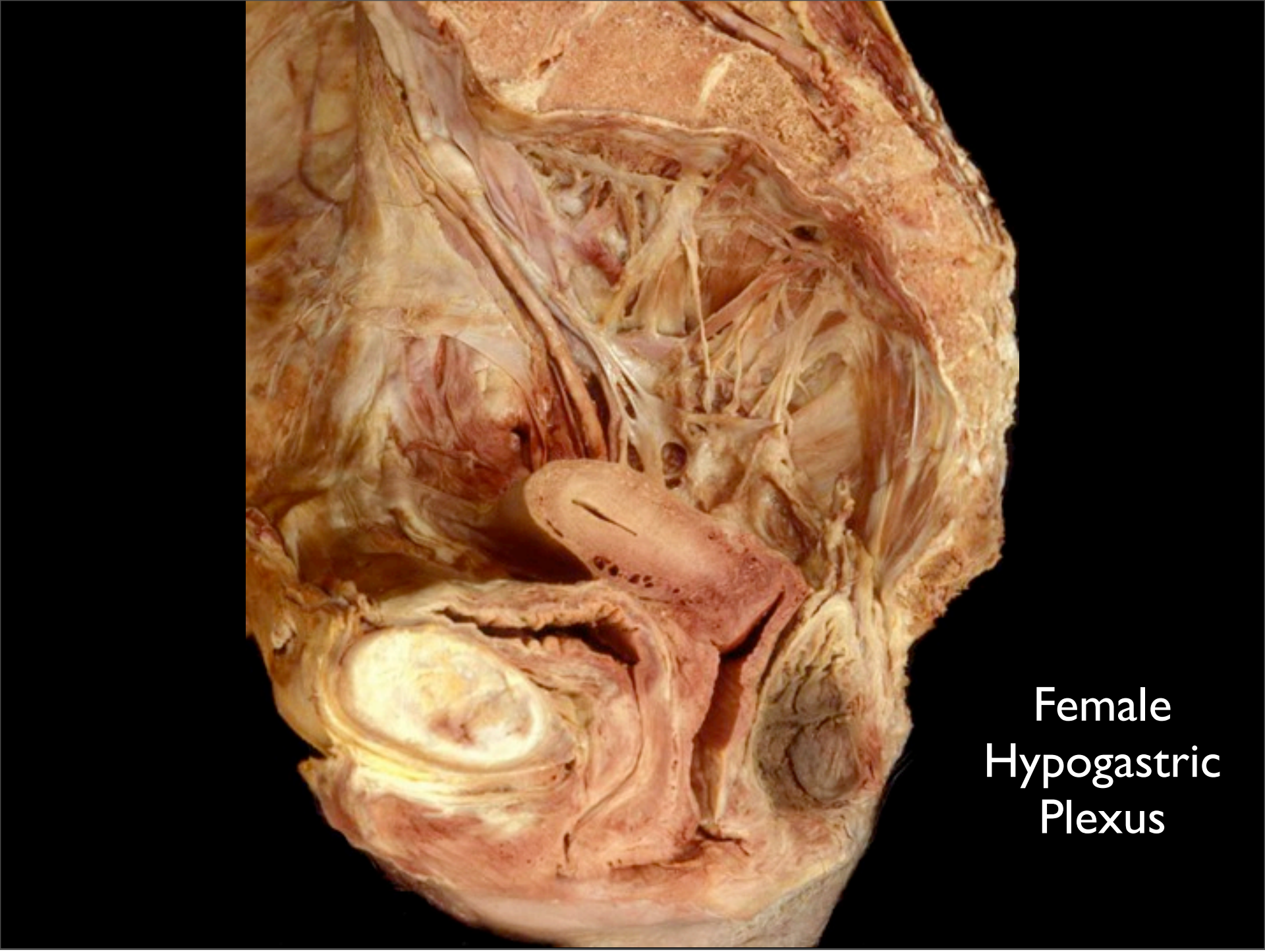


Hydronephros and Viscerosomatic Integration

- Infants with unilateral hydronephros develop increased sensitivity to the abdominal skin reflex

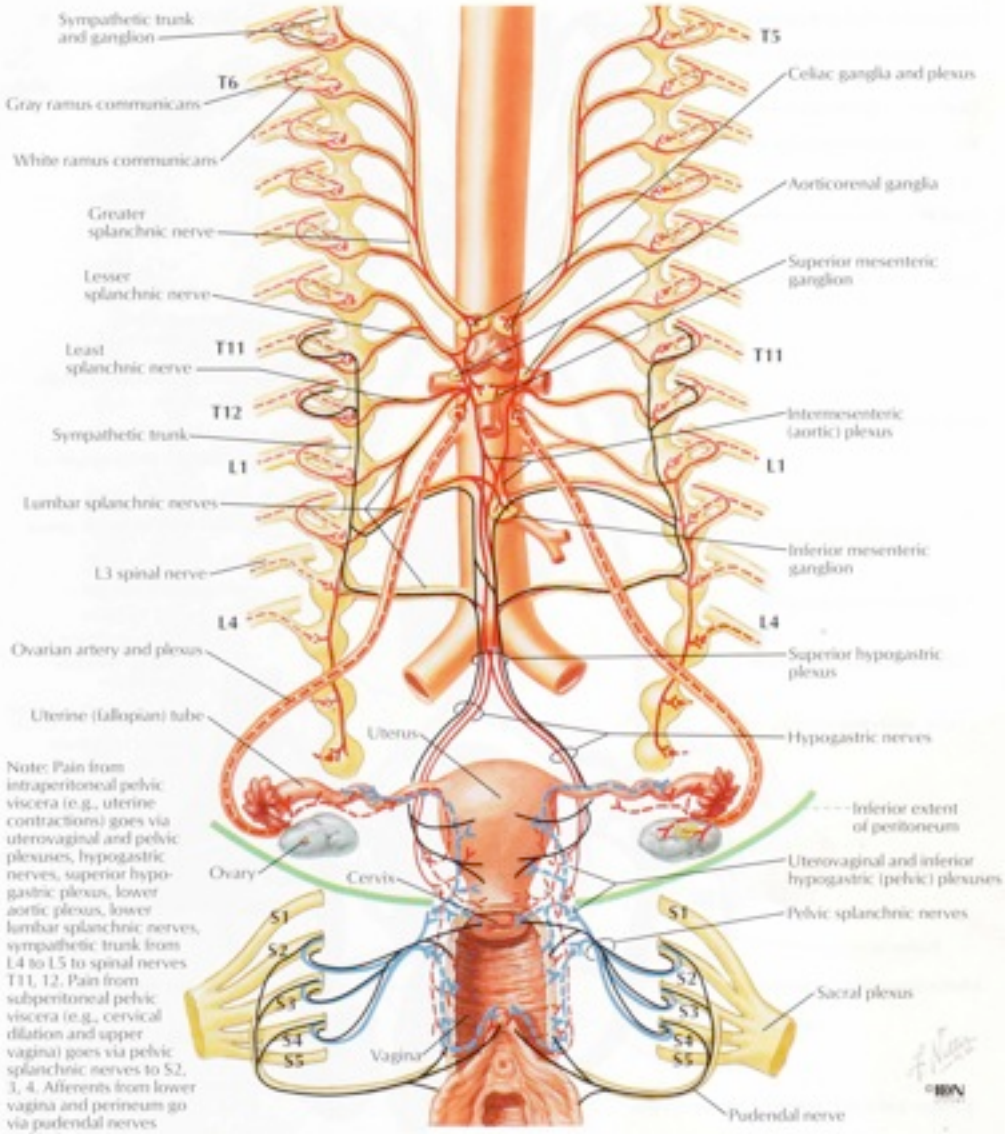
  - K. A. Andrews, D. Desai, H. K. Dhillon, D. T. Wilcox, and M. Fitzgerald. Abdominal sensitivity in the first year of life: comparison of infants with and without prenatally diagnosed unilateral hydronephrosis. *Pain* 100 (1-2):35-46, 2002.




Female
Hypogastric
Plexus

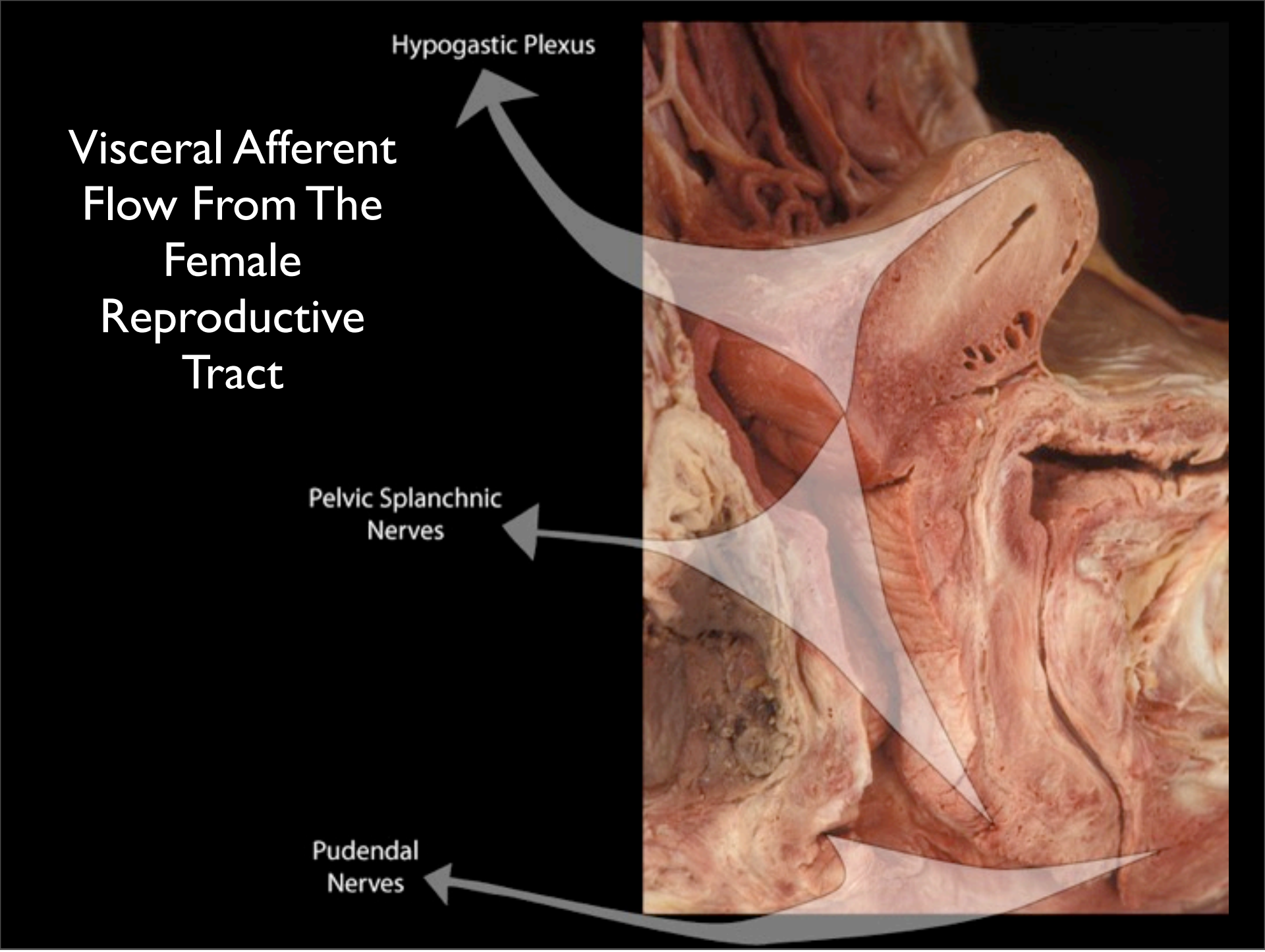
Innervation of Female Reproductive Organs: Schema

SEE ALSO PLATE 153



Visceral Afferent Flow From The Female Reproductive Tract

Visceral Afferent Flow From The Female Reproductive Tract



Sensory Innervation of the Female Reproductive Tract

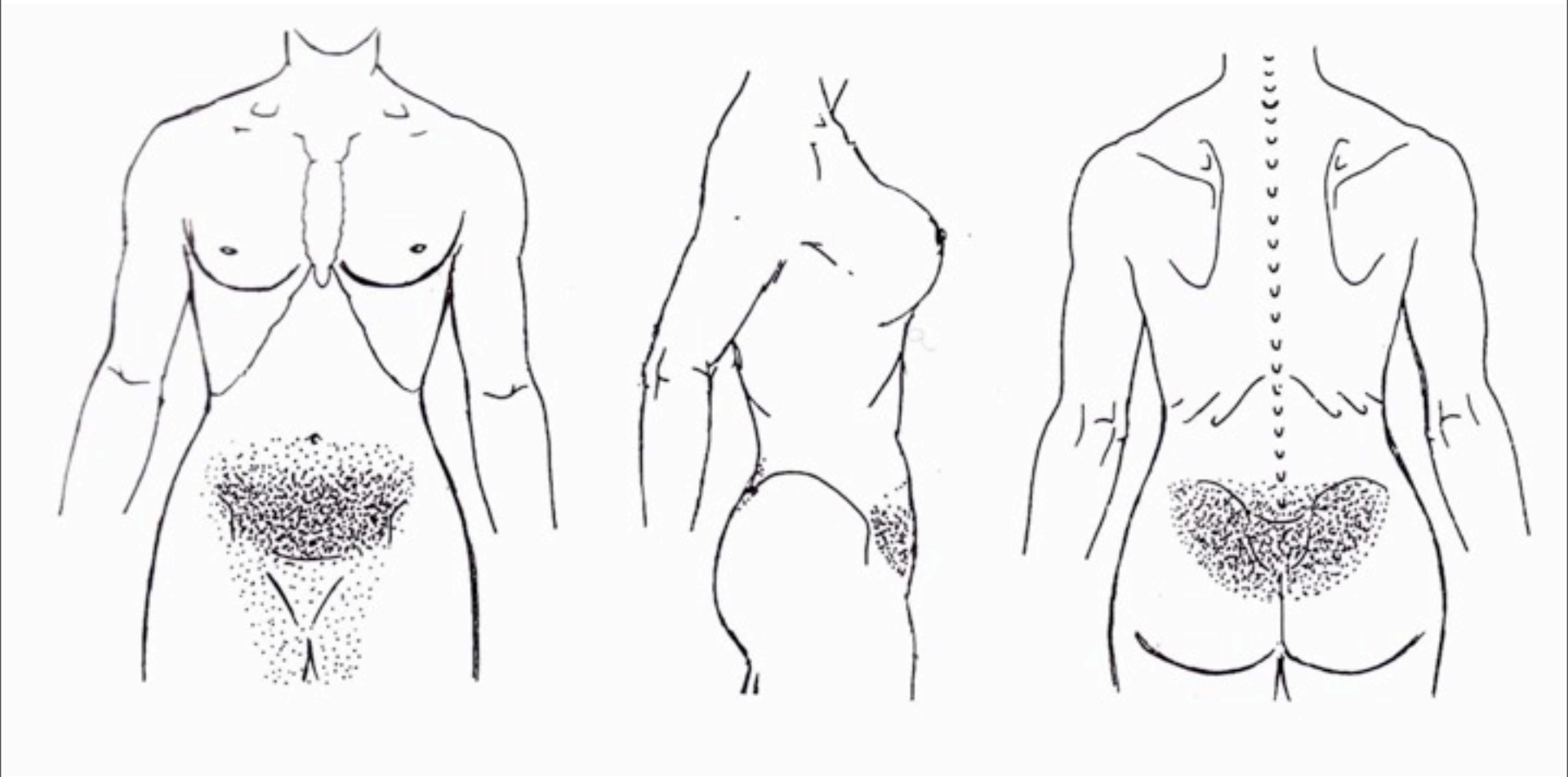
- Ovaries
  - Low thoracic cord (T10-T11)
- Uterus and Uterine tubes
  - Thoracolumbar junction (T11-L2)
- Cervix and vagina:
  - Sacral cord (S2-S4)

