Spinal Reflexes & Neuronal Integration

Reflex = an inherent, subconscious, relatively consistent responses to a particular stimulation.

> In contrast . . .
> **Reaction** = an inherent, subconscious, relatively consistent responses to a particular stimulation, involving the cerebellum and cerebral cortex; e.g., hopping reaction & tactile placing reaction.

Examples of brainstem reflexes include:
— eyelids close when the cornea is touched (corneal reflex)
— lip moves in response to a noxious stimulation (pin prick)

Examples of spinal reflexes, involving spinal nerves and the spinal cord, include:
— extensor thrust: paw proprioceptors trigger limb extension
— panniculus reflex: pricking skin triggers contraction of cutaneus trunci (panniculus) m.
— myotatic reflex: muscle stretch is resisted by reflex contraction of the muscle
— withdrawal reflex: limb flexes to withdraw from a noxious stimulus

NOTE:

Reflex responses are determined by interneurons which "hard-wire" afferent input to efferent output. Interneurons organize efferent neurons (motor units) into meaningful movement components, which can be utilized by either spinal input or descending pathways.

Also, interneurons form **pattern generators** for repetitive movements. Locomotor pattern generators exist in the spinal cord (e.g., on a treadmill, hind limbs exhibit stepping even in a cat that has its spinal cord transected in the thoracic region, i.e., isolated from the brain).

Since "voluntary movement" and "involuntary reflex/reaction" compete for control of the same interneurons circuits, they cannot be independent on one another. Thus, brain activity will influence spinal reflex responses, making clinical reflex evaluation an interpretive art.

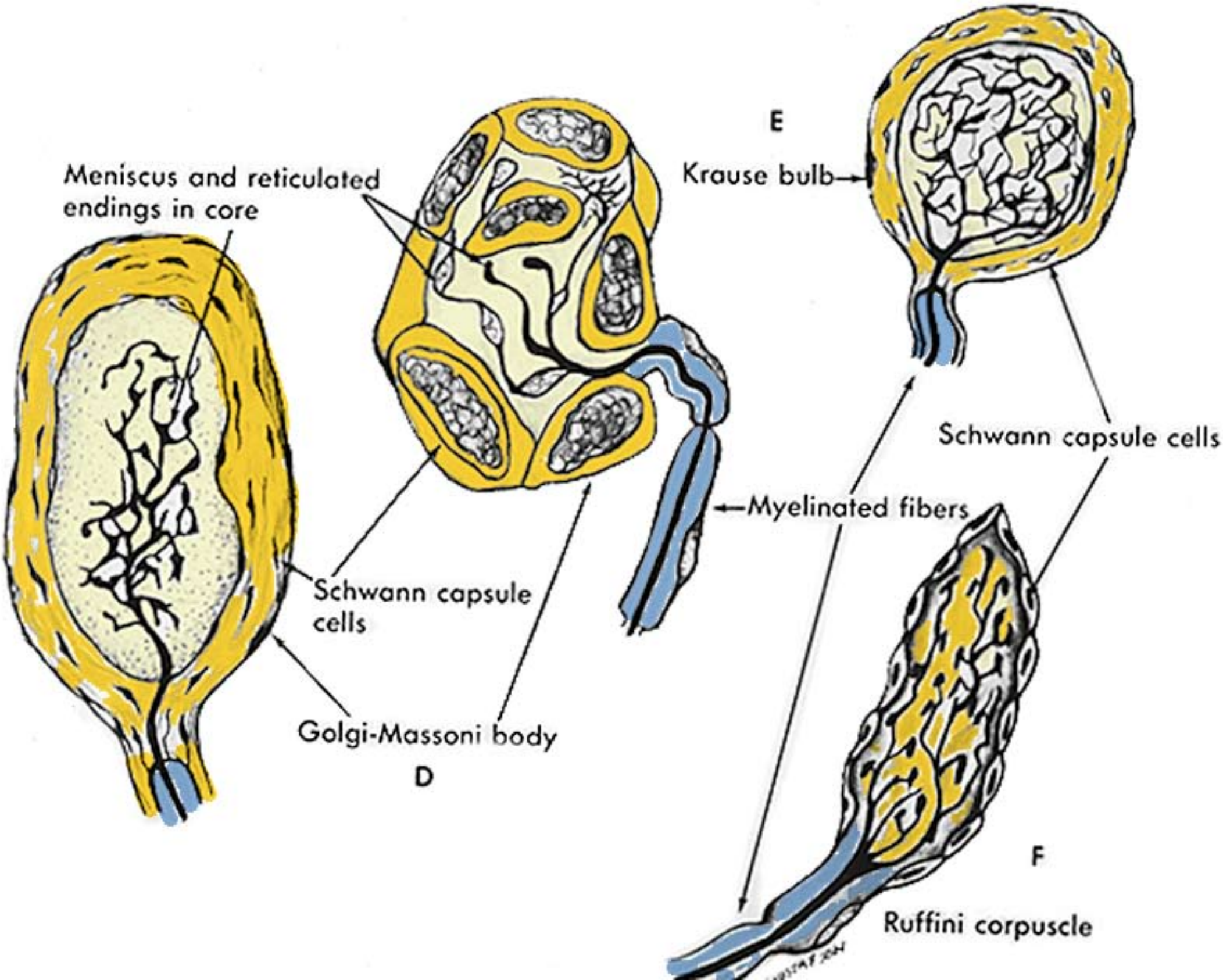
BACKGROUND INFORMATION ABOUT PROPRIOCEPTION

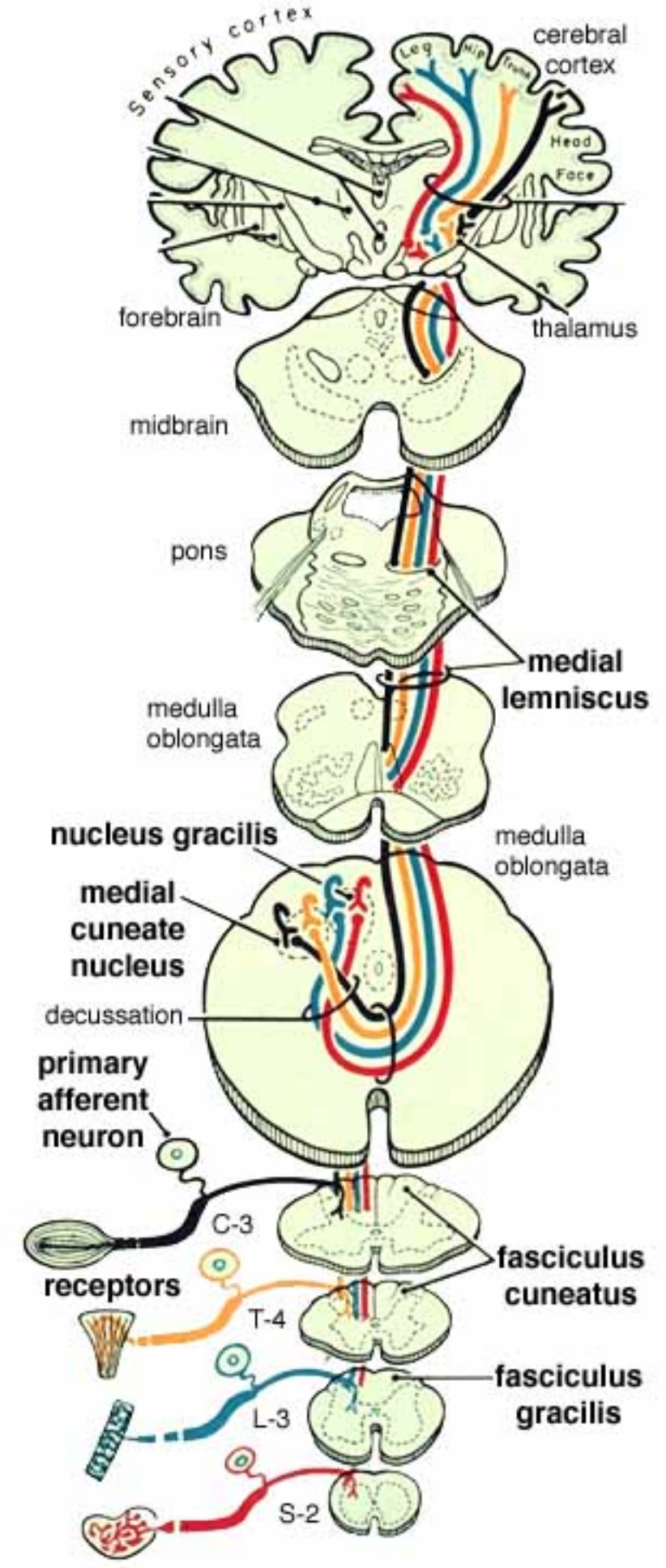
Proprioceptors are mechanoreceptors, located in muscles/tendons & joint capsules/ligaments.

Proprioceptors provide:
- *subconscious feedback* about the status of muscles & joints,
- conscious *kinesthesia* (sense of position & movement), and
- *pain*

Joint receptors:
- *free nerve endings* that respond to extreme movement or inflammation *(pain)*
- *encapsulated receptors:*
  — tonic: signal joint position
  — phasic: respond to rate of change in joint position (largely *subconscious)*

Muscle & tendon proprioceptors:
free nerve endings: pain
(Golgi) tendon organs: located in series with muscle fibers *(tension detector)*
muscle spindles: located in muscle belly *(length detector)*


Meniscus and reticulated endings in core
Schwann capsule cells
Golgi-Massoni body
D
E
Krause bulb
Myelinated fibers
Schwann capsule cells
F
Ruffini corpuscle


Sensory cortex
cerebral cortex
Leg
Hip
Trunk
Head
Face
forebrain
thalamus
midbrain
pons
medial lemniscus
medulla oblongata
nucleus gracilis
medulla oblongata
medial cuneate nucleus
decussation
primary afferent neuron
C-3
receptors
fasciculus cuneatus
T-4
fasciculus gracilis
L-3
S-2