Uterosomatic Reflexes

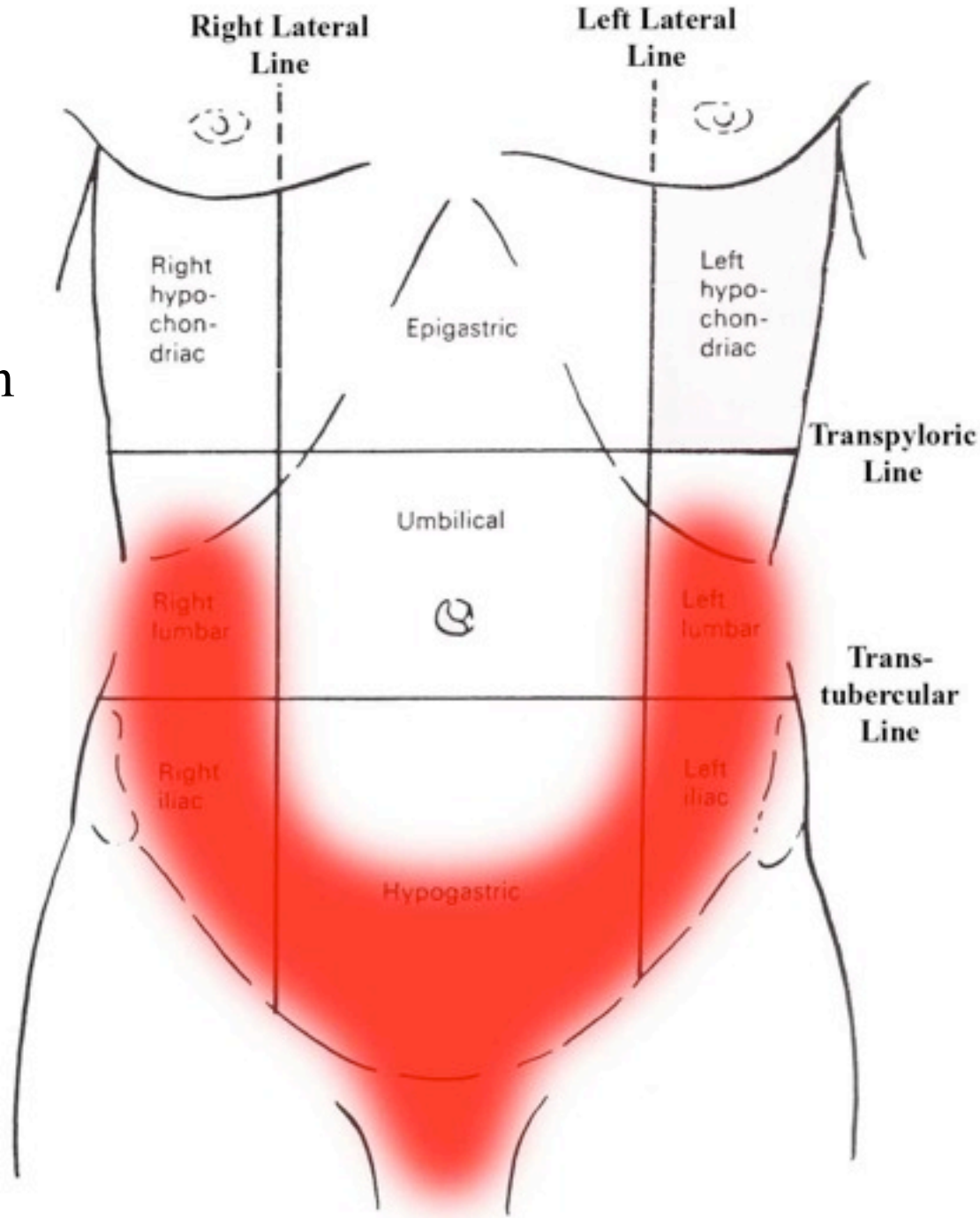
- Paraspinal muscle spasms
  - Thoracolumbar junction and sacrum

- Referred pain
  - Thoracolumbar junction and sacrum

Referred Uterine Pain



Colonic Pattern



Referred Pain From The Uterus

Referred Pain From The Uterus

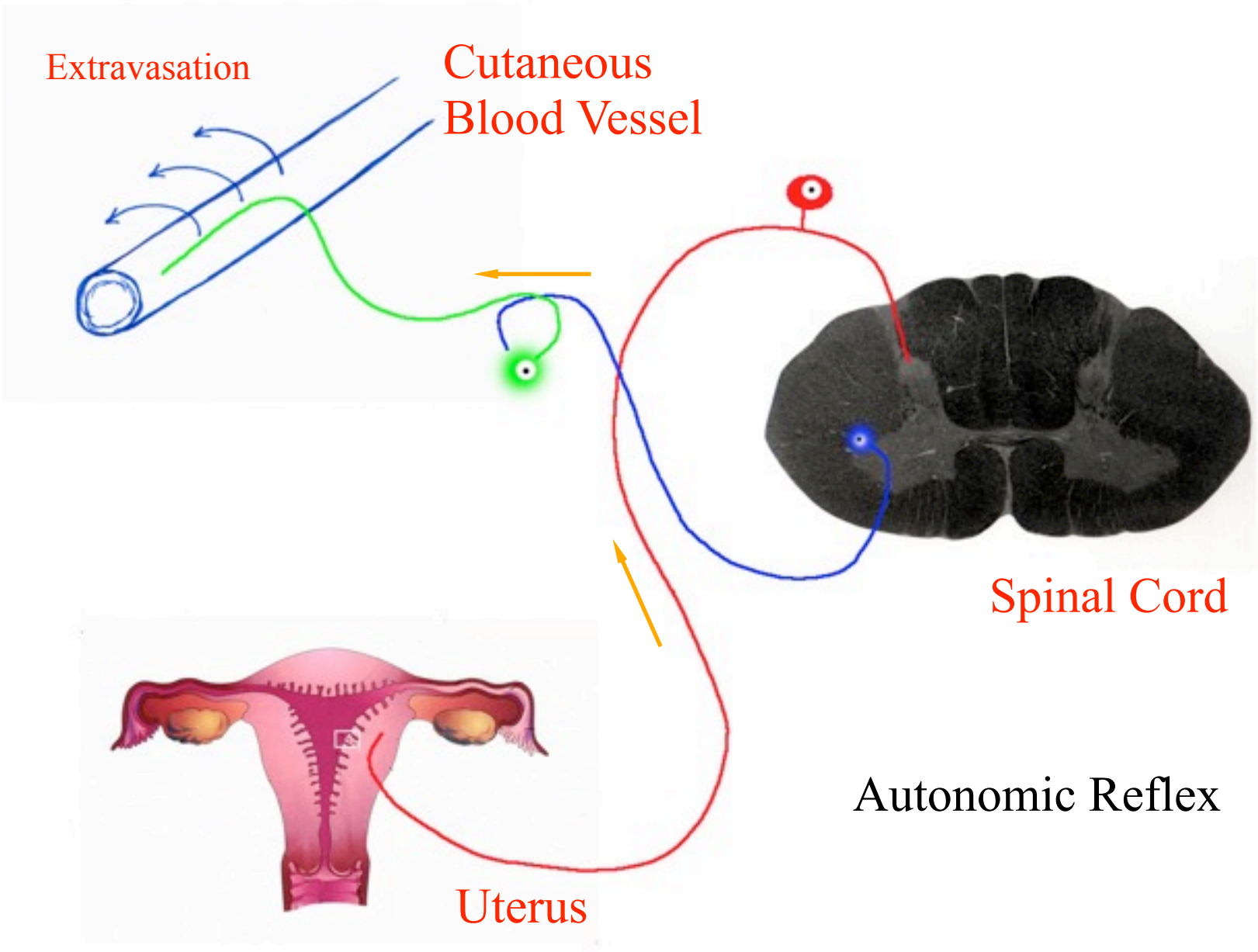
- Rats pretreated with Evans Blue vital dye

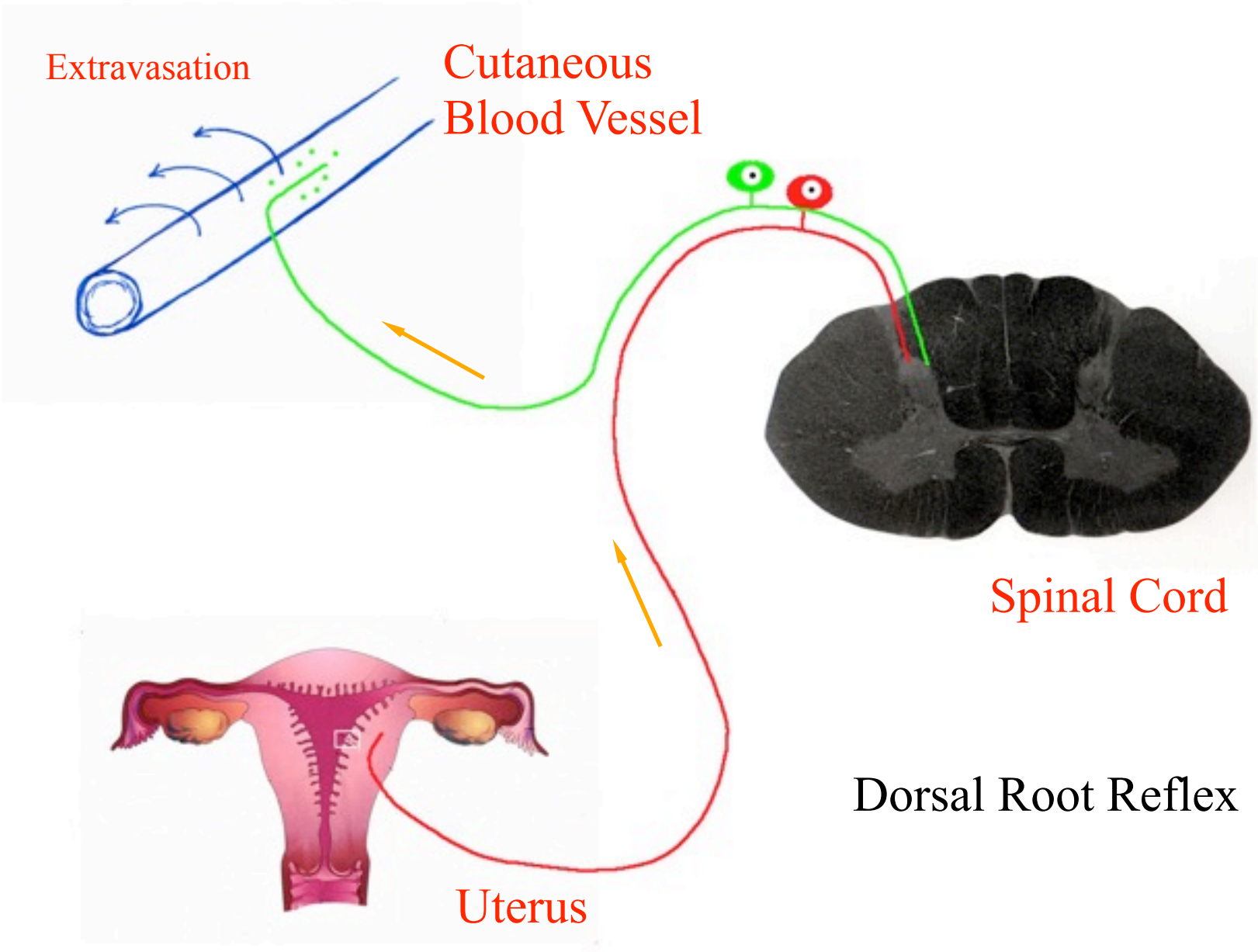
Referred Pain From The Uterus

- Rats pretreated with Evans Blue vital dye
- Subjected to noxious uterine stimulation

Referred Pain From The Uterus

- Rats pretreated with Evans Blue vital dye
- Subjected to noxious uterine stimulation
- Extravasation of dye over the low abdomen and back, sacral and perineal region
    - U. Wesselmann and J. Lai. Mechanisms of referred visceral pain: uterine inflammation in the adult virgin rat results in neurogenic plasma extravasation in the skin. *Pain* 73 (3):309-317, 1997.

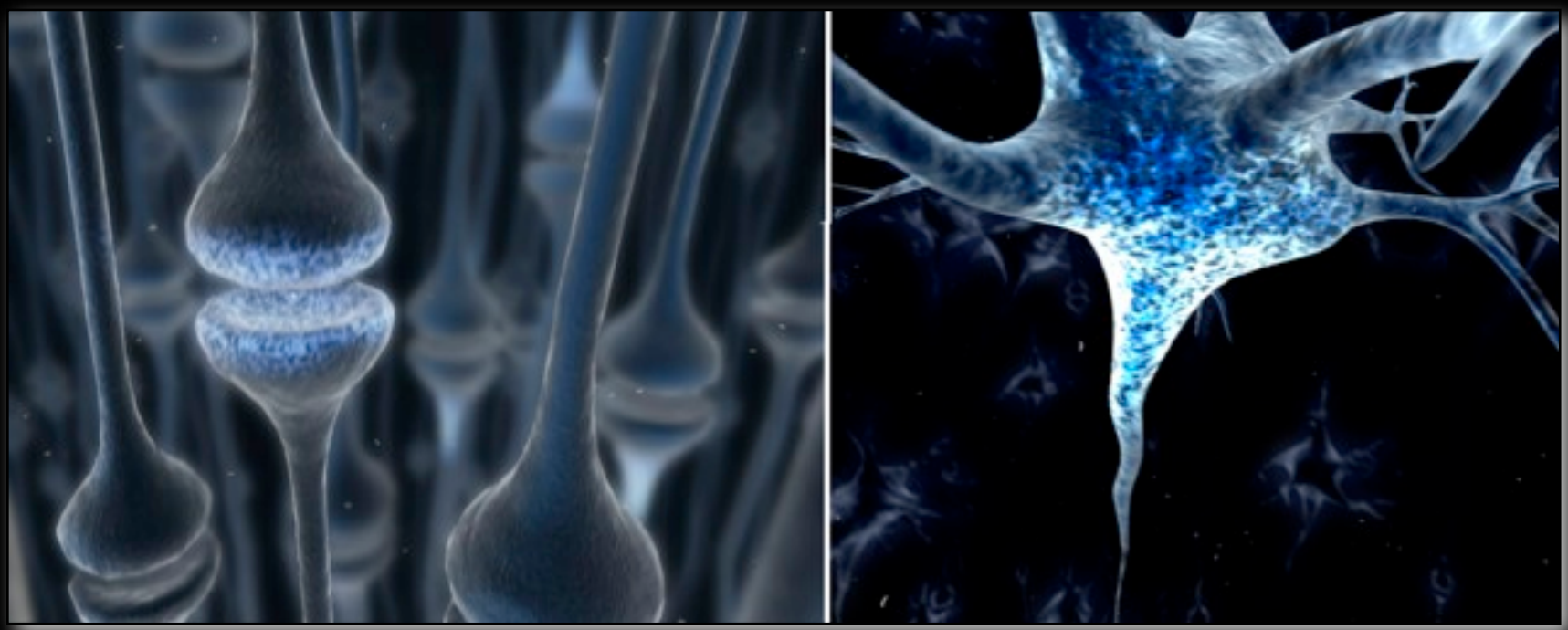

Extravasation
Cutaneous
Blood Vessel
Spinal Cord
Uterus
Autonomic Reflex


Extravasation
Cutaneous
Blood Vessel
Spinal Cord
Uterus
Dorsal Root Reflex

Peripheral & Central Sensitization

Peripheral & Central Sensitization

Peripheral & Central Sensitization



This is a 41-y-o male with worsening chest and epigastric pain

This is a 41-y-o male with worsening chest and epigastric pain

- Presents with intense, paroxysms of chest pain

This is a 41-y-o male with worsening chest and epigastric pain

- Presents with intense, paroxysms of chest pain
- History of failed back surgery

This is a 41-y-o male with worsening chest and epigastric pain

- Presents with intense, paroxysms of chest pain
- History of failed back surgery
- Increasing low back pain and leg weakness

This is a 41-y-o male with worsening chest and epigastric pain

- Presents with intense, paroxysms of chest pain
- History of failed back surgery
- Increasing low back pain and leg weakness
- Right testicular pain