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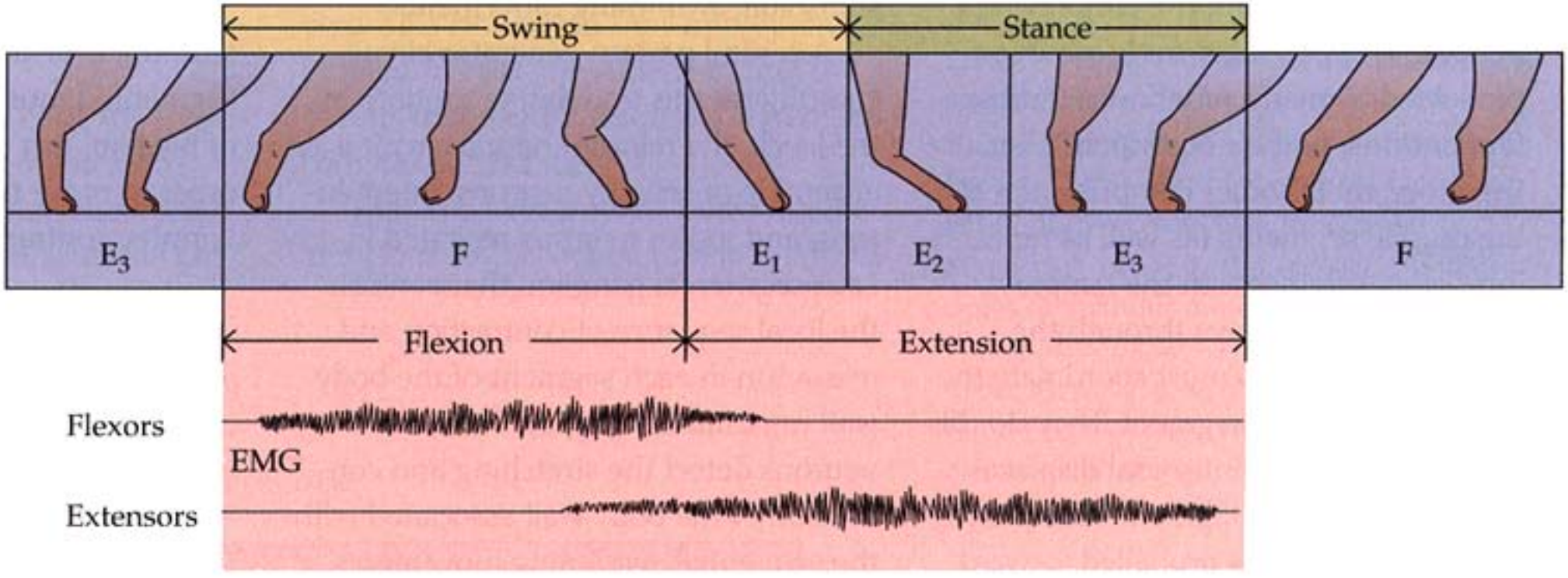
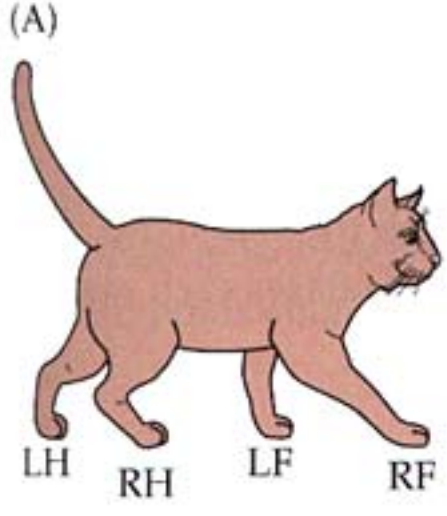
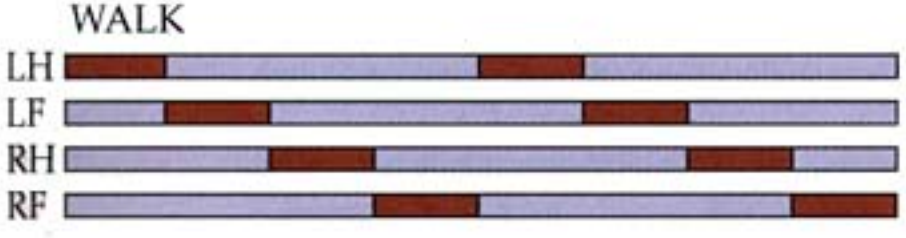
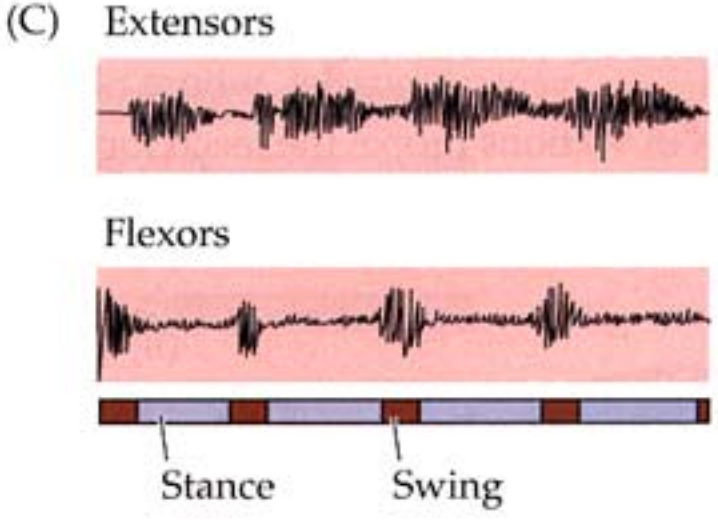
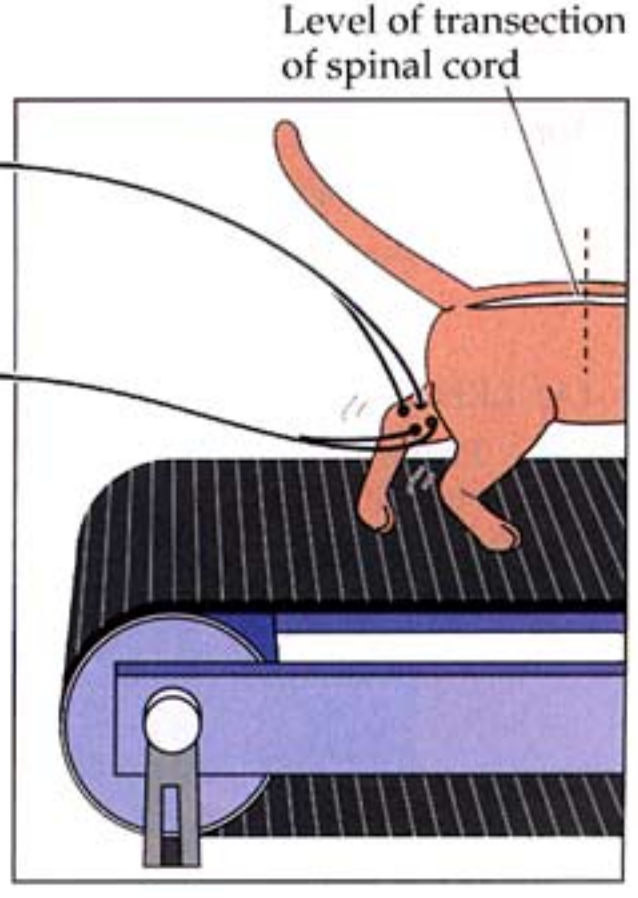

Swing
Stance
E3
F
E1
E2
E3
F
Flexion
Extension
Flexors
EMG
Extensors


(A)
LH
RH
LF
RF


WALK
LH
LF
RH
RF

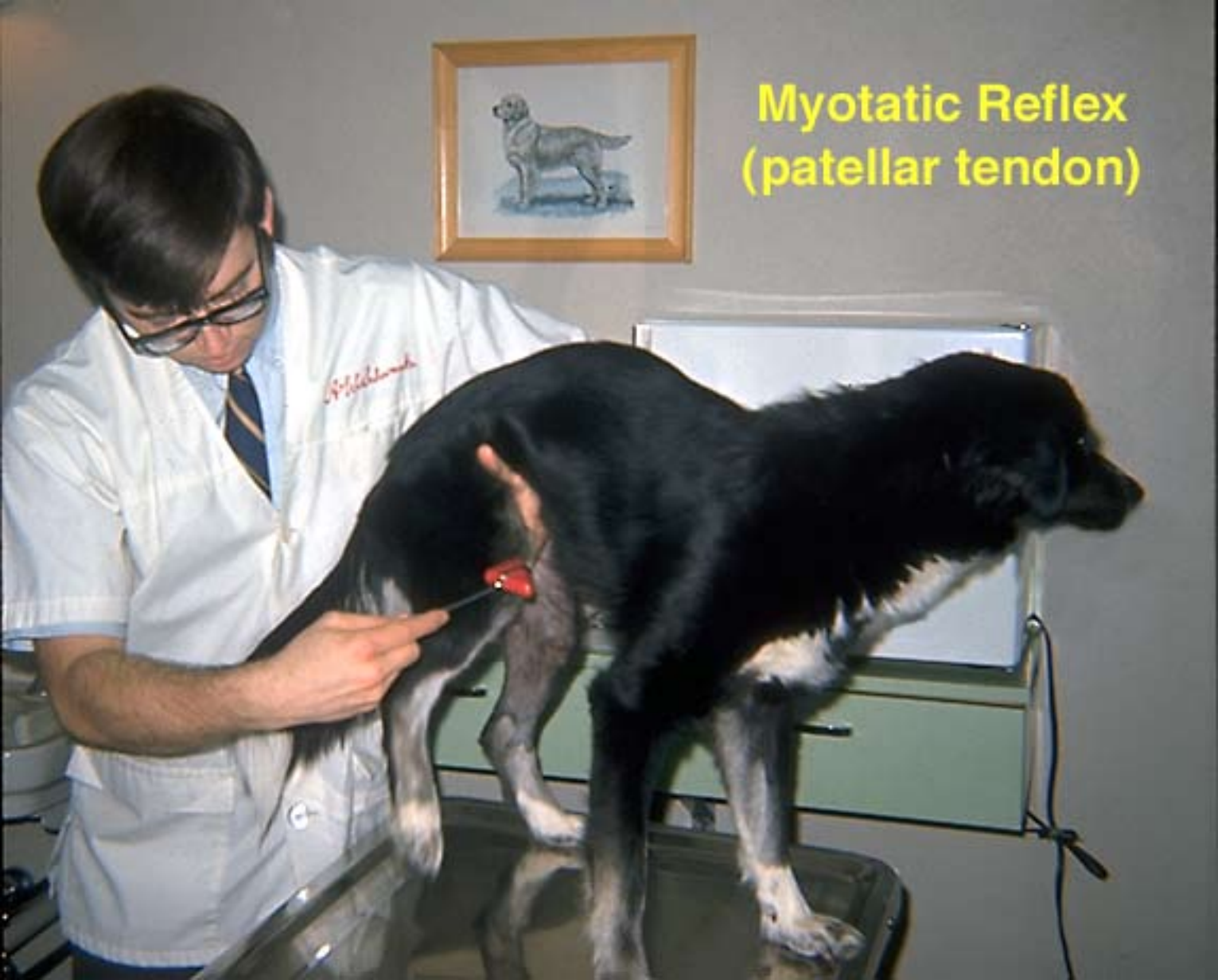

(C)
Extensors
Flexors
Stance
Swing

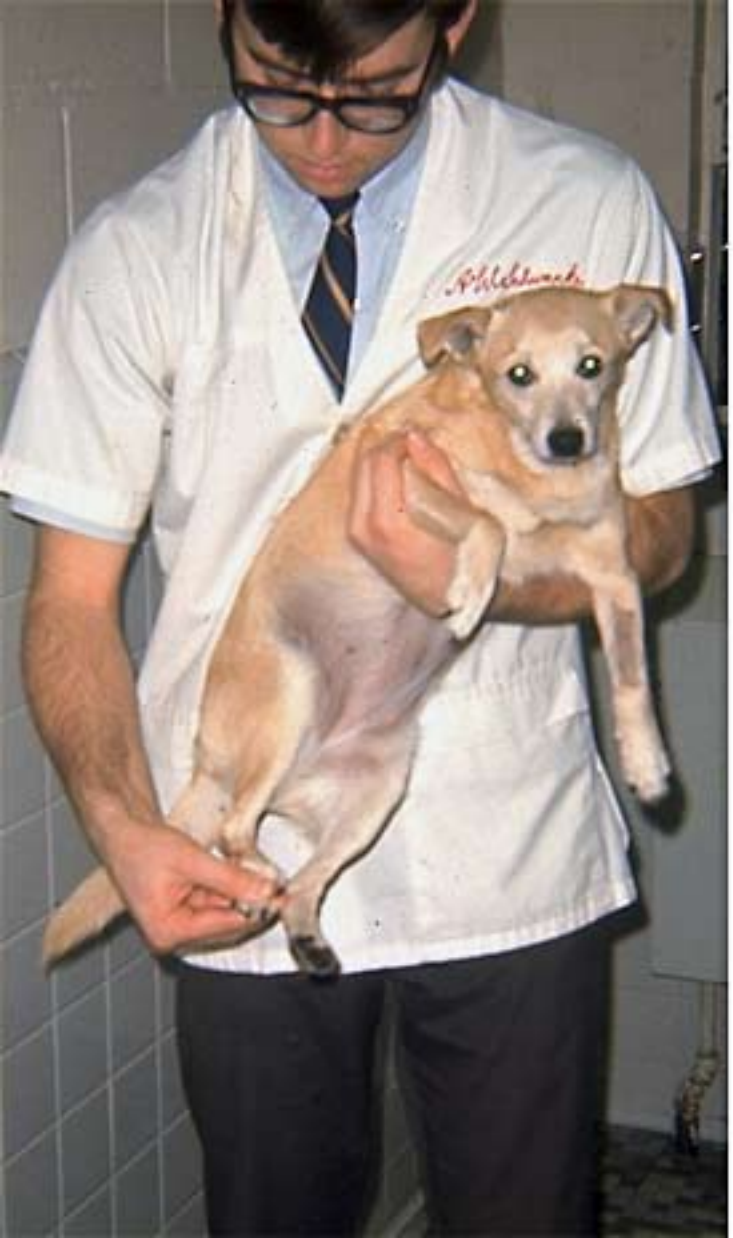

Level of transection
of spinal cord


Tactile Placing
Reaction


Hopping
Reaction

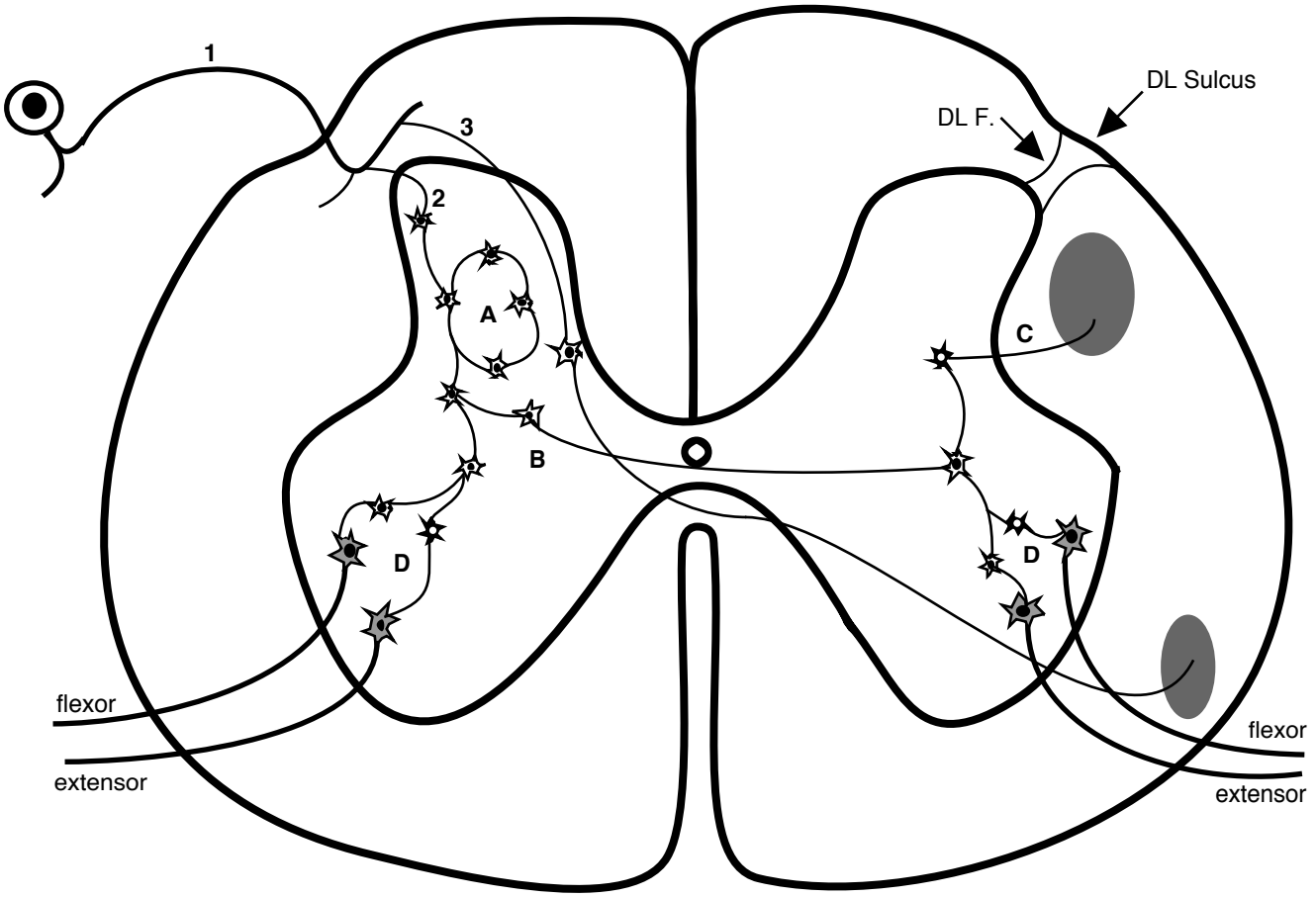

Panniculus Reflex
Cutaneus Trunci Reflex


Myotatic Reflex
(patellar tendon)




Withdrawal Reflex
Felxor (Crossed Extensor) Reflex

Withdrawal Reflex



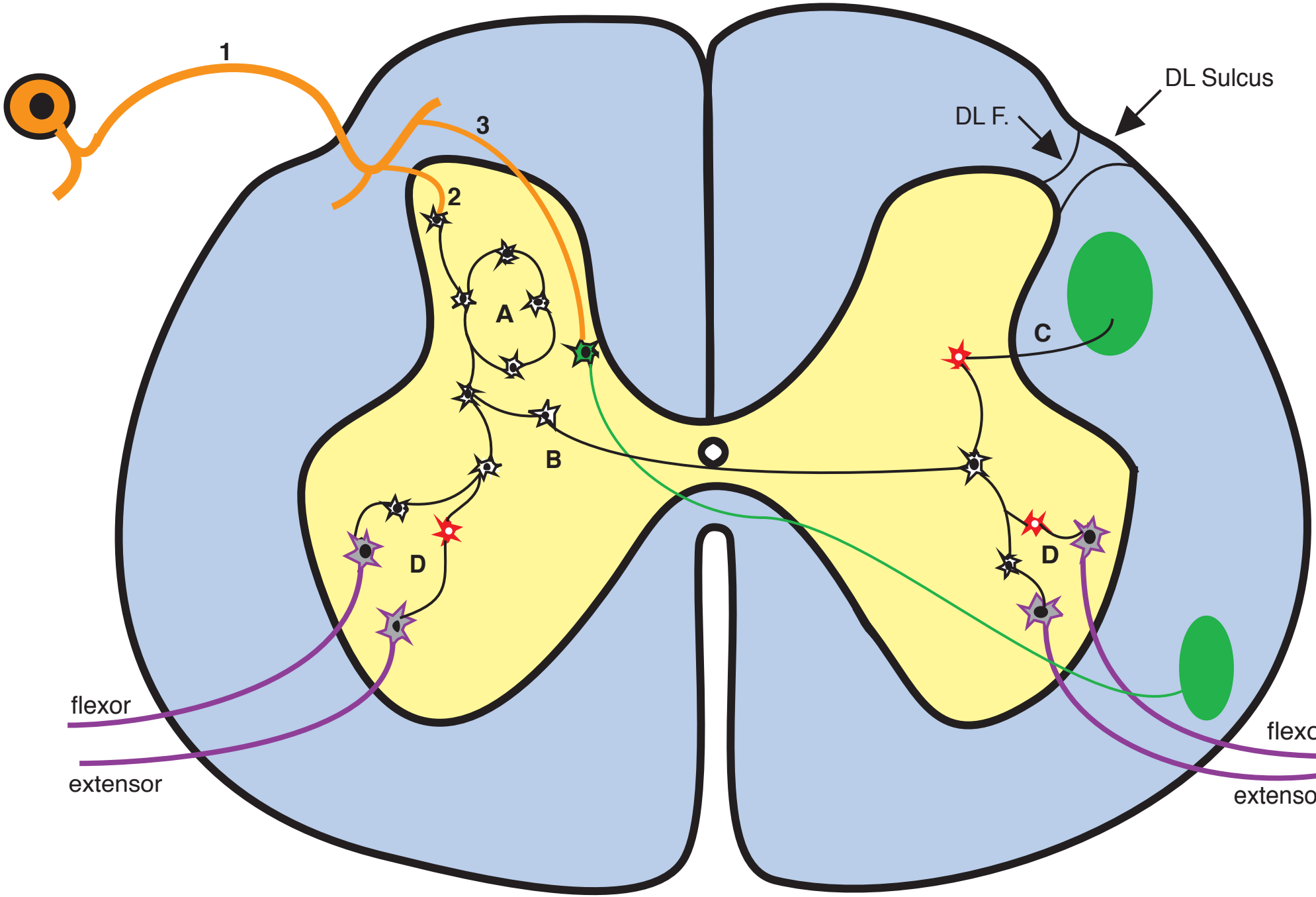
Withdrawal Reflex = Flexor (Crossed Extensor) Reflex

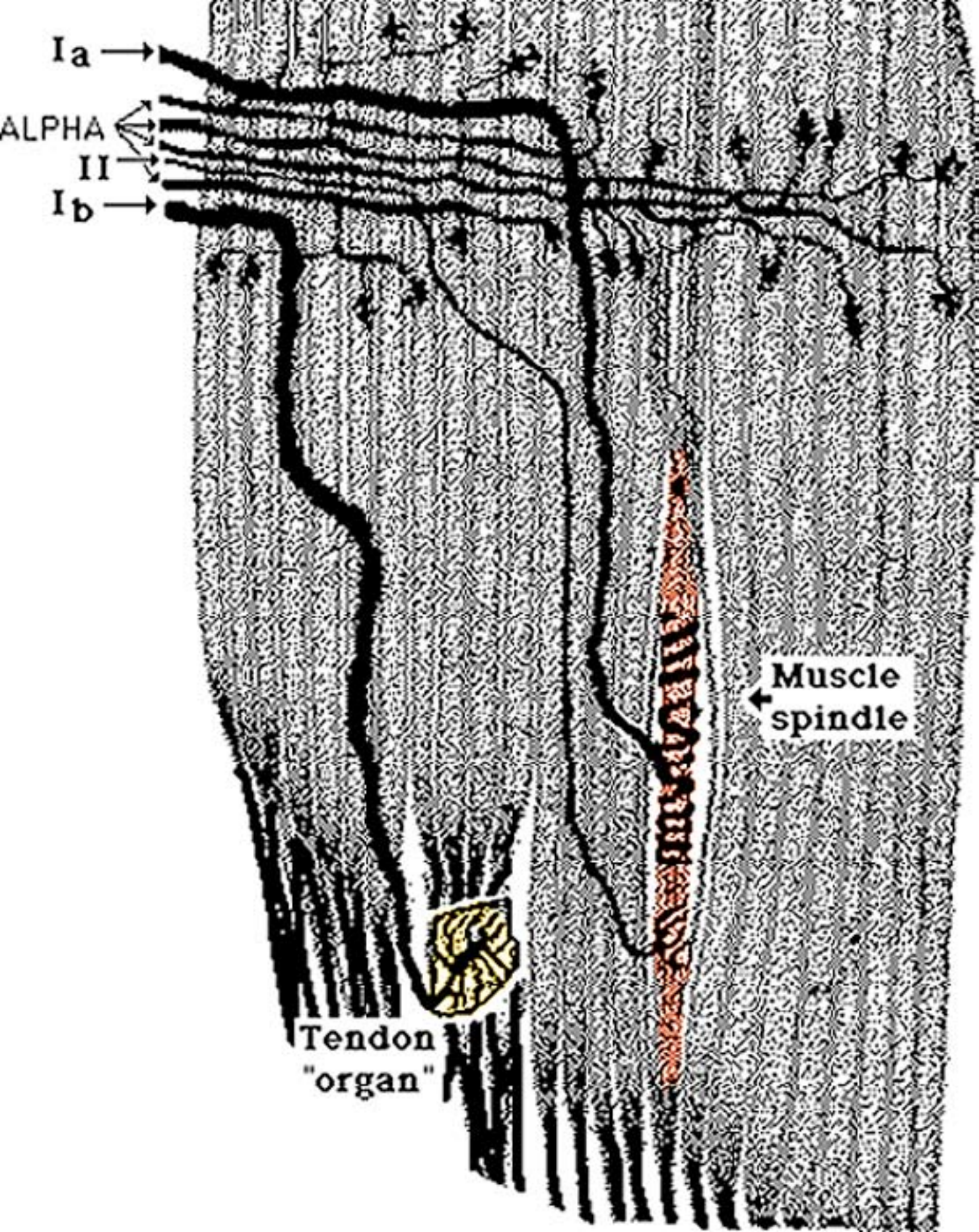
Features of the reflex *(diagrammed above)* include . . .