Patient A

Patient A

Patient A

Patient B

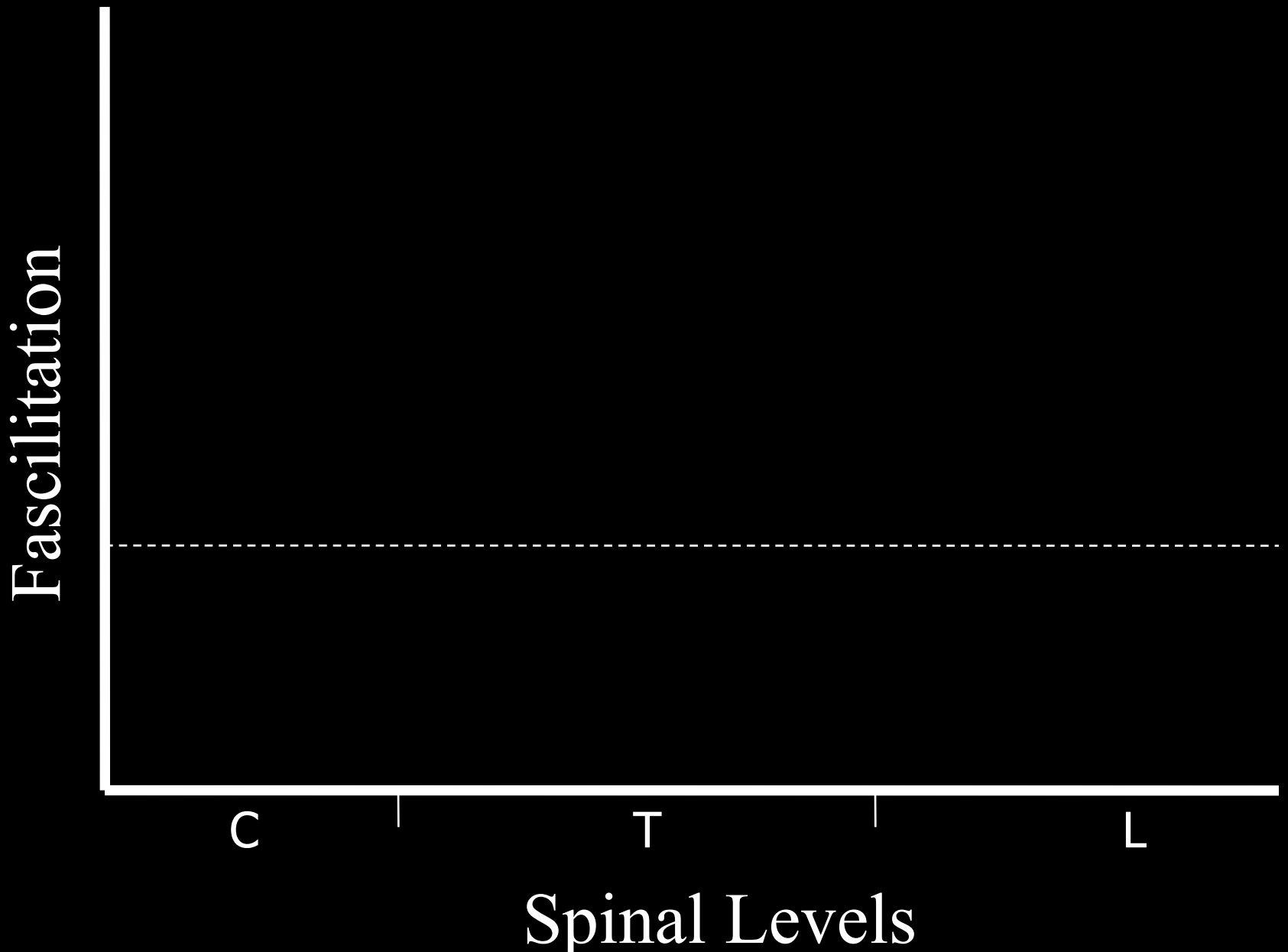
Patient A

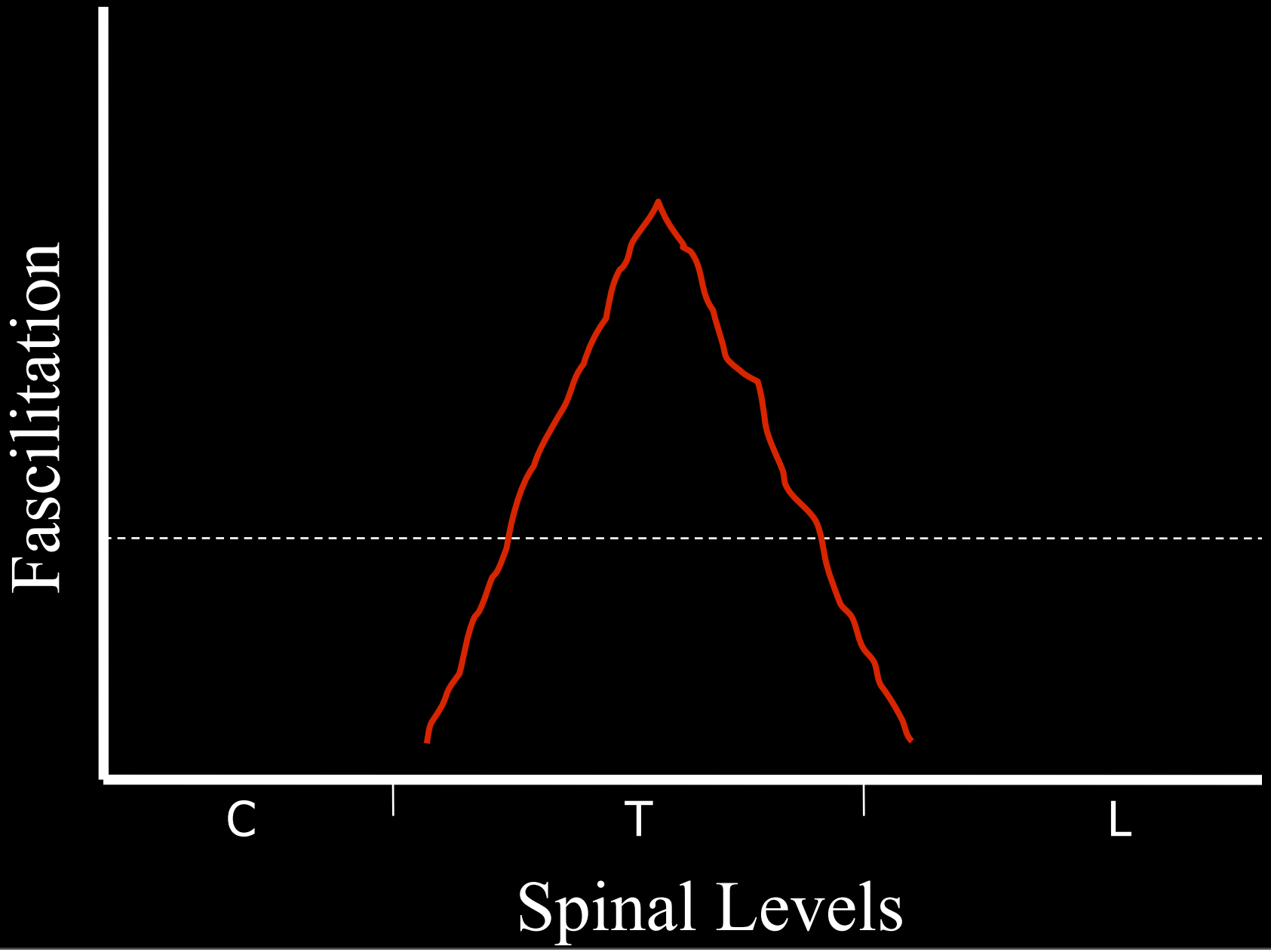
Patient B

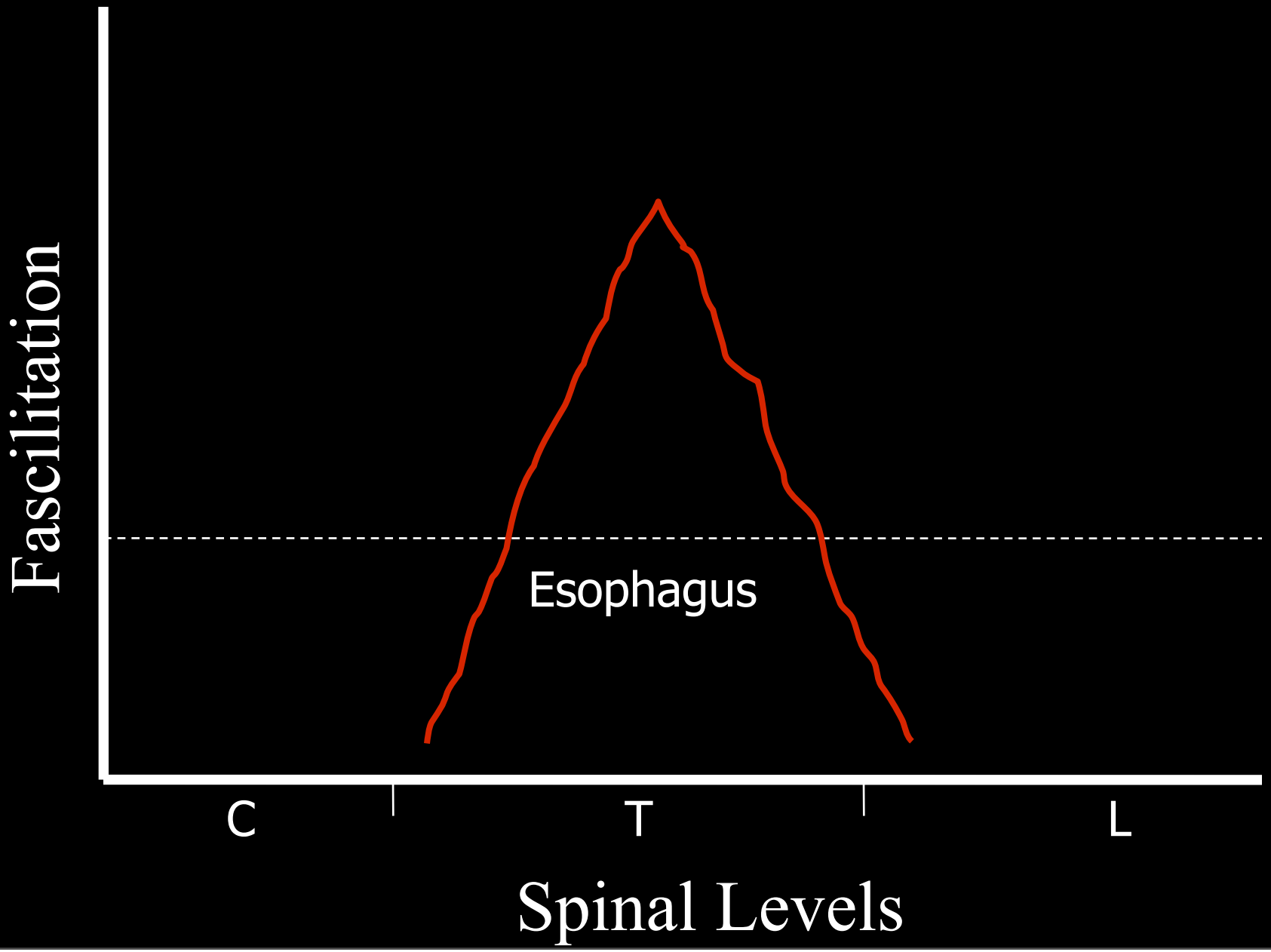
GERDs

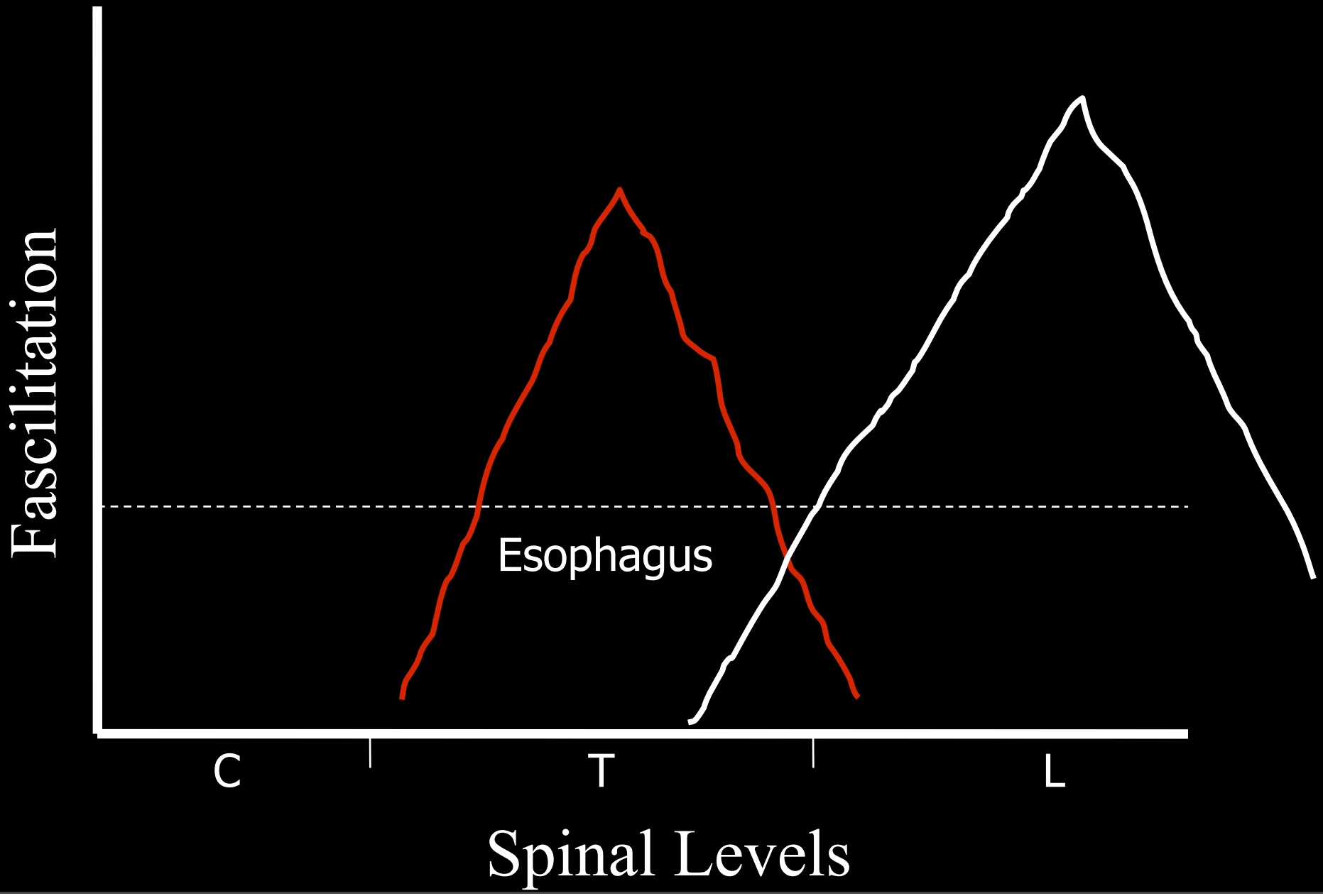
Patient A

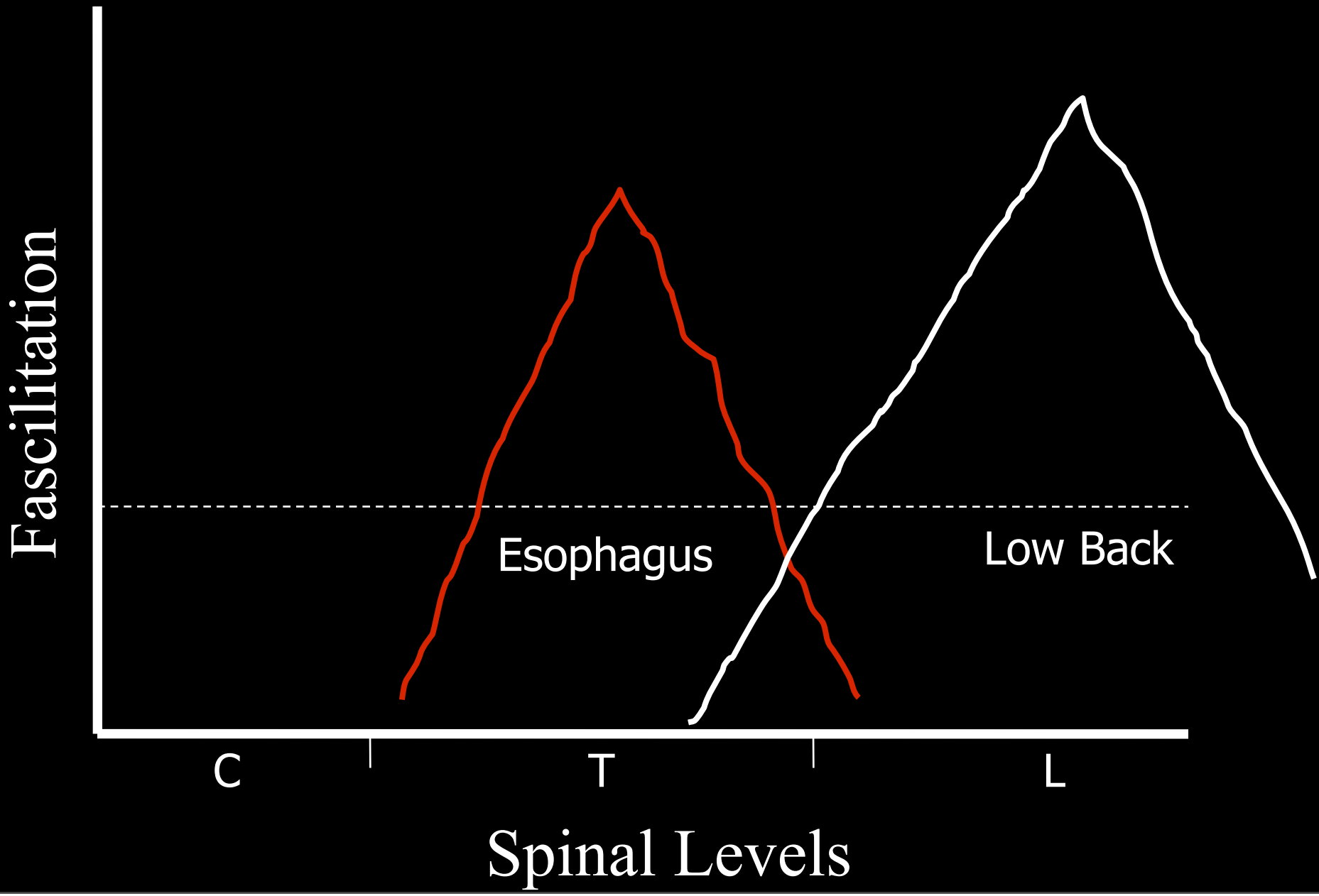
Patient B

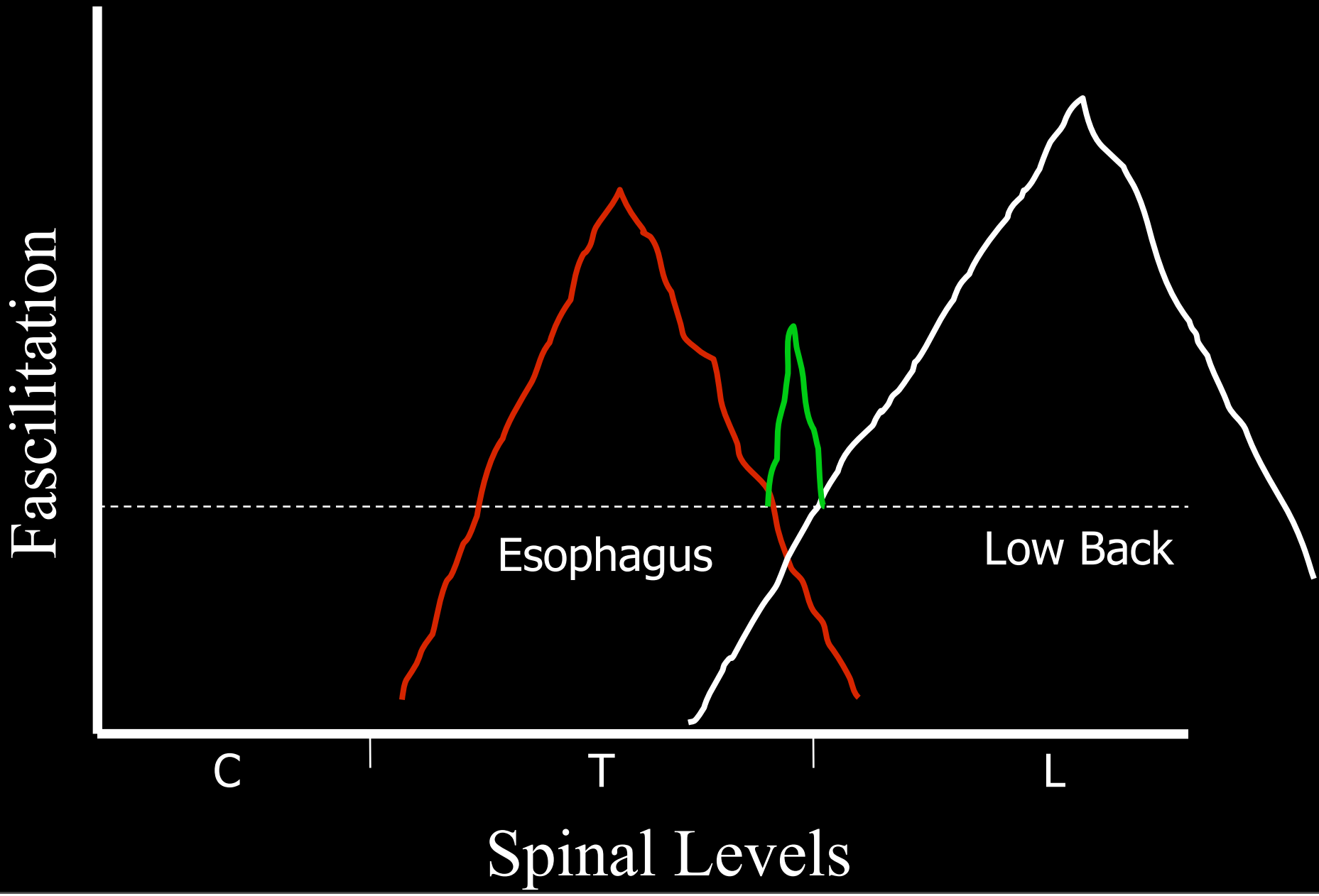

Fascilitation
C
T
L
Spinal Levels

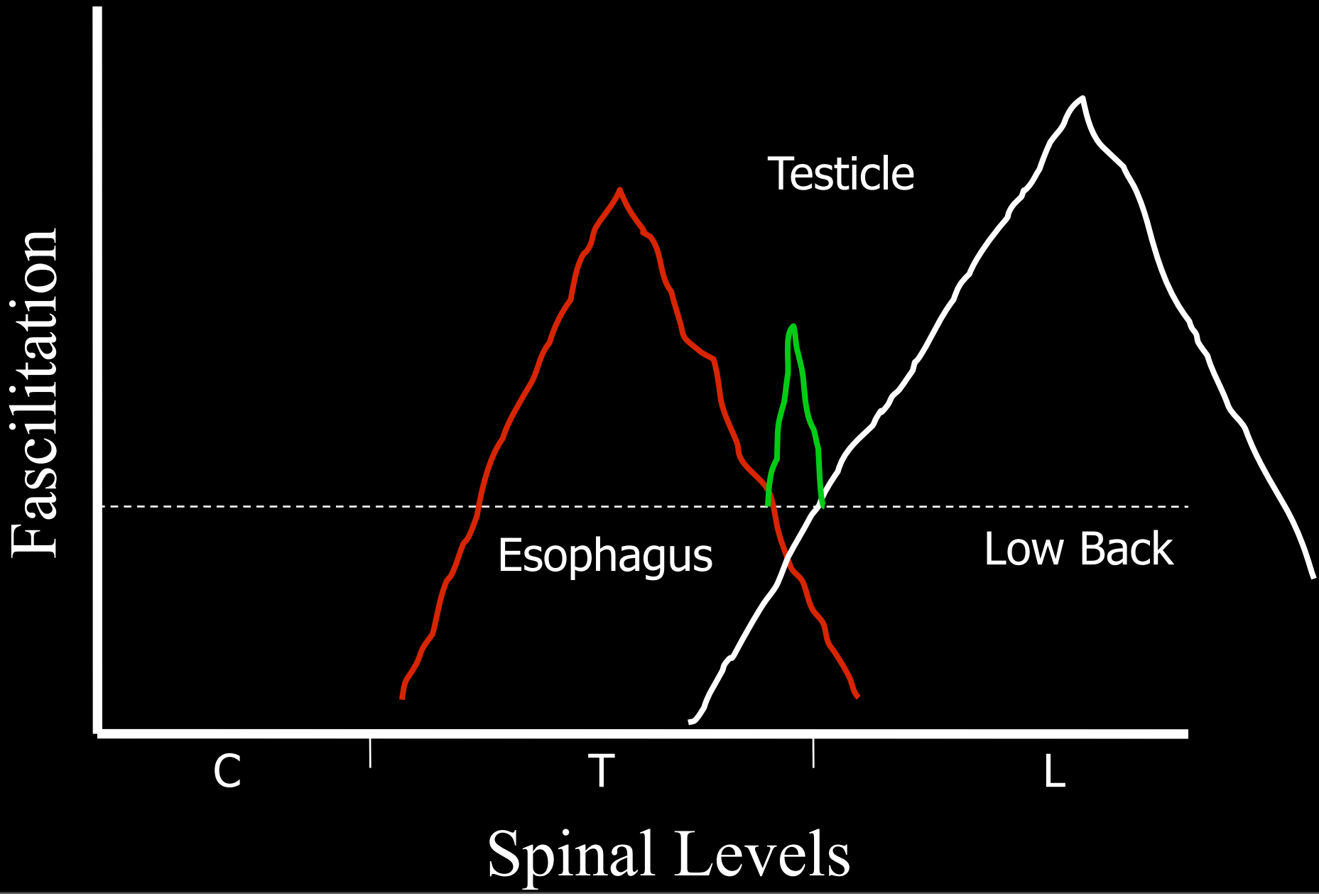

Fascilitation
C
T
L
Spinal Levels

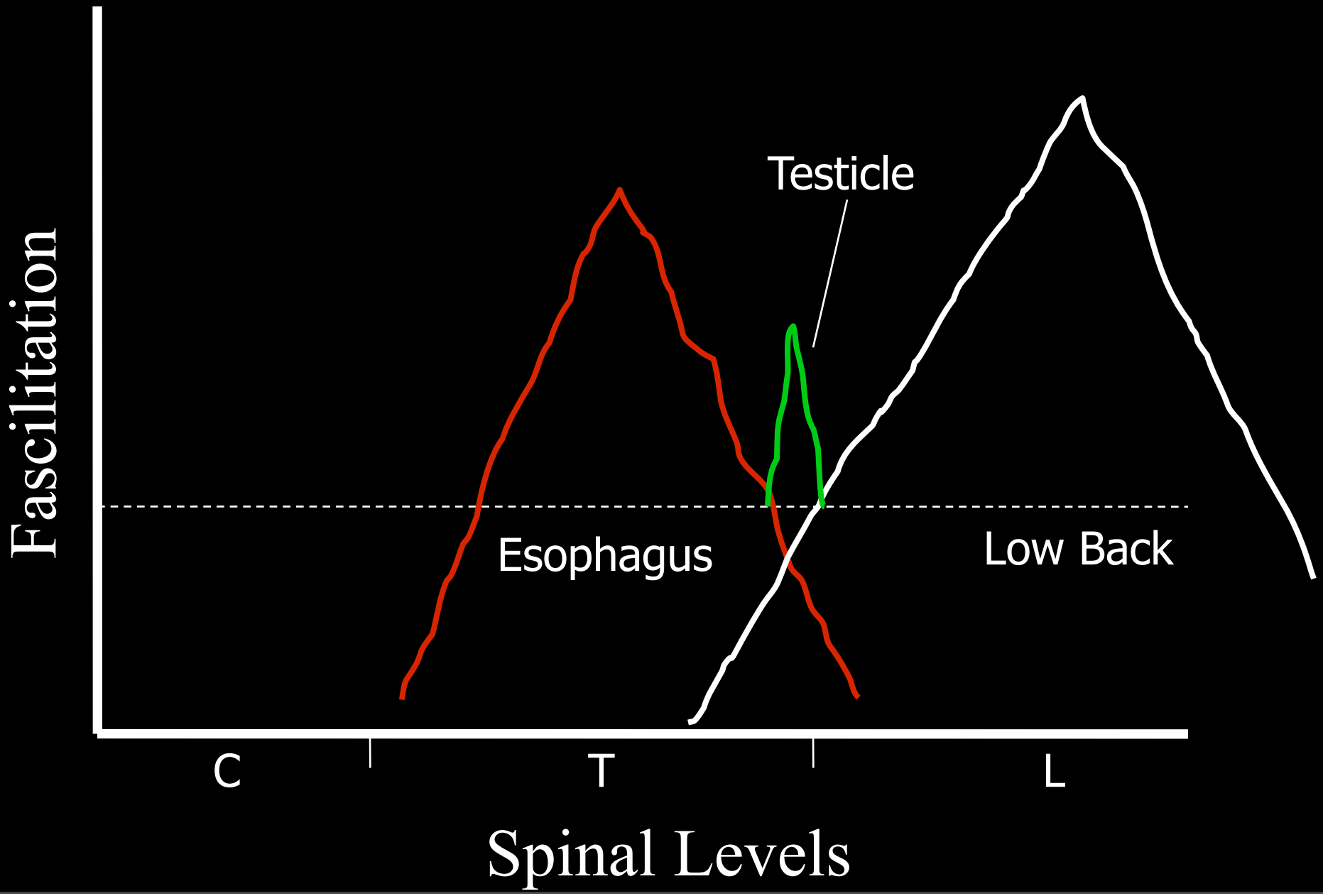

Fascilitation
Esophagus
C
T
L
Spinal Levels

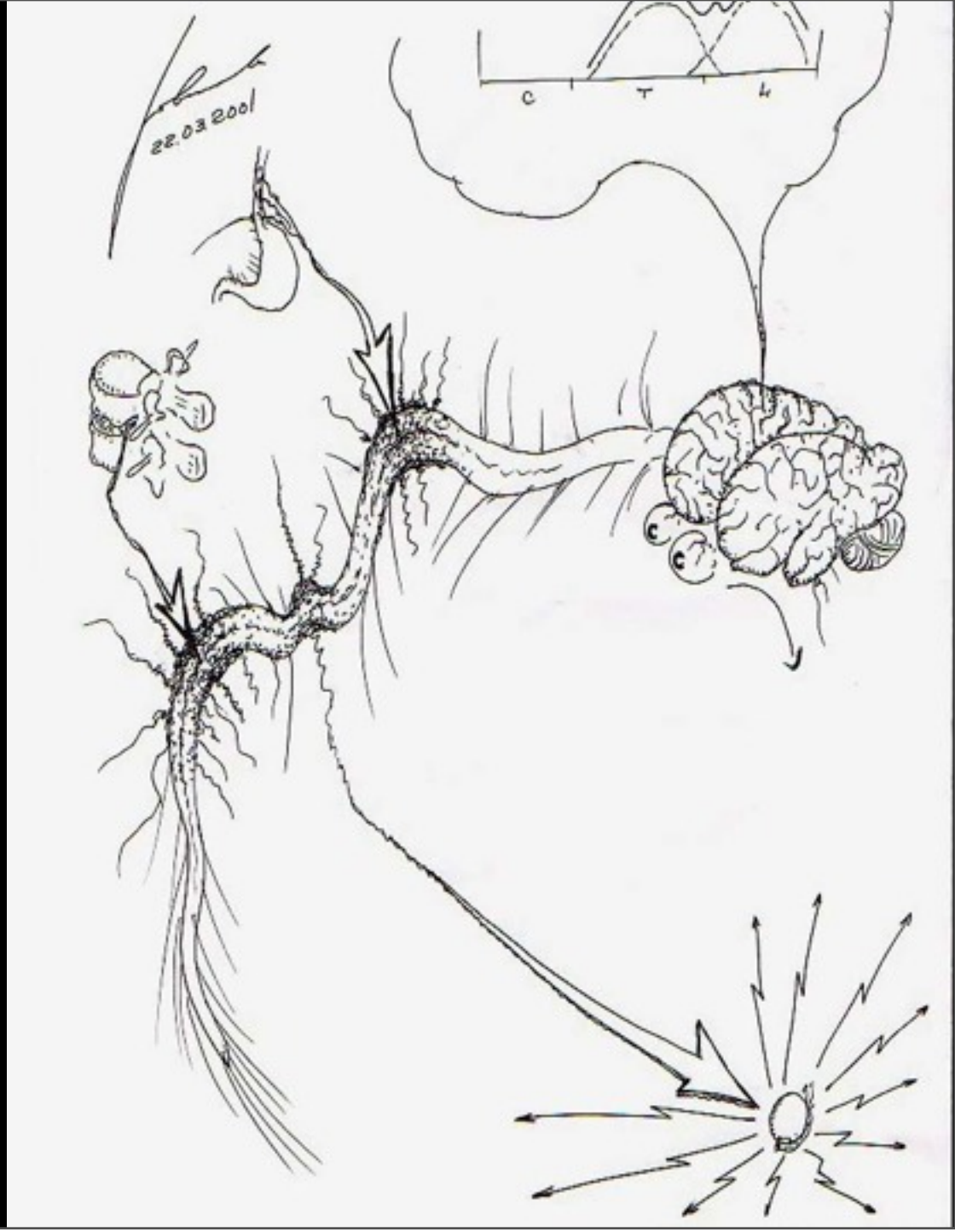

Fascilitation
Esophagus
C
T
L
Spinal Levels


Fascilitation
Esophagus
Low Back
C
T
L
Spinal Levels

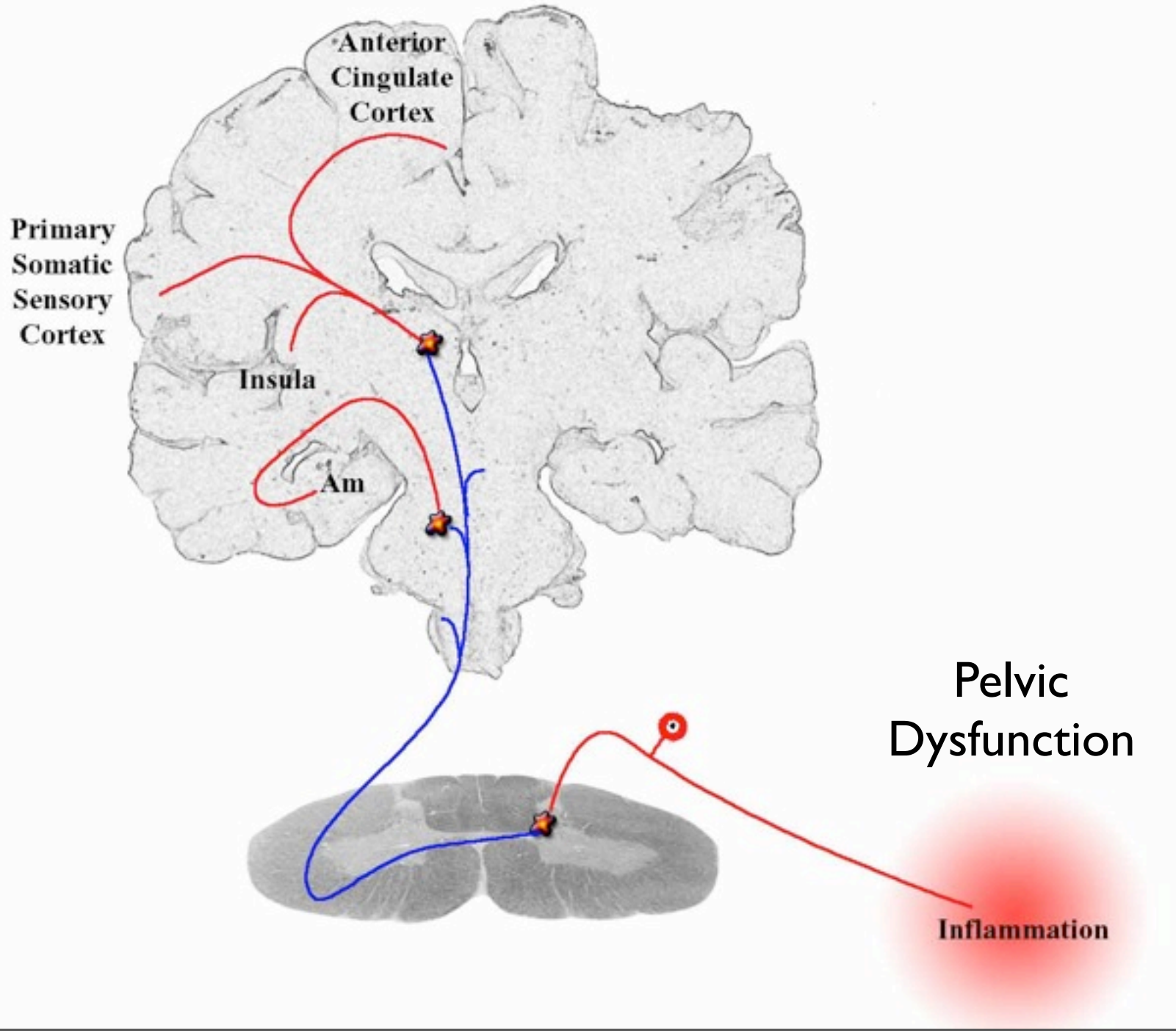

Fascilitation
Esophagus
Low Back
C
T
L
Spinal Levels


Fascilitation
Testicle
Esophagus
Low Back
C
T
L
Spinal Levels


Fascilitation
Testicle
Esophagus
Low Back
C
T
L
Spinal Levels


22.03.2001
C
T
L