— primary afferent neuron (1) participates in both reflexes (2) and ascending pathways (3);
— divergent interneuronal circuit propagates to several segments and right and left sides (B);
— positive feedback prolongs the reflex beyond the time of the stimulus (A);
— individual interneurons are either excitatory or inhibitory (black cells) in their effect;
— antagonists are inhibited while agonists are excited (reciprocal innervation) (D);
— descending pathways (C) modify reflex circuit (reflex is not independent of brain control).

NOTES:

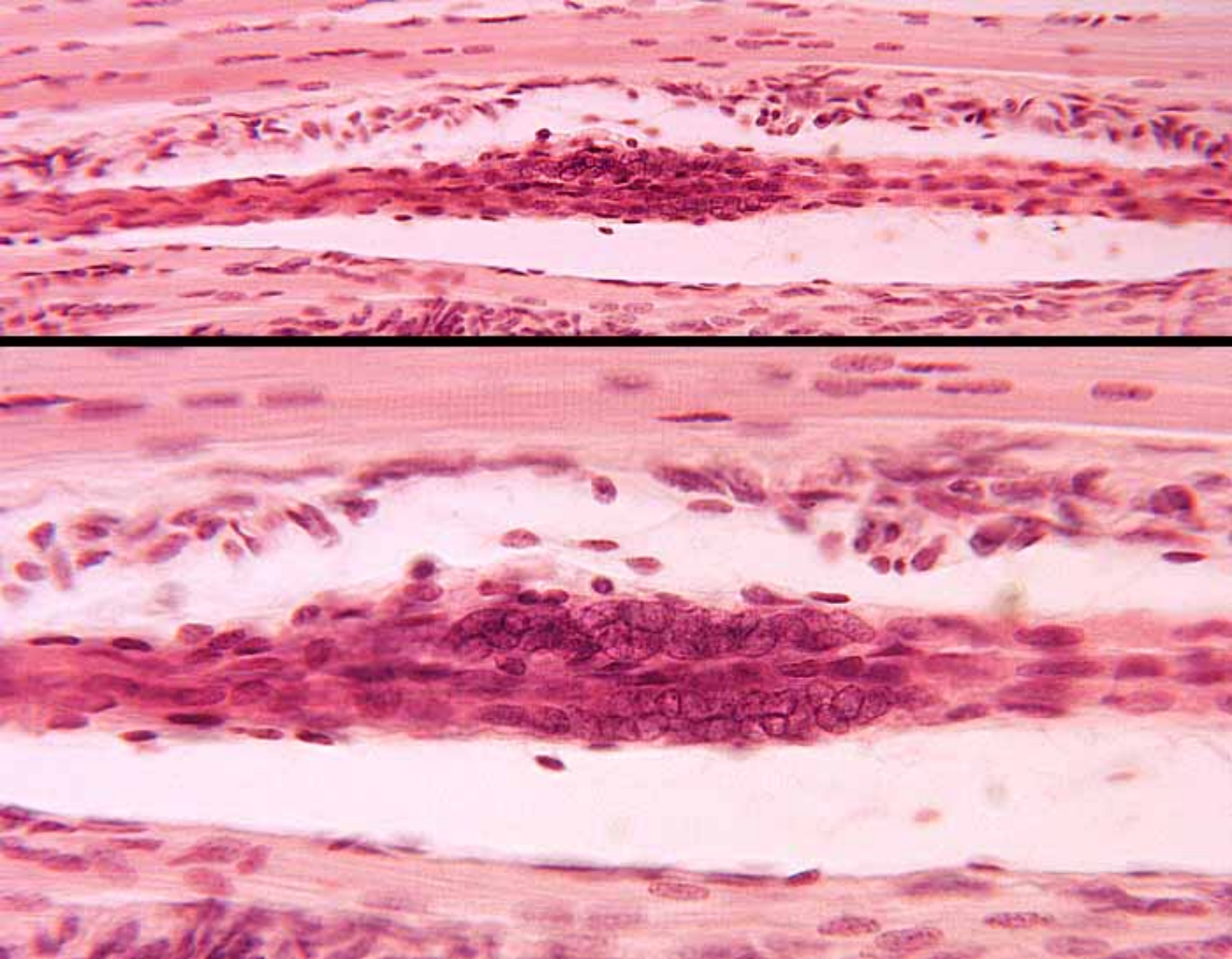
- As the reflex is tested clinically, the *crossed extension* component disappears after the first 3 weeks of age as descending pathways mature to inhibit the extension; but later in life, the normally inhibited crossed extension reappears if "upstream" damage to descending fibers removes the inhibition.
- The withdrawal reflex is often elicited to assess depth of anesthesia.

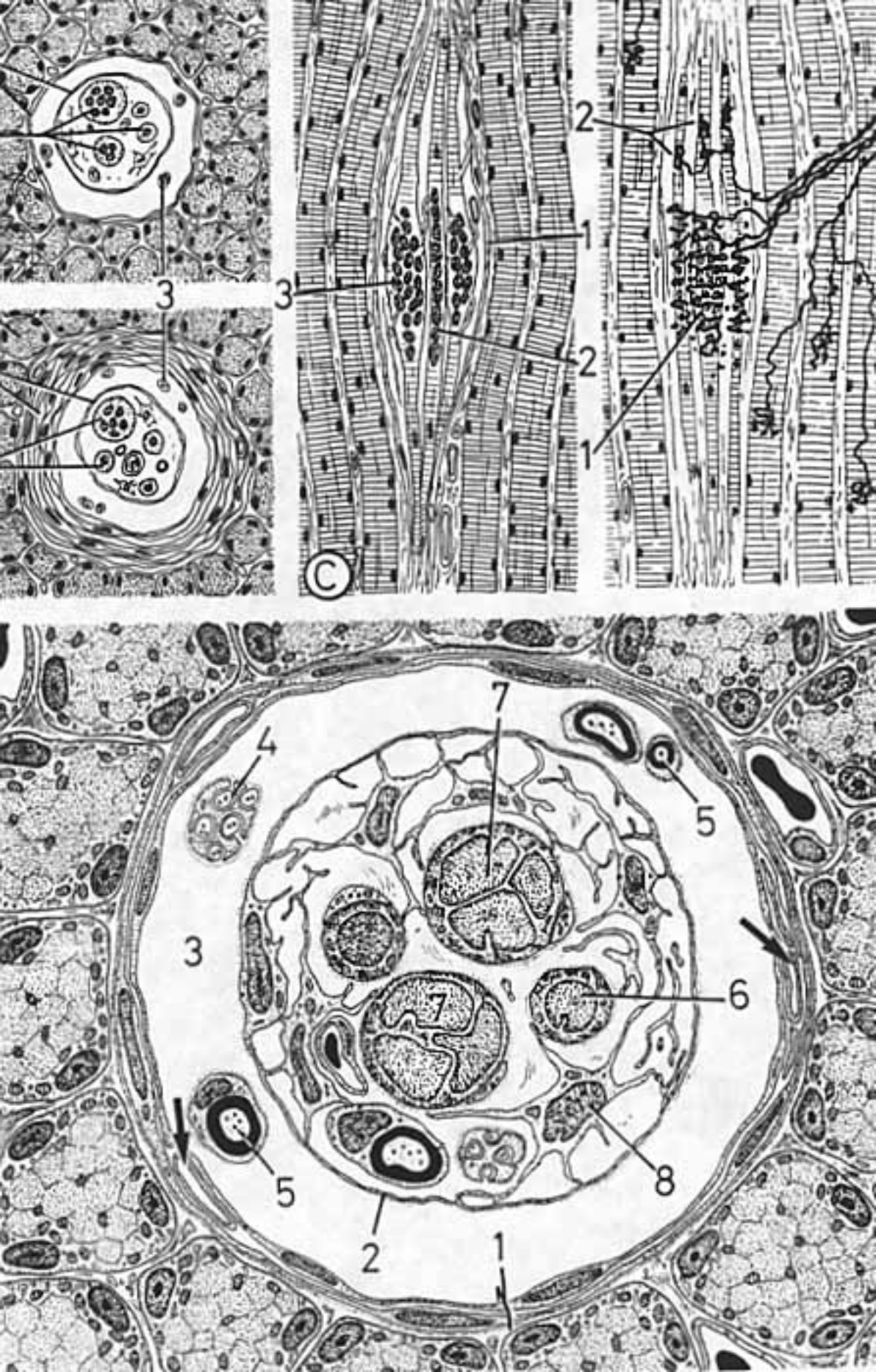

1
2
3
A
B
C
D
D
DL Sulcus
DL F.
flexor
extensor
flexor
extensor


Ia
ALPHA
II
Ib
Muscle spindle
Tendon "organ"

9
6
5
4
6
8
7
1
2

3
1
3
1
3
9
2
3
8
10
7
1
7
1
5
6




3
3
1
2
2
1
C
7
4
5
3
6
5
8
2
1

Muscle Spindle and Myotatic Reflex

Muscle spindles are:

- elaborate proprioceptors positioned in parallel with muscle fibers;
- designed to signal muscle length
- about 3mm long & 0.5 mm wide.

Morphologically, a muscle spindle consists of a connective tissue capsule enclosing:

— two kinds of mechanoreceptors,
— two kinds of intrafusal muscle fibers,
— two kinds of gamma efferent neurons.

Intrafusal muscle fibers:

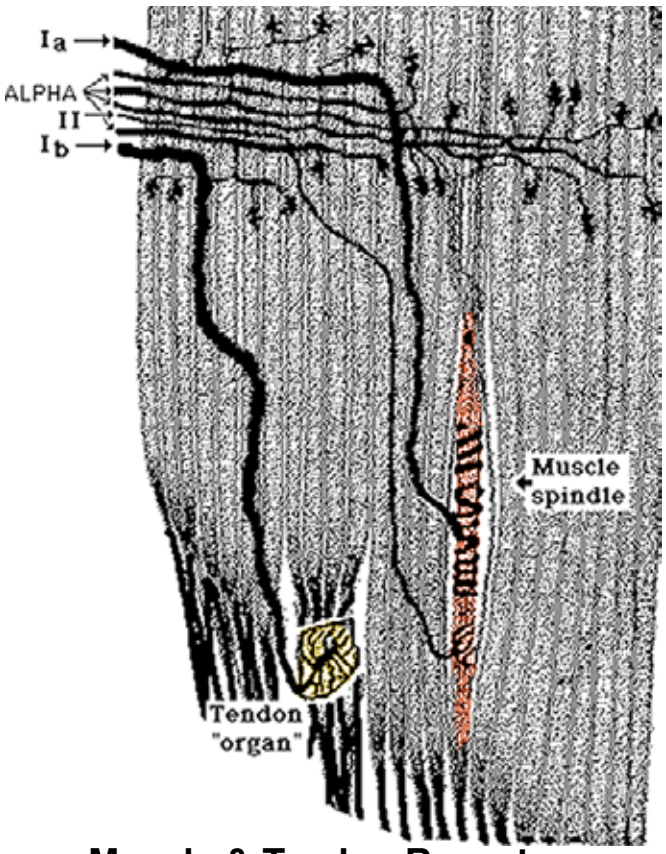
vs. extrafusal (typical) muscle fibers

- very small, anchored in endomysium
- do not contribute anything to whole muscle tension
- center of each fiber is packed with nuclei & lacks myofilaments
- polar regions are striated and innervated by gamma neurons
- two kinds of intrafusal muscle fibers:

nuclear bag fibers — central region is dilated; fiber extends beyond the capsule;

nuclear chain fibers — smaller, central region contains chain of nuclei.

Types of nerve fibers found in a muscle nerve



Muscle & Tendon Receptors

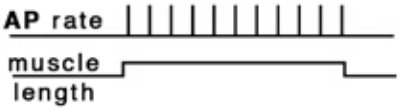
Mechanoreceptors within muscle spindle :

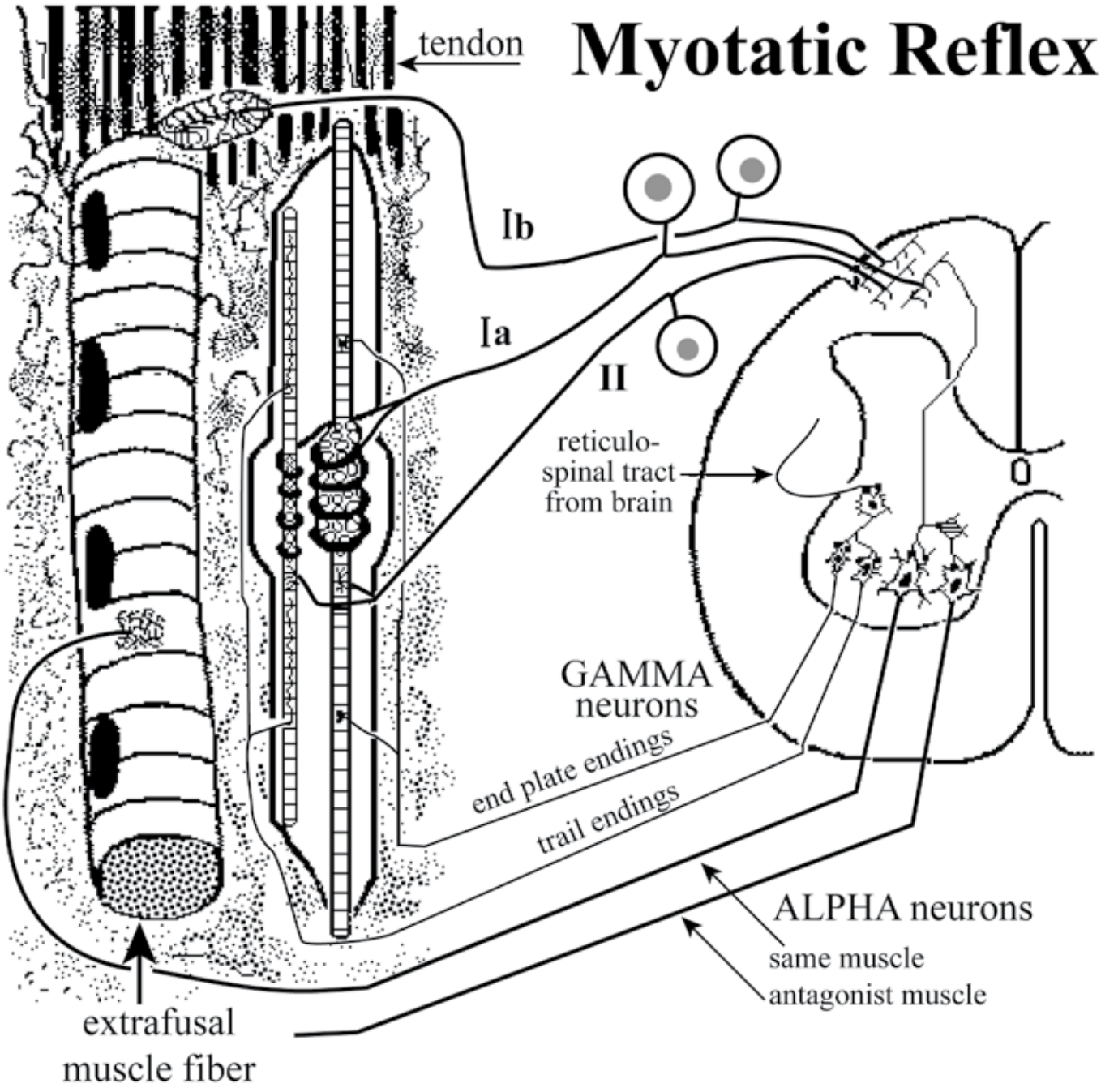
They are activated by stretch of the central region, which is stretched *either*

1) by contraction of polar regions of intrafusal muscle fibers, *or*
2) by passive stretch of the whole muscle (including the intrafusal fibers)

1] primary (annulospiral) endings — spiral around central (nuclear) regions; they are endings of large nerve fibers (type $\mathbf{I_A}$); initially AP frequency reflects rate of stretch; then steady AP frequency reflects degree of stretch

2] secondary endings — "flower-spray" formations adjacent to nuclear chain regions; they are endings of type **II** nerve fibers; AP frequency is proportional to degree of stretch.



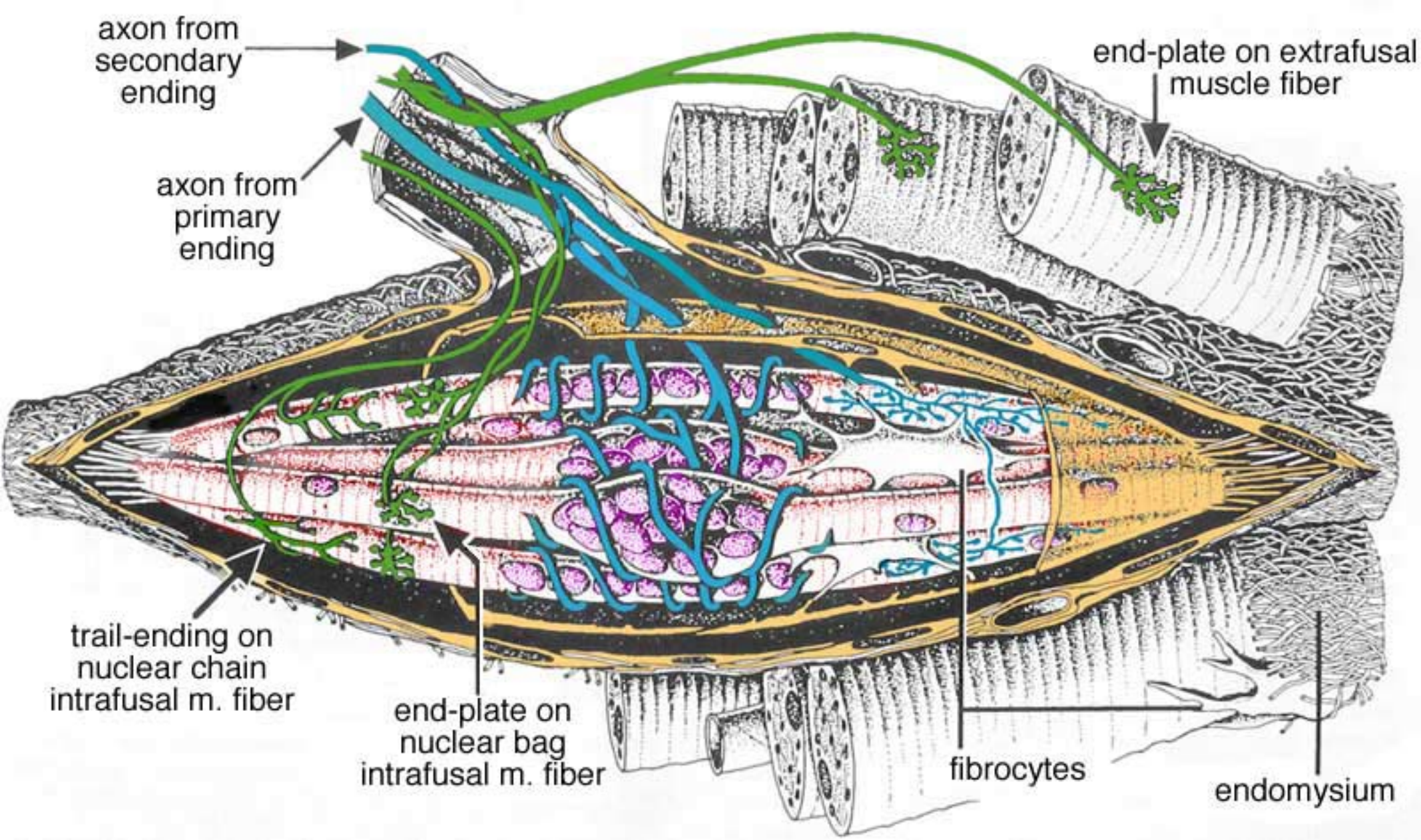


Myotatic Reflex

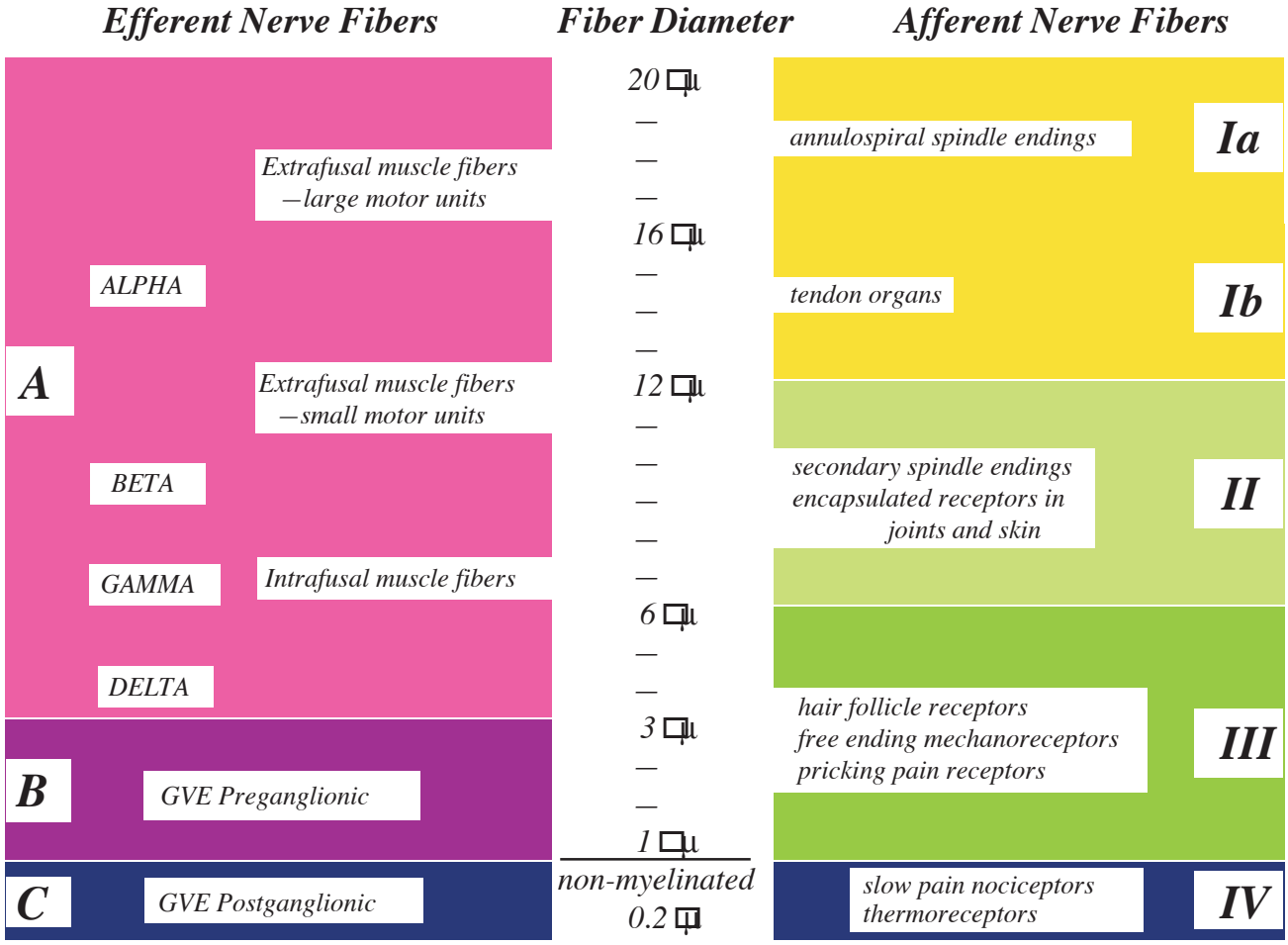
Clinically, a myotatic reflex is elicited by abruptly tapping a tendon (e.g., the patellar tendon). Suddenly deforming/displacing a tendon effectively stretches the associated muscle.