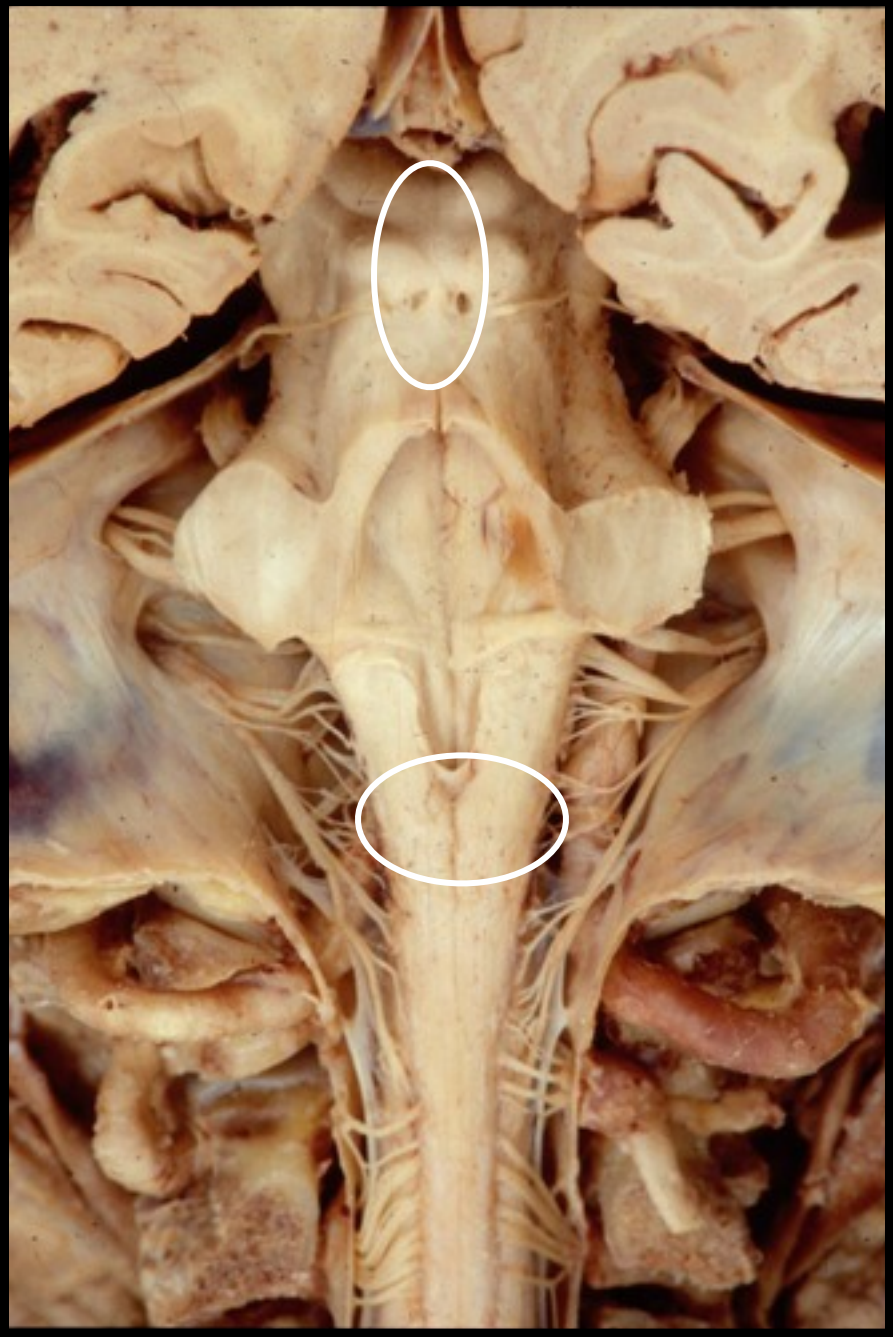
Central Processing Of Pain

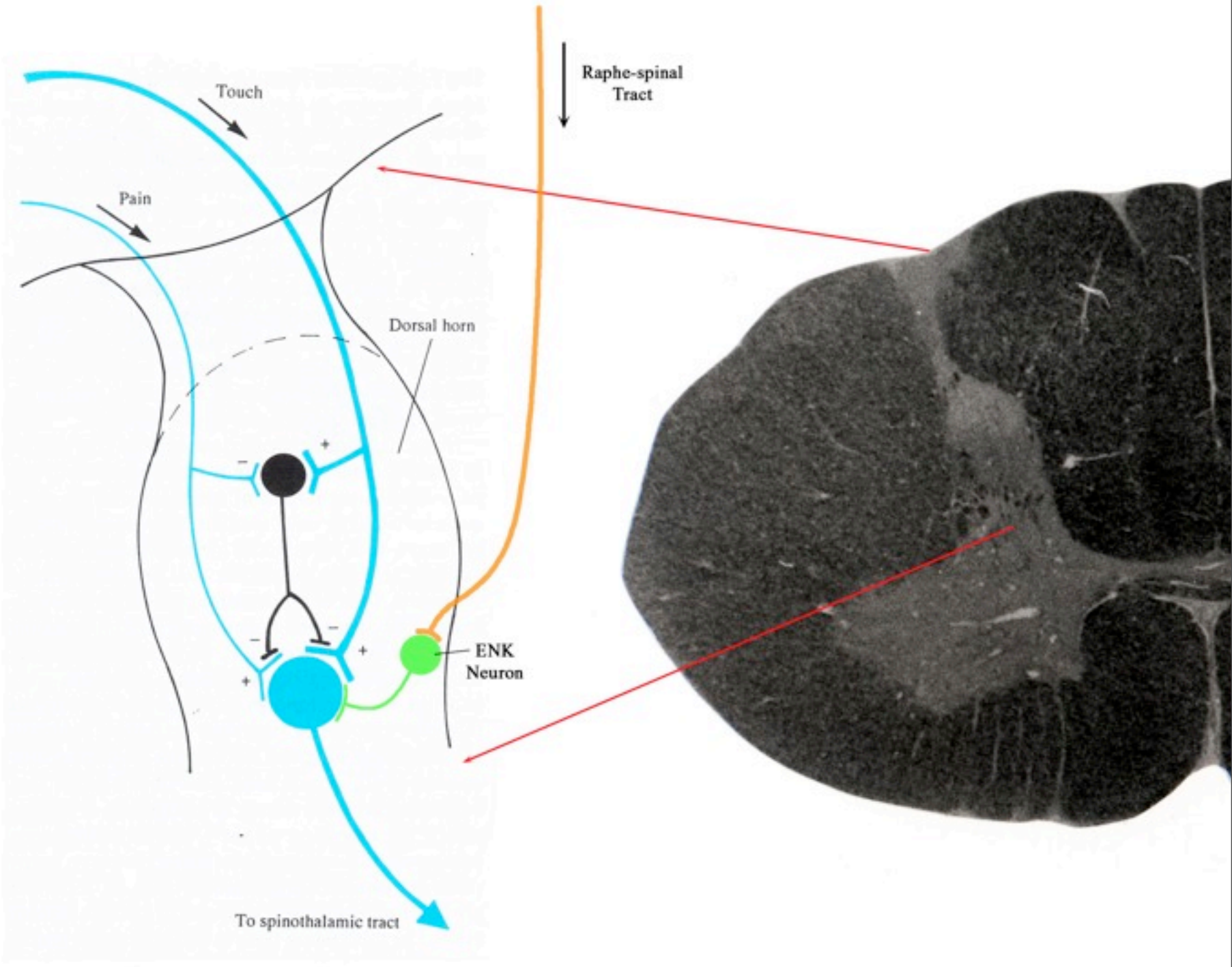

Anterior
Cingulate
Cortex
Primary
Somatic
Sensory
Cortex
Insula
Am
Pelvic
Dysfunction
Inflammation

Descending Spinal Control Systems

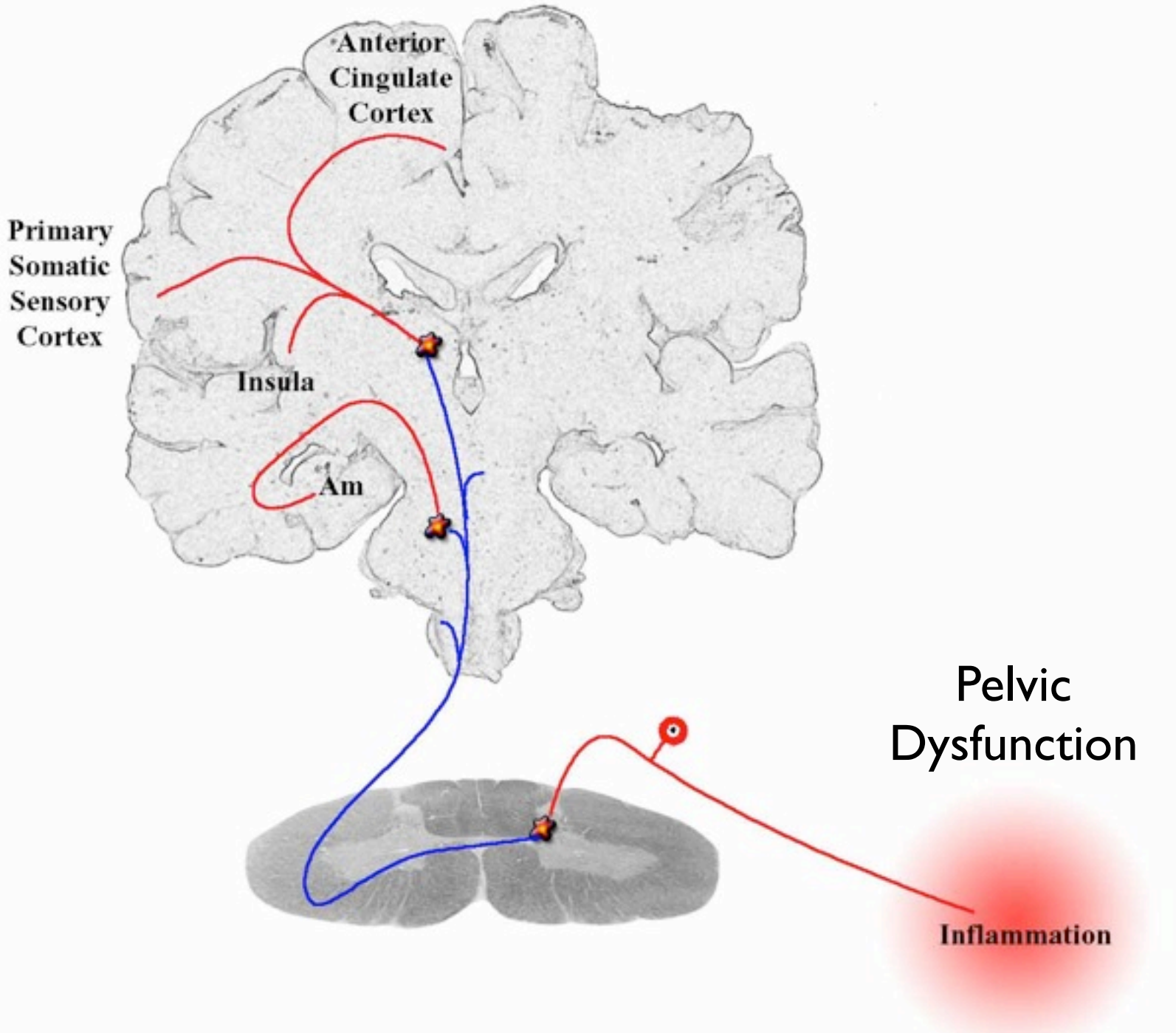
Endogenous Pain Control
Raphe-spinal system
Noradrenergic-spinal system

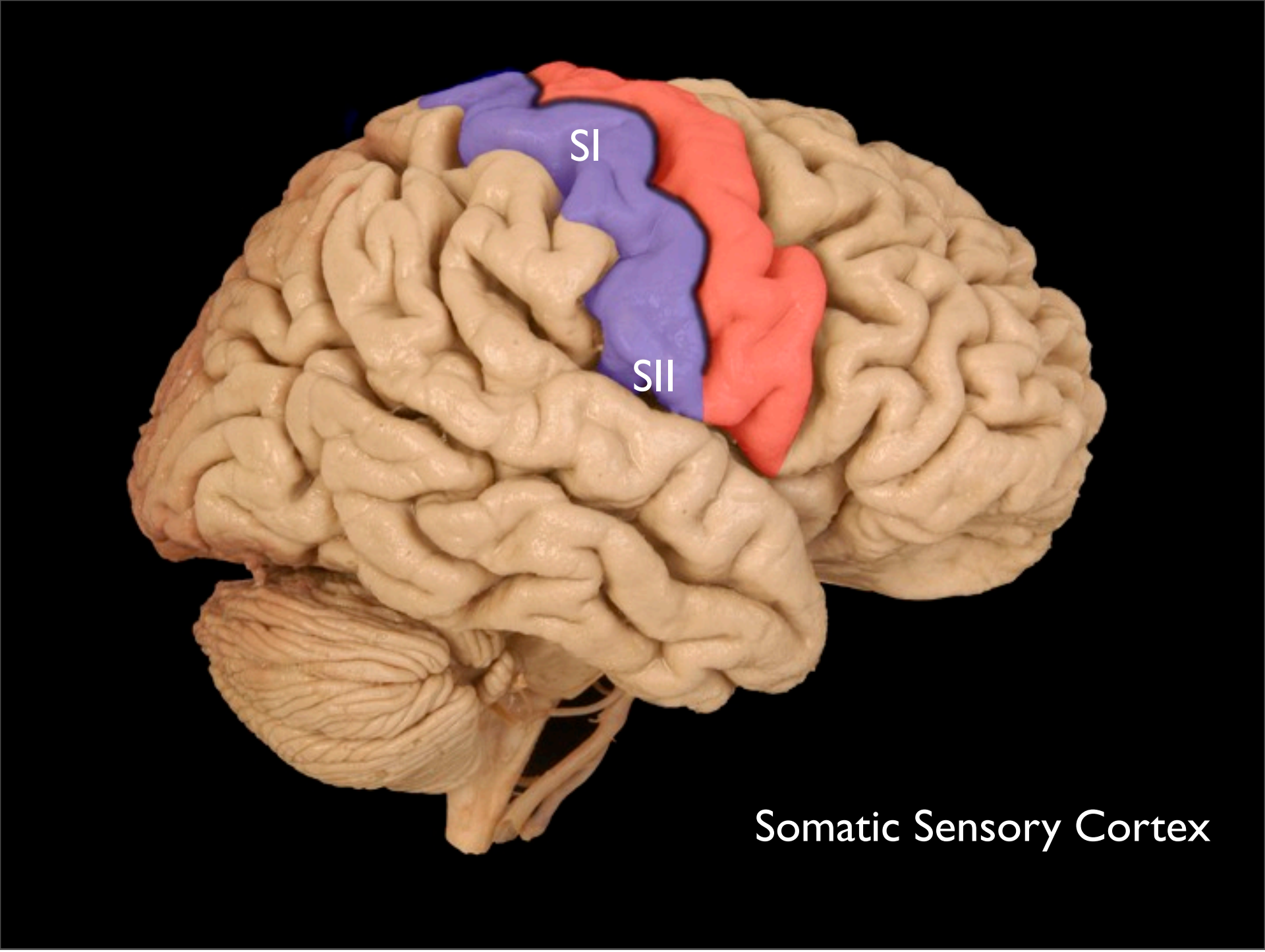
Diffuse Noxious Inhibitory Control
Spino-Reticulospinal Loop