When a whole muscle is suddenly stretched (as a result of tendon deformation), annulospiral receptors in muscle spindles are simultaneously excited, triggering a volley of action potentials in $\mathbf{I_A}$ afferent axons. Within the CNS, the axons activate excitatory synapses on alpha motor neurons that innervate the muscle that was stretched. Also, alpha motor neurons to antagonistic muscles are inhibited via interneurons. As a result, the stretched muscle immediately contracts.

Thus, the **myotatic reflex functions to oppose muscle stretch**. Since interneurons are by-passed in eliciting the contraction, the response is rapid, localized, and relatively resistant to hypoxia, fatigue, drugs, etc.


axon from secondary ending
axon from primary ending
end-plate on extrafusal muscle fiber
trail-ending on nuclear chain intrafusal m. fiber
end-plate on nuclear bag intrafusal m. fiber
fibrocytes
endomysium

Size Range of Peripheral Nerve Fibers

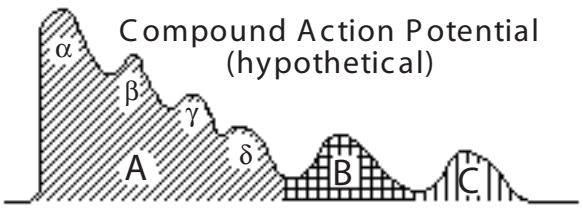


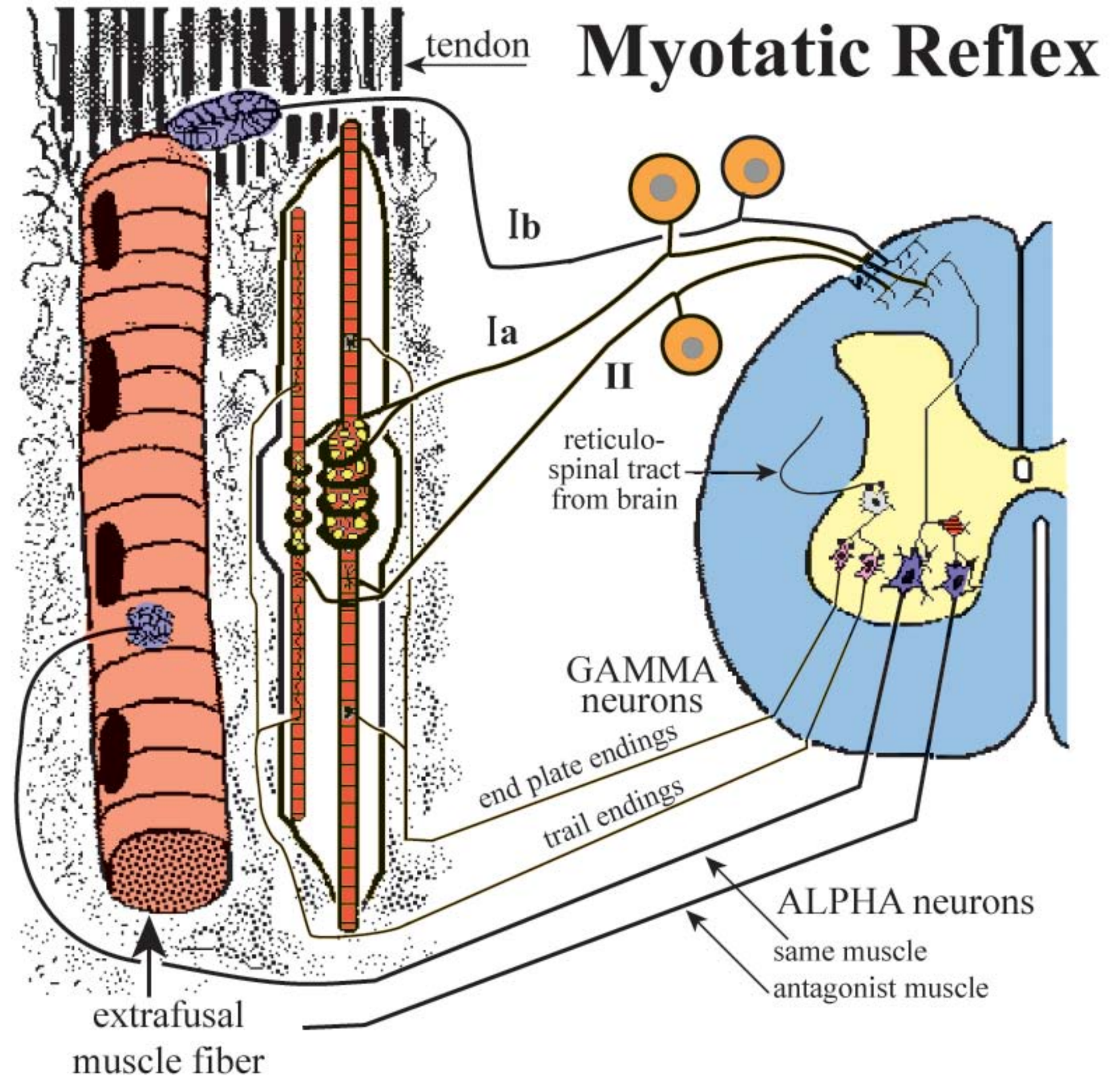
NOTE: Nerve fiber = axon + myelin for myelinated fibers and axon for nonmyelinated fbers.
Conduction velocity (m/sec) = fiber diameter (μm) X 6 (approximately).
Thus, a 20μm fiber conducts at approximately 120m/s = 270 mph.

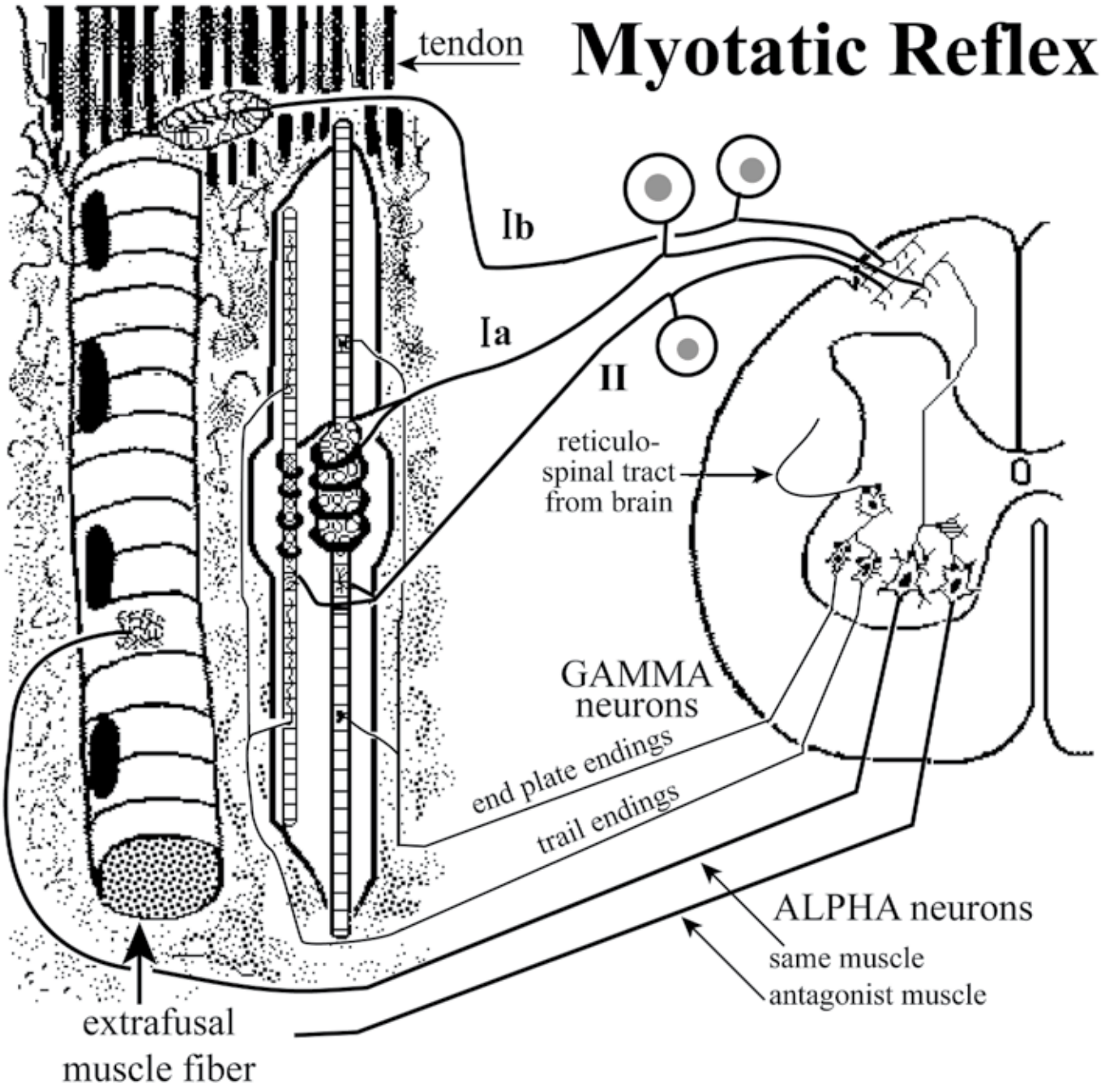
Two classification schemes for peripheral nerve fibers:

1] Based solely on nerve fiber diameter (I—IV). . .
commonly applied to afferent fibers.

2] Derived from the compound action potential:




Myotatic Reflex
tendon
Ib
Ia
II
reticulo-
spinal tract
from brain
GAMMA
neurons
end plate endings
trail endings
ALPHA neurons
same muscle
antagonist muscle
extrafusal
muscle fiber



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Reflex sensitivity:

Sensitivity of the myotatic reflex (the extent to which a muscle can be stretched before it reflexly contracts) is determined ultimately by the contractile state of the polar regions of the intrafusal muscle fibers—because the degree of contraction of the polar regions determines the pre-existing bias (degree of stretch of intrafusal central regions) when the whole muscle is stretched.

Thus, since gamma neurons innervate intrafusal polar regions, **sensitivity of the myotatic reflex is set by the frequency of AP's in axons of gamma neurons**, and gamma neuron excitability is controlled by descending tracts from the hindbrain *(reticulospinal tracts & vestibulospinal tracts)*.

Functions of the myotatic reflex:

• Muscle tone = the resistance muscles offer when being stretched (lengthened)
= the resistance encountered when a limb is manipulated clinically

Tone is set by: brain ——> descending pathways ——> gamma neuron firing rate.
Normal tone is variable, but appropriate to the animal's current behavioral state.

vs. hypertonia (spasticity) = fixed excessive tone, i.e., excess resistance to manipulation
— due to excessive gamma neuron excitation (rate of firing)

or hypotonia ("weakness") = fixed deficient tone, e.g., "rag-doll" appendages
— the result of insufficient gamma neuron excitation.

• Posture maintenance *under changing conditions of load & fatigue*

By using myotatic reflexes, the brain is able to set muscle lengths and fix joint position (i.e., posture) without concern for load and fatigue. The brain sets lengths of intrafusal muscle fibers to correspond to desired whole-muscle lengths.

Any muscle that is longer than the desired length will have its spindle receptors activated and the resultant myotatic reflex will persist until the muscle has shortened to the proper length. After posture is set, motor neurons will receive a burst of excitatory synaptic input whenever a muscle becomes stretched and they will lose that excitation once the muscle shortens sufficiently.

By analogy, this is a servosystem, e.g., one sets a thermostat [the brain sets gamma neuron excitation] to control a furnace [myotatic reflex] to maintain a desired temperature [posture].