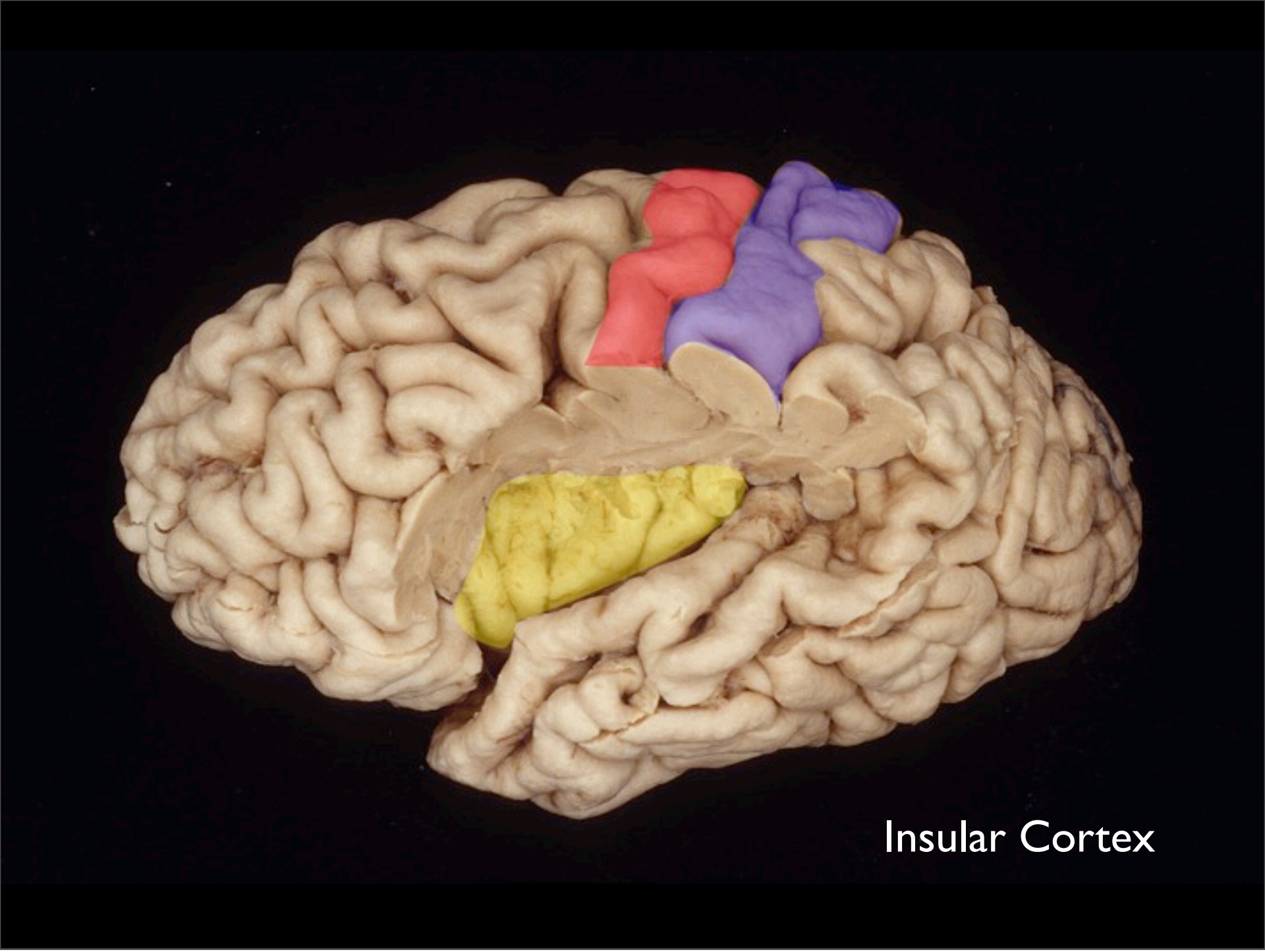


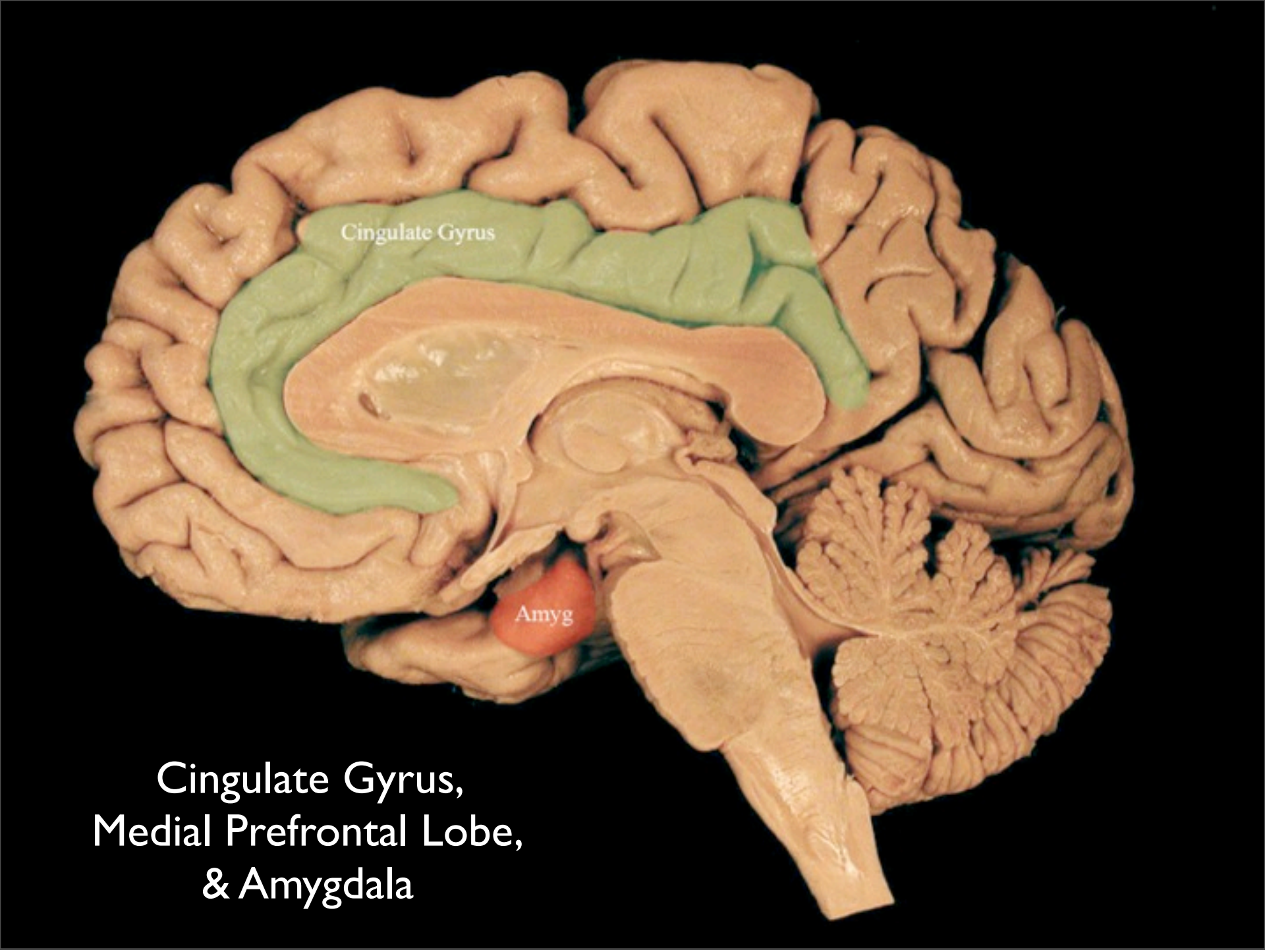

Touch
Pain
Raphe-spinal Tract
Dorsal horn
ENK Neuron
To spinothalamic tract

Pain and the Emotional Brain


Anterior
Cingulate
Cortex
Primary
Somatic
Sensory
Cortex
Insula
Am
Pelvic
Dysfunction
Inflammation


SI
SII
Somatic Sensory Cortex

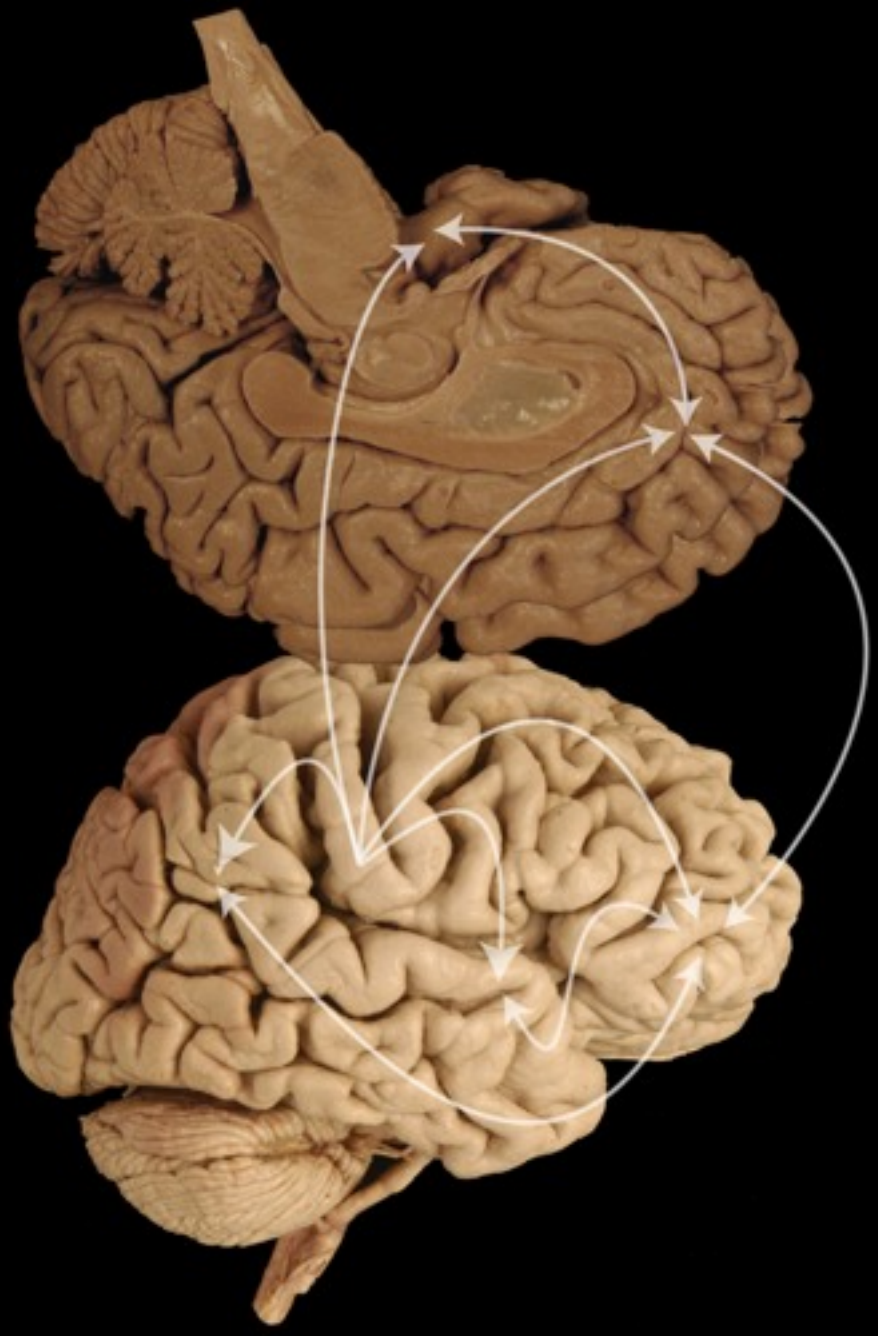

Insular Cortex



Cingulate Gyrus, Medial Prefrontal Lobe, & Amygdala

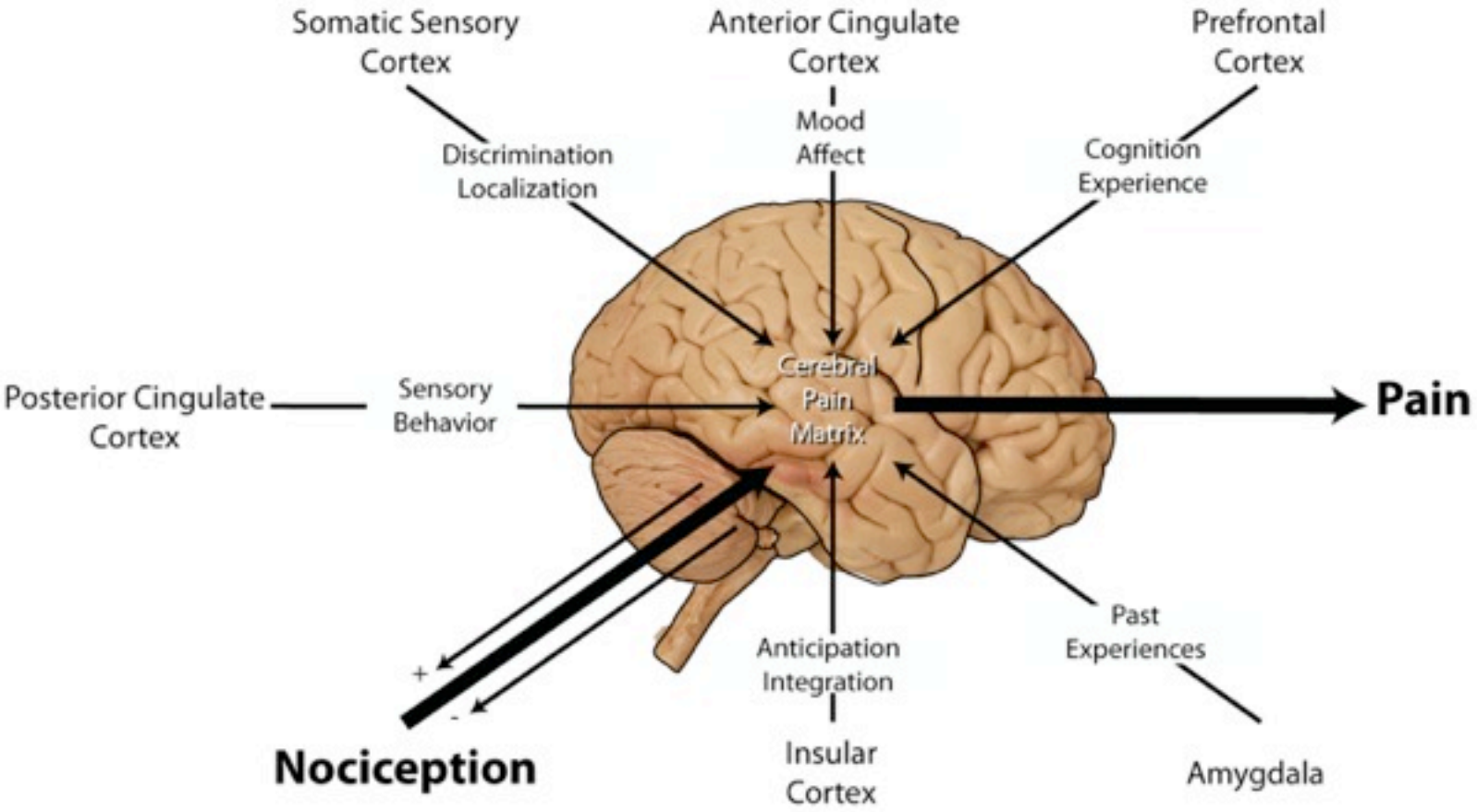
Dorsolateral Prefrontal Cortex

Orbital
Prefrontal
Cortex

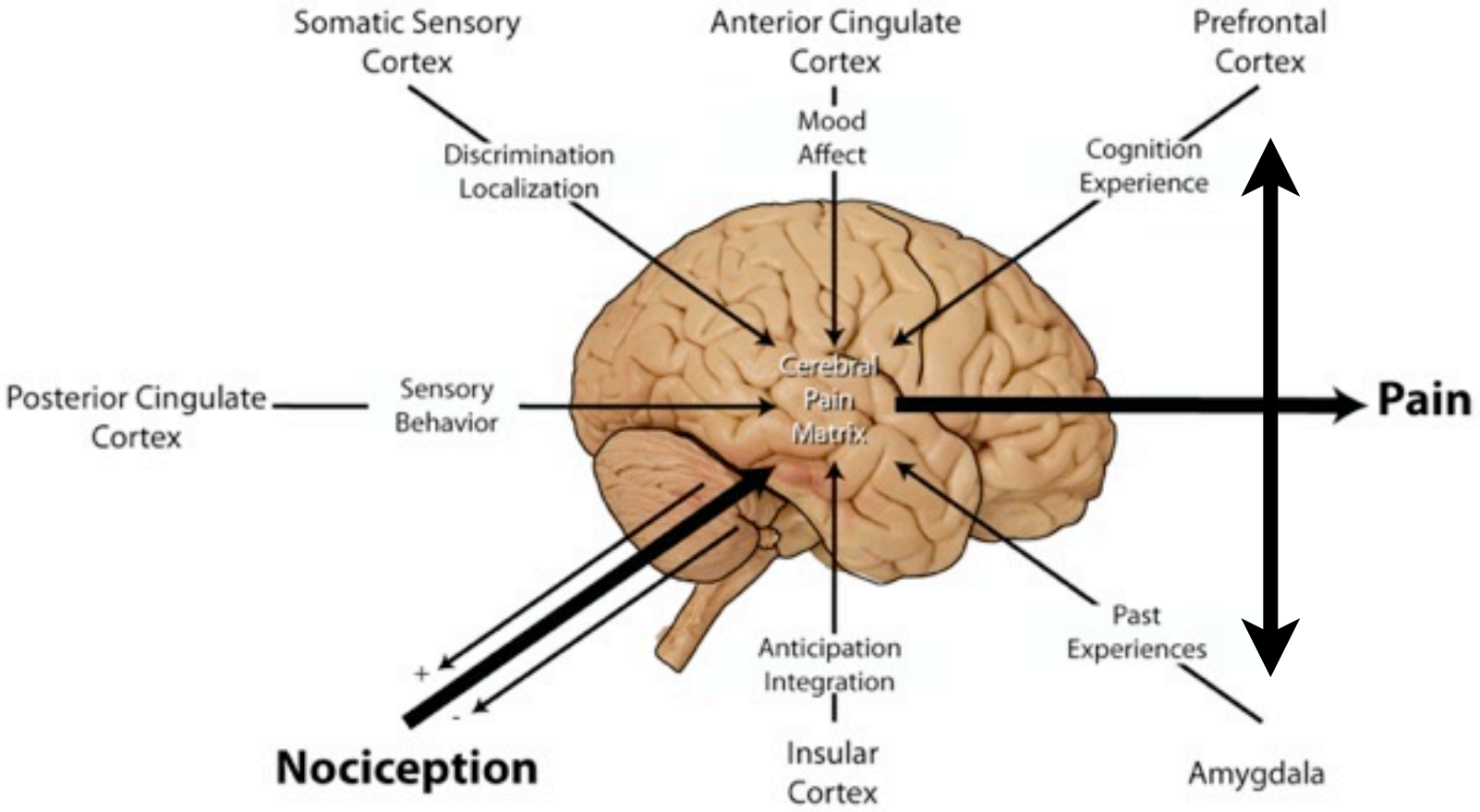


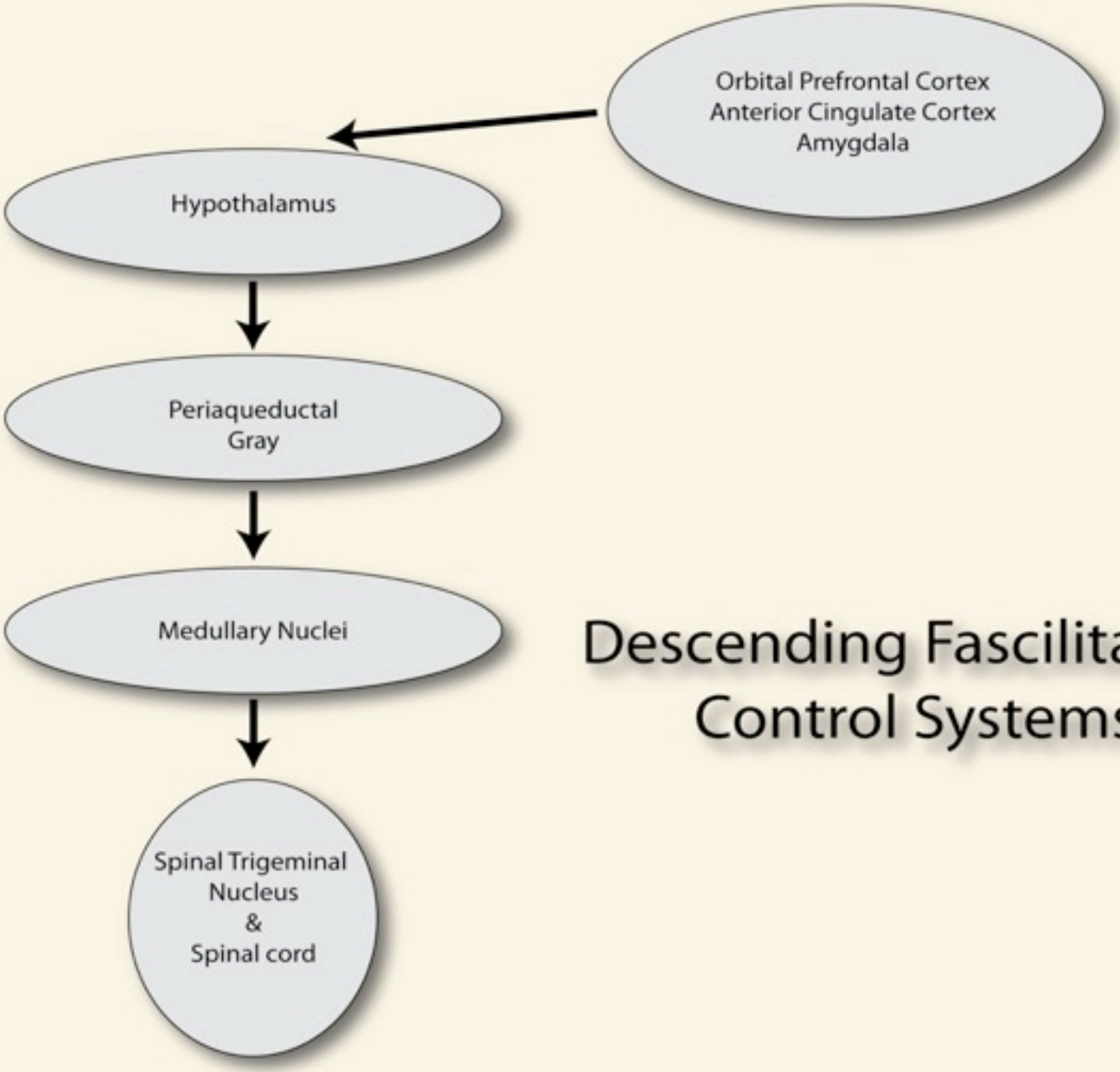
Pain
Neuromatrix

Pain Neuromatrix

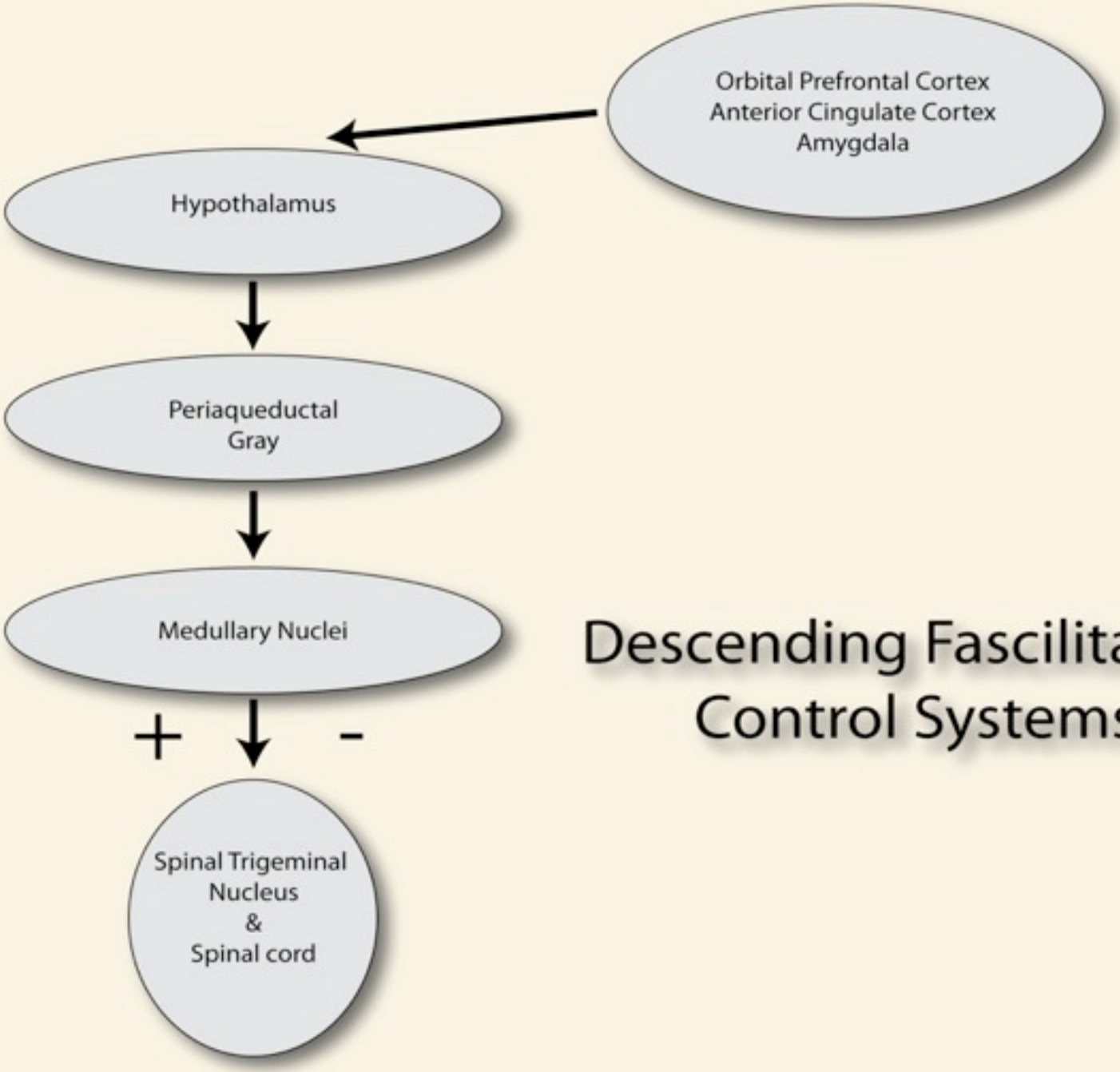


Pain Neuromatrix

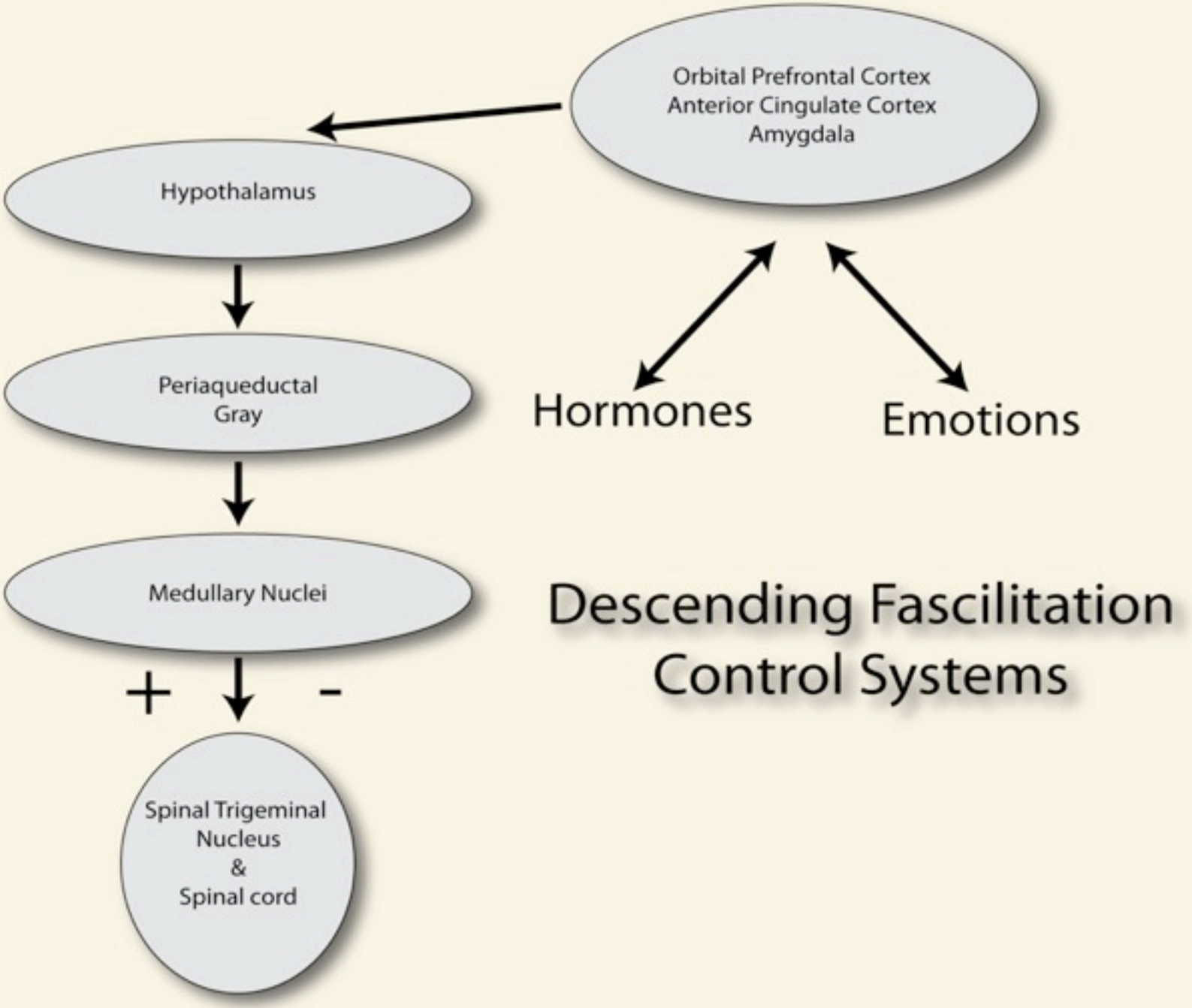


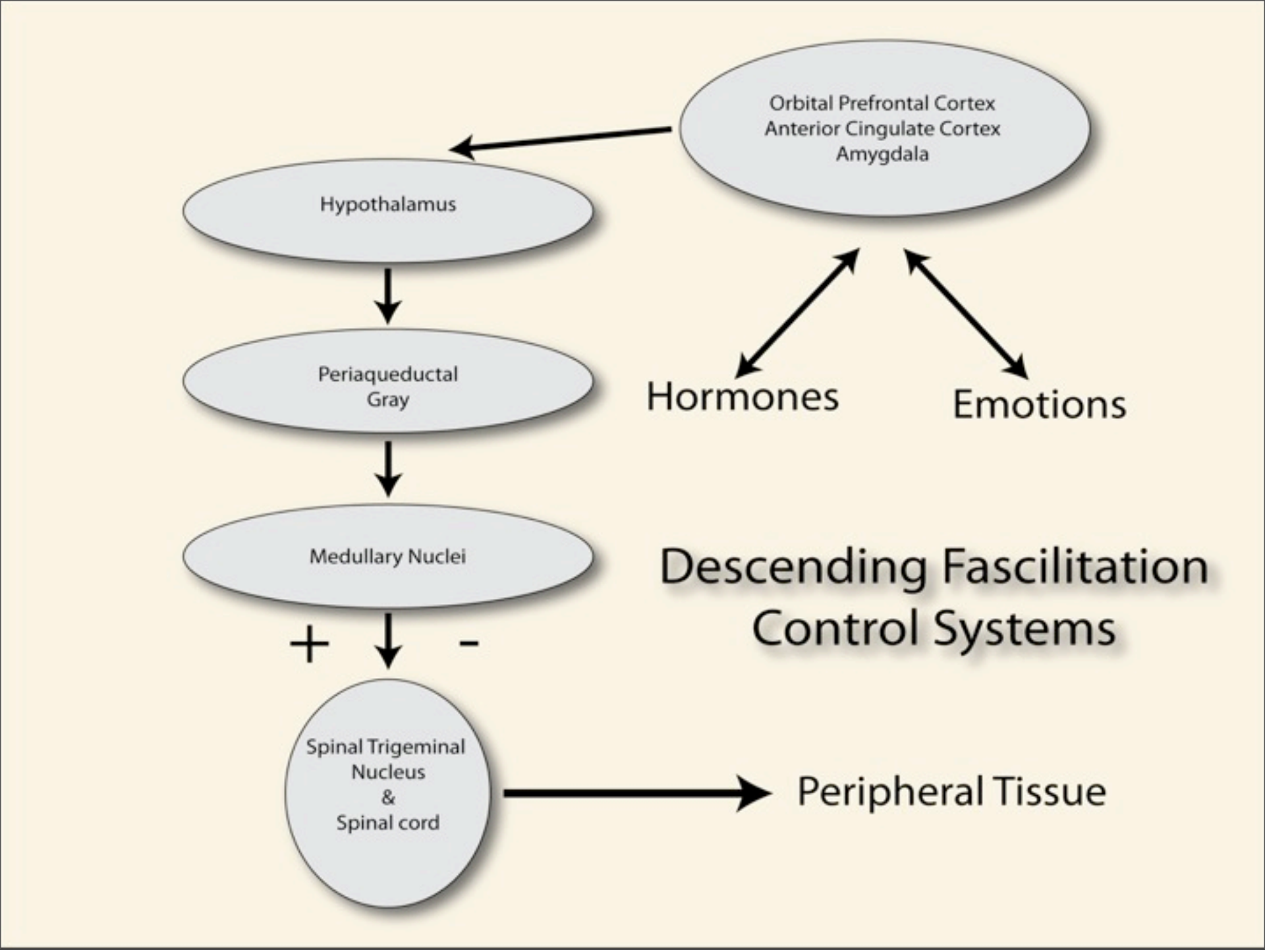


Descending Fascilitation Control Systems

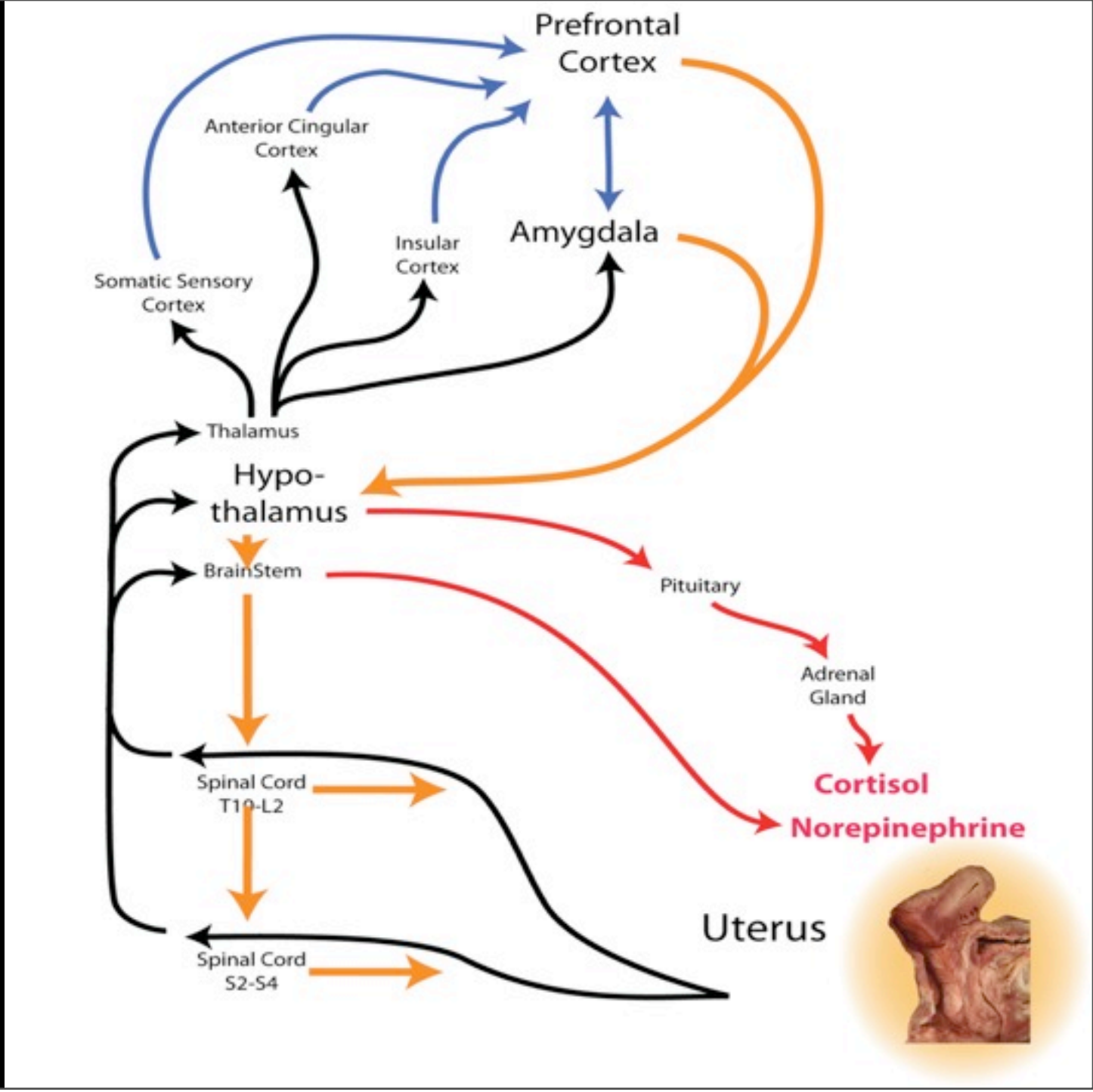


Descending Fascilitation Control Systems


Orbital Prefrontal Cortex
Anterior Cingulate Cortex
Amygdala
Hypothalamus
Periaqueductal Gray
Medullary Nuclei
+
-
Spinal Trigeminal Nucleus & Spinal cord
Hormones
Emotions
Descending Fascilitation Control Systems