• Voluntary movement

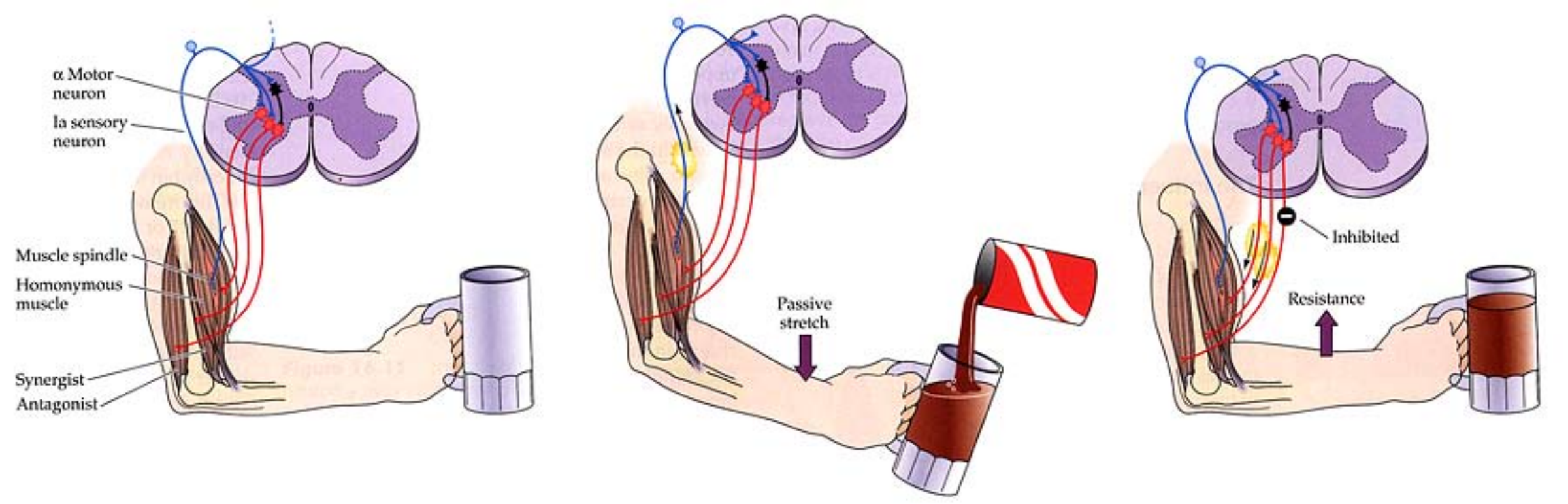
Posture can be sequentially adjusted to produce movement, e.g., hindlimb scratching the flank; learning any new movement sequence; etc. Also, gamma neurons (myotatic reflexes) must be inhibited in antagonistic muscles as agonists are excited.

During voluntary movements, the brain co-activates alpha & gamma neurons to maintain spindle sensitivity while muscles shorten. If a load is excessive for a given amount of initial apha activity, myotatic activity can kick in to boost alpha neuron excitability to levels sufficient for the particular load. Thus the servosystem mentioned for posture works for movement as well, via co-activation of alpha & gamma neurons.

Clinical Considerations

A clinician taps a tendon in order to :

1) verify the integrity of local peripheral nerves and spinal cord segments; and
2) evaluate brain control and the integrity of descending tracts,
looking particularly for evidence of fixed hypertonia or hypotonia.


α Motor neuron
Ia sensory neuron
Muscle spindle
Homonymous muscle
Synergist
Antagonist
Passive stretch
Inhibited
Resistance

Neuronal Integration

A typical multipolar neuron in the CNS receives many thousands of synaptic inputs (excitatory/inhibitory; axosomatic/axodendritic; from interneurons/projection neurons; etc.). How does a neuron integrate all of its diverse synaptic input? How does it make "sense" of the diversity and "fire" appropriately to effectively influence other neurons in its circuit? The answer — neuronal integrtion.

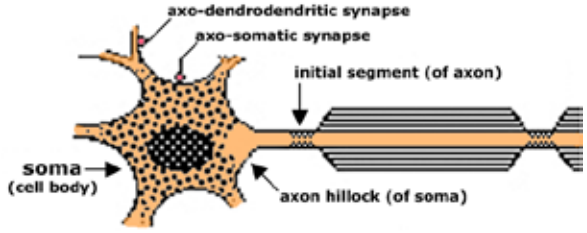
Synaptic inputs — predominantly on dendrites & soma (receptive zone):

axosomatic excitatory synapses — depolarize entire soma (cell body) surface. The cell body acts like a sphere (charges/ions distribute evenly over a spherical surface). Although each EPSP affects the whole soma, a single EPSP has a very limited effect.

axodendritic excitatory synapses — depolarize preferentially toward the soma. The EPSP is passively conducted toward a lower resistance (asymmetrical diameter = asymmetrical resistance).

NOTE:

Inhibitory synapses behave like excitatory ones, except that they produce IPSPs that hyperpolarize the soma and cancel EPSPs).



Neuronal output:

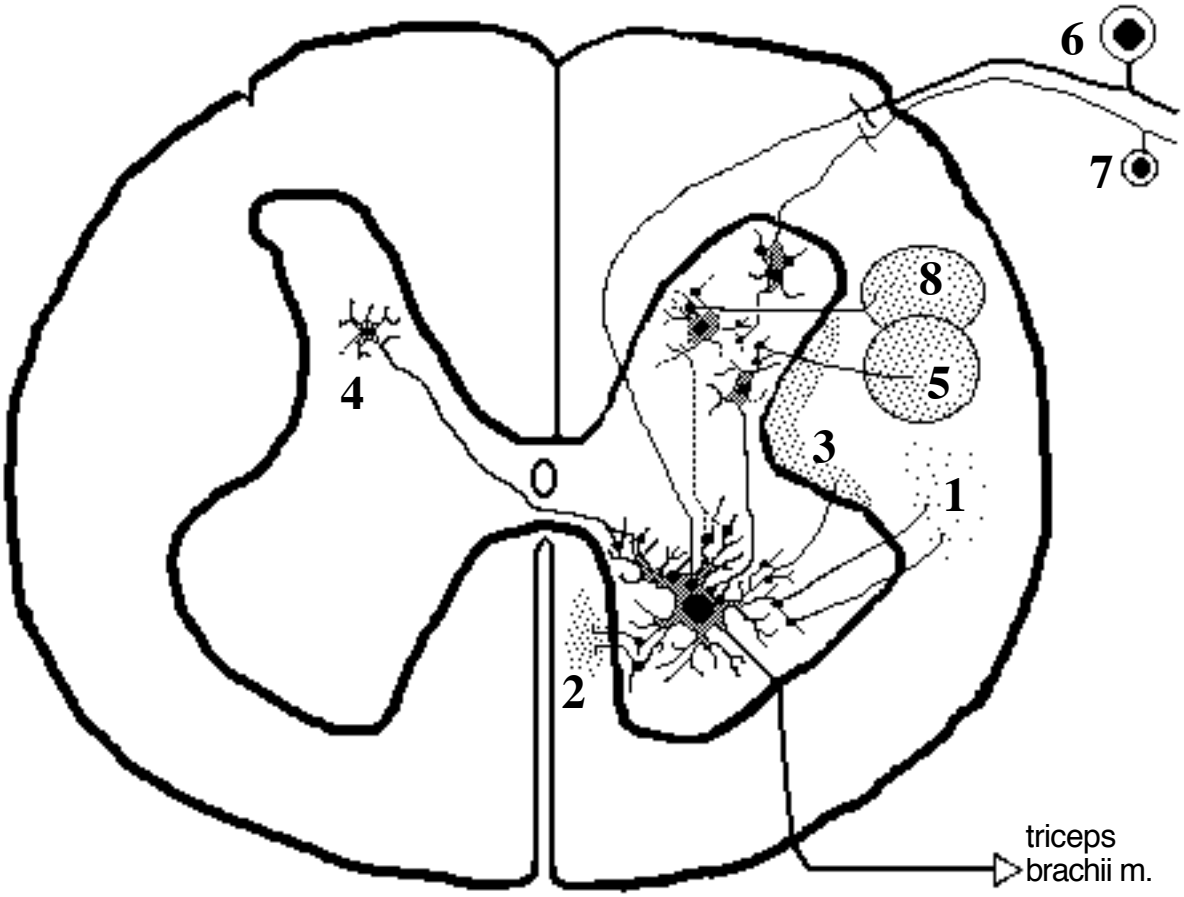
- an action potential **(AP)** originates at the initial segment of the axon where high density of voltage-gated Na^+ channels are present;
- the initial segment is greatly influenced by the massive soma adjacent to it, i.e., the soma continually depolarizes or hyperpolarizes the initial segment at each instant of time;
- whenever the initial segment reaches threshold depolarization, it generates an **AP** that travels along the entire axon.

Thus, **the soma membrane of each neuron integrates total synaptic input at each moment of time!** Integration is the result of algebraic summation of synaptic activity (EPSPs and IPSPs). The floating soma membrane potential reflects the net excitatory and inhibitory synaptic input to a particular neuron at a particular time.

The magnitude of soma depolarization (an *analog signal* ideal for integration) is converted to frequency of APs along the axon (a *digital signal* ideal for distance conduction).

Factors influencing synaptic effectiveness:

- for a given competing input source, impact on a target neuron depends on:
  1) number of source synapses on the target neuron;
  2) locations of source synapses on the target neuron.
- for an individual synapse, effectiveness is related to synaptic location on the target neuron
  most effective {axon hillock >> soma >> proximal dendrite >> distal dendrite} *least effective*
- a given amount of synaptic input will have more effect in a small (vs. large) neuron cell body; thus, within a neuronal pool, small neurons are recruited first, large neurons last.
- synaptic effect is increased by repetitive firing (temporal summation);
- synaptic effect is increased by collaborative firing of different sources (spatial summation).



Neuronal Integration Scenario

Final common pathway neuron

anatomically = ventral horn neuron or neuron cranial nerve motor nucleus
electrophysiologically = alpha motor neuron
clinically = lower motor neuron (as opposed to upper motor neuron)

A final common pathway (FCP) neuron innervates skeletal muscle. The neuron and the skeletal muscle fibers it innervates constitute a motor unit. The nervous system controls skeletal muscles by controlling FCP neurons.

A given FCP neuron receives thousands of synapses, mostly from interneurons. Some of the inputs are excitatory, others are inhibitory. Some of the input originates in the brain, other from receptors and primary afferent neurons. Some of the sources of input have a major effect on the neuron, other inputs provide merely background excitation.

Typical inputs to a FCP motor neuron innervating an extensor muscle:

Background excitation — (axodendritic synapses; merely predispose neurons to fire)
1. reticulospinal axons = muscle activity for standing
2. vestibulospinal tract = balance and muscle activity for standing
3. propriospinal axons = intersegmental reflexes

Major excitatory inputs — (axosomatic synapses; excite neurons to fire APs)
4. commissural interneurons = crossed-extensor reflex
5. rubrospinal tract = voluntary movement
6. primary muscle spindle afferent axon (I_A) = stretch (myotatic) reflex

Inhibitory inputs — (inhibitory axodendritic or axosomatic synapses; cancel excitatory synapses)
7. pain afferent axon = inhibits extensor muscles
8. pyramidal tract axon = controls distal muscles (inhibits extensor muscles)

Clinical note: Damage to FCP neurons (or axons in peripheral nerves) results in flaccid paralysis of skeletal muscles (neither voluntary movement nor reflex activity is present).

Neuronal Integration

A typical multipolar neuron in the CNS receives many thousands of synaptic inputs (excitatory/inhibitory; axosomatic/axodendritic; from interneurons/projection neurons; etc.). How does a neuron integrate all of its diverse synaptic input? How does it make "sense" of the diversity and "fire" appropriately to effectively influence other neurons in its circuit? The answer — neuronal integrtion.

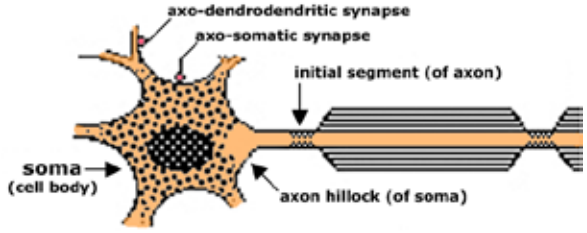
Synaptic inputs — predominantly on dendrites & soma (receptive zone):

axosomatic excitatory synapses — depolarize entire soma (cell body) surface. The cell body acts like a sphere (charges/ions distribute evenly over a spherical surface). Although each EPSP affects the whole soma, a single EPSP has a very limited effect.

axodendritic excitatory synapses — depolarize preferentially toward the soma. The EPSP is passively conducted toward a lower resistance (asymmetrical diameter = asymmetrical resistance).