Orbital Prefrontal Cortex
Anterior Cingulate Cortex
Amygdala
Hypothalamus
Periaqueductal Gray
Medullary Nuclei
+
-
Spinal Trigeminal Nucleus & Spinal cord
Hormones
Emotions
Descending Fascilitation Control Systems
Peripheral Tissue

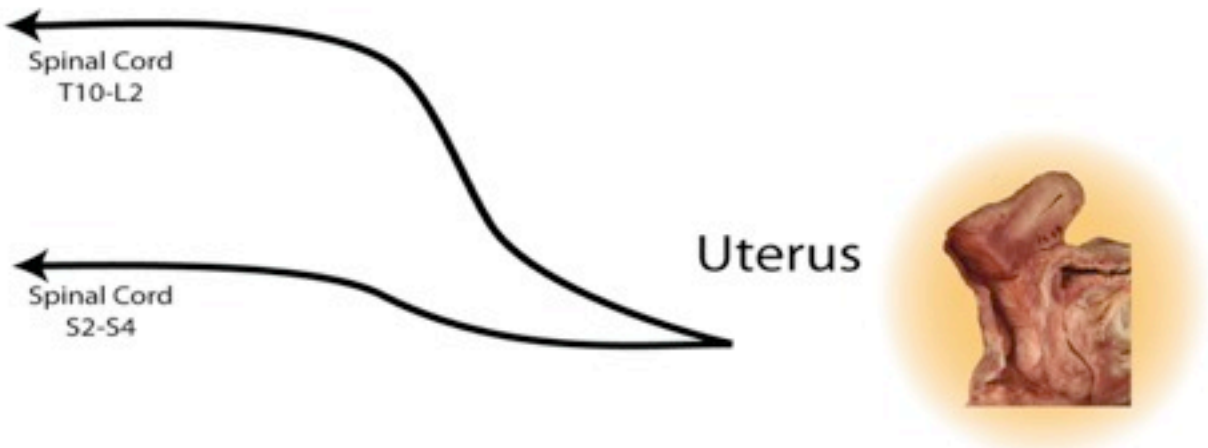
Pelvic Pain Circuit



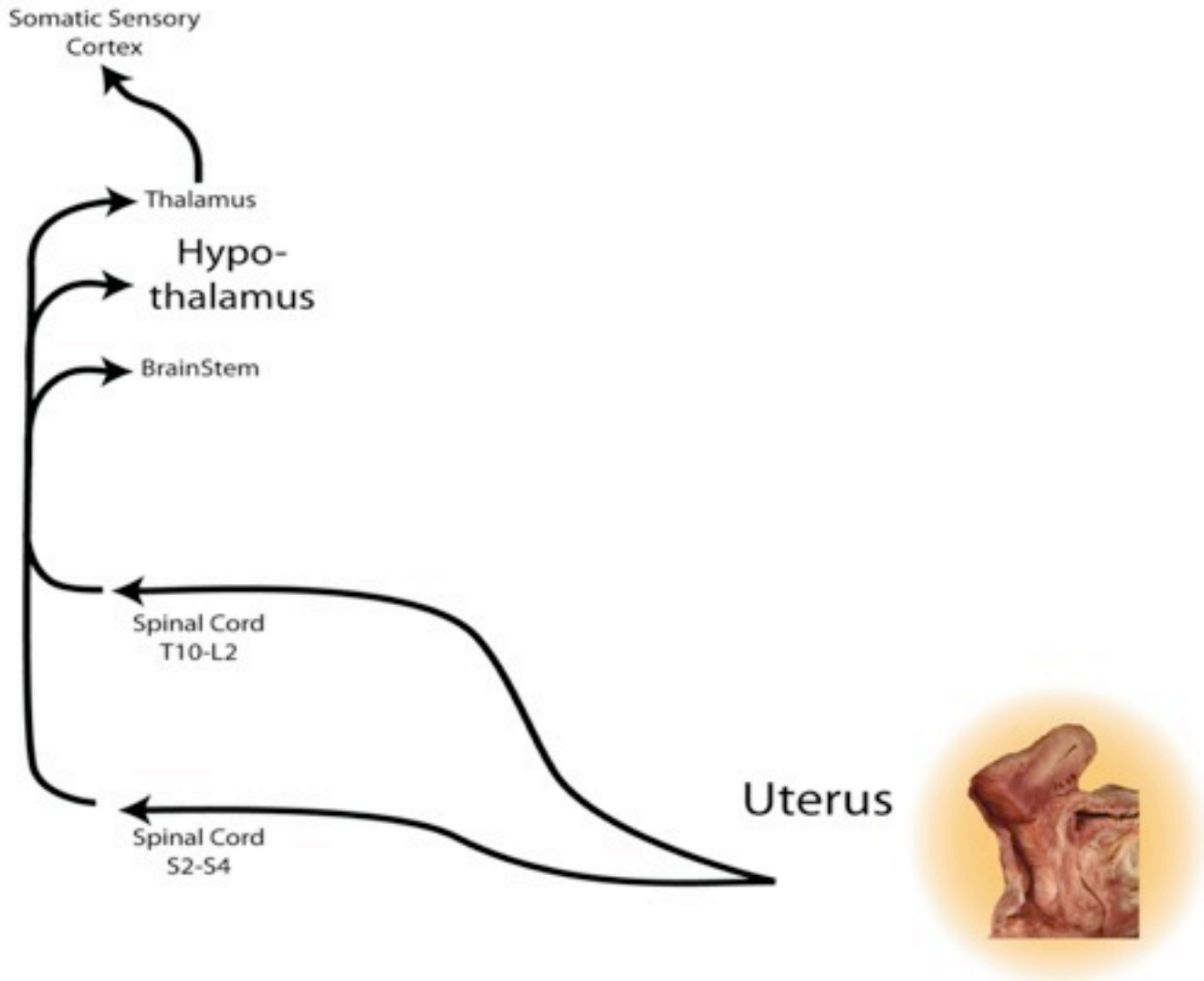
Pelvic Pain Circuit

Uterus

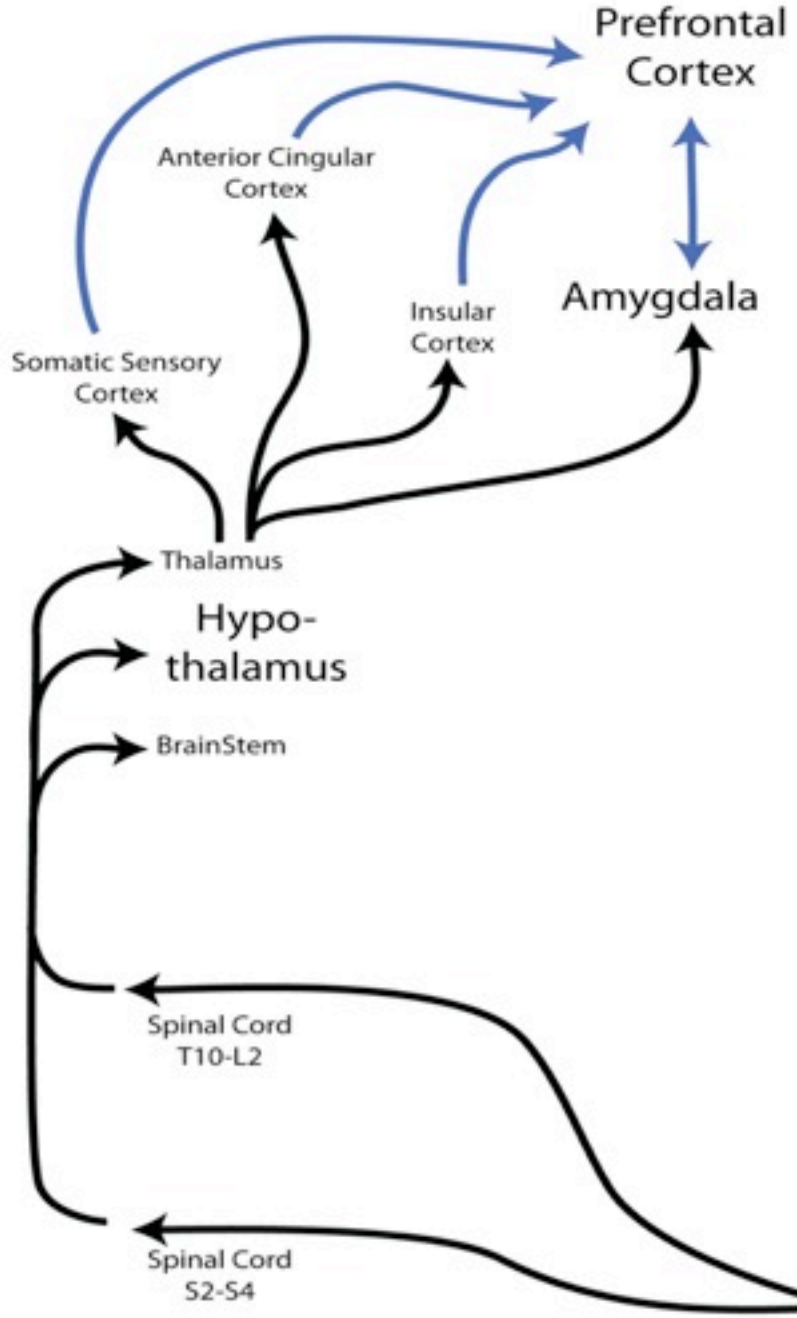
Pelvic Pain Circuit



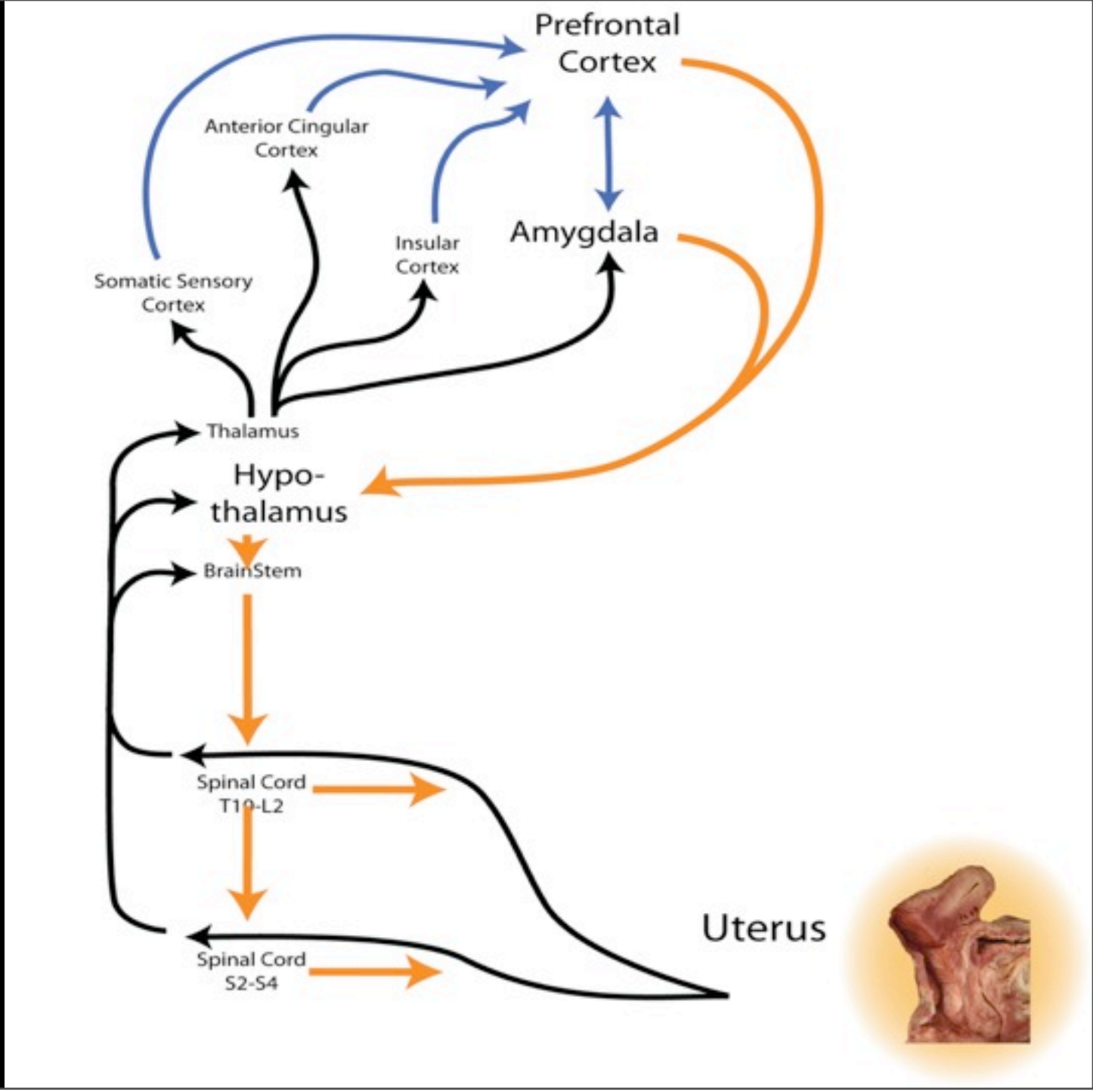
Pelvic Pain Circuit



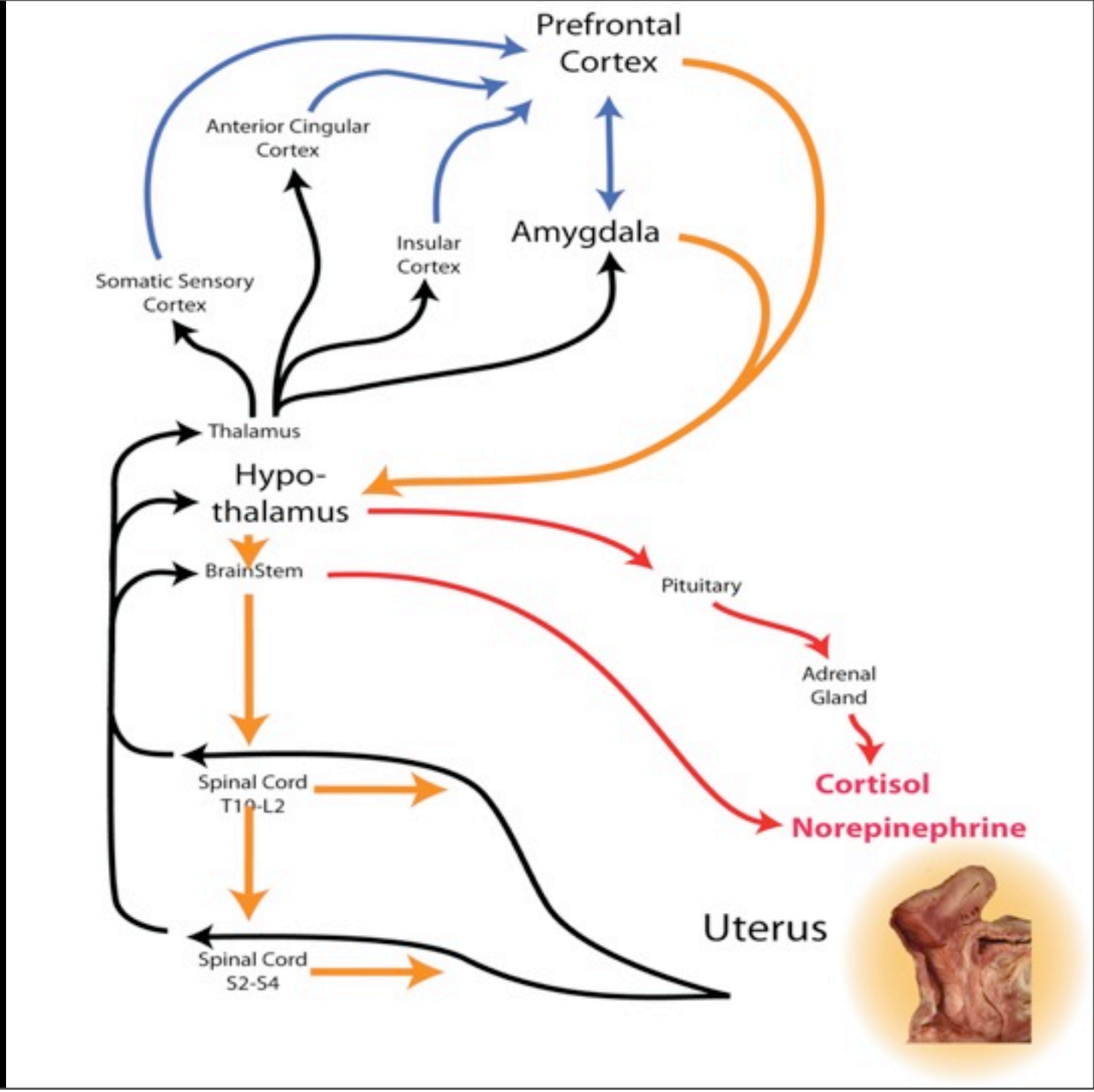
Pelvic Pain Circuit



Pelvic Pain Circuit



Pelvic Pain Circuit



Peripheral & Central Sensitization

Peripheral & Central Sensitization

Peripheral & Central Sensitization

Peripheral & Central Sensitization