NOTE:

Inhibitory synapses behave like excitatory ones, except that they produce IPSPs that hyperpolarize the soma and cancel EPSPs).



Neuronal output:

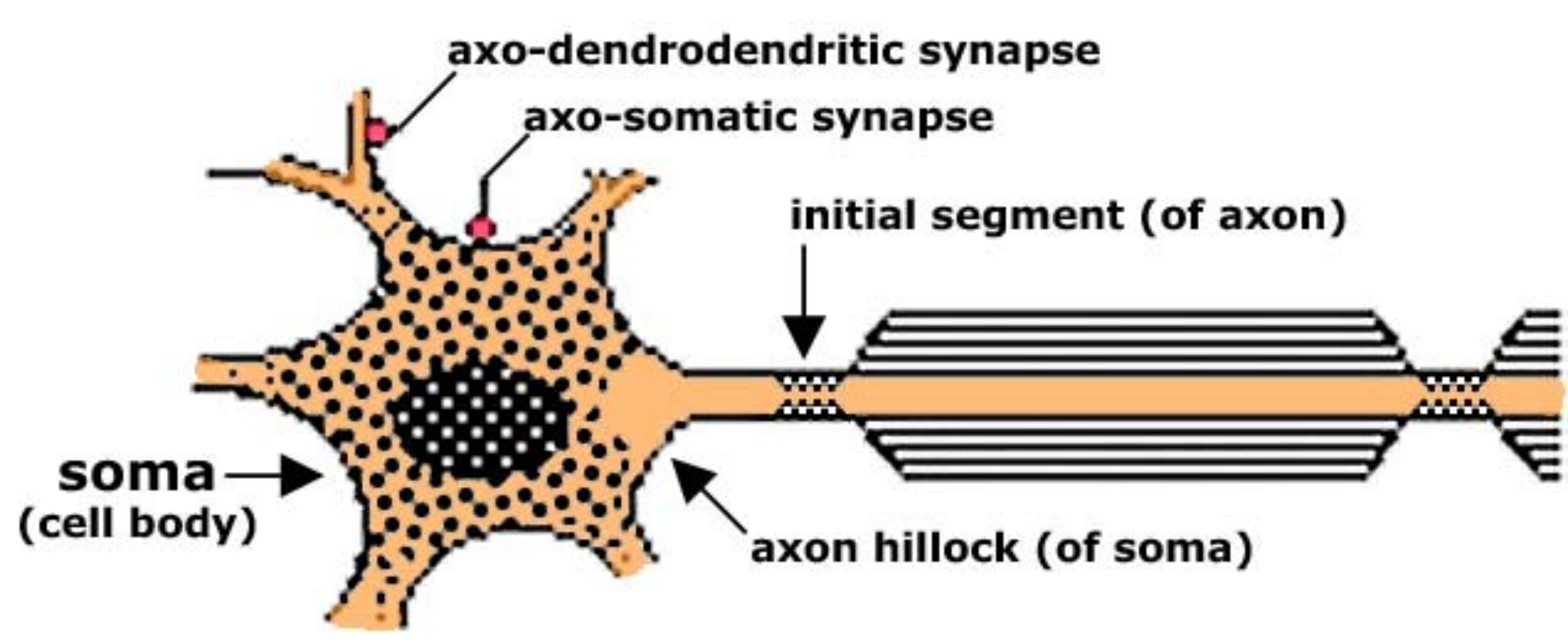
- an action potential **(AP)** originates at the initial segment of the axon where high density of voltage-gated Na^+ channels are present;
- the initial segment is greatly influenced by the massive soma adjacent to it, i.e., the soma continually depolarizes or hyperpolarizes the initial segment at each instant of time;
- whenever the initial segment reaches threshold depolarization, it generates an **AP** that travels along the entire axon.

Thus, **the soma membrane of each neuron integrates total synaptic input at each moment of time!** Integration is the result of algebraic summation of synaptic activity (EPSPs and IPSPs). The floating soma membrane potential reflects the net excitatory and inhibitory synaptic input to a particular neuron at a particular time.

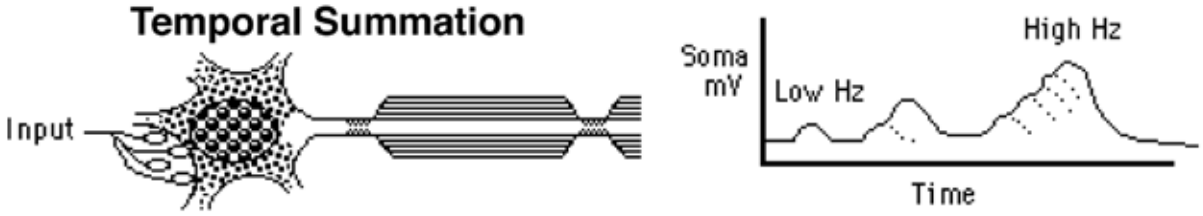
The magnitude of soma depolarization (an *analog signal* ideal for integration) is converted to frequency of APs along the axon (a *digital signal* ideal for distance conduction).

Factors influencing synaptic effectiveness:

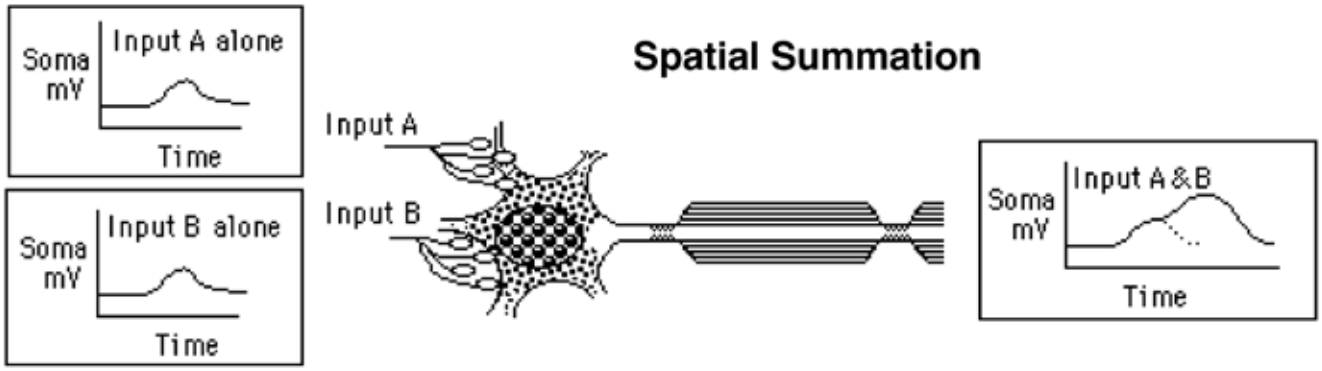
- for a given competing input source, impact on a target neuron depends on:
  1) number of source synapses on the target neuron;
  2) locations of source synapses on the target neuron.
- for an individual synapse, effectiveness is related to synaptic location on the target neuron
  most effective {axon hillock >> soma >> proximal dendrite >> distal dendrite} *least effective*
- a given amount of synaptic input will have more effect in a small (vs. large) neuron cell body; thus, within a neuronal pool, small neurons are recruited first, large neurons last.
- synaptic effect is increased by repetitive firing (temporal summation);
- synaptic effect is increased by collaborative firing of different sources (spatial summation).


axo-dendrodendritic synapse
axo-somatic synapse
initial segment (of axon)
soma
(cell body)
axon hillock (of soma)

Temporal summation: repeated synaptic input can sum to produce an increased effect, when subsequent PSPs arrive before previous PSPs completely decay



Spatial summation: synaptic input from a second source can sum with that of a primary source to produce an increased effect..



NOTE

It is significant that a given quantity of synaptic input will have a greater effect in a small neuron cell body than in a large neuron cell body. It means that small neurons are recruited first and large neurons require more intense synaptic input.

Small neurons innervate:

— relatively few muscle fibers per neuron (small motor units)

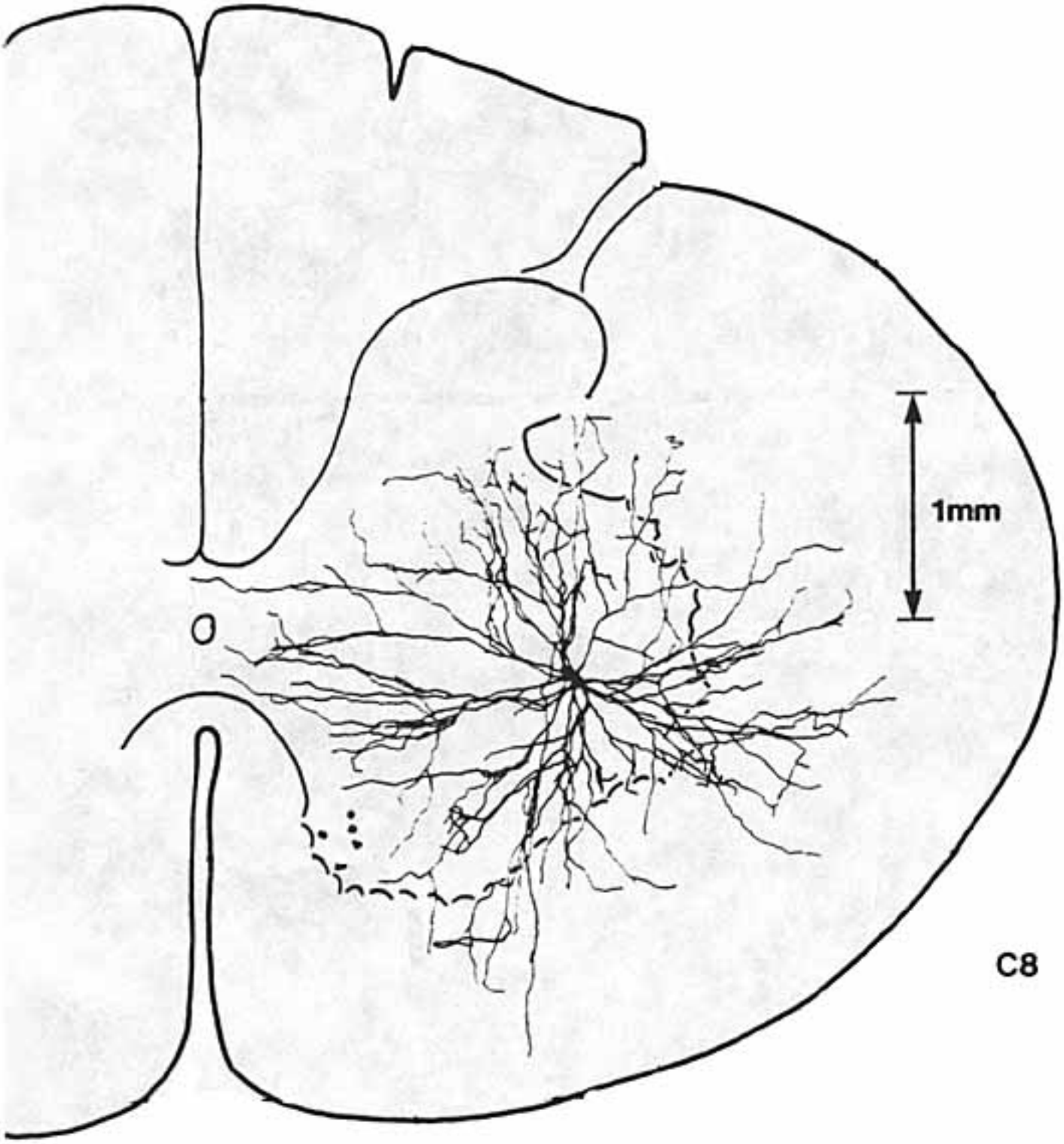
— slow twitch, fatigue-resistant muscle fibers (Type I muscle fibers).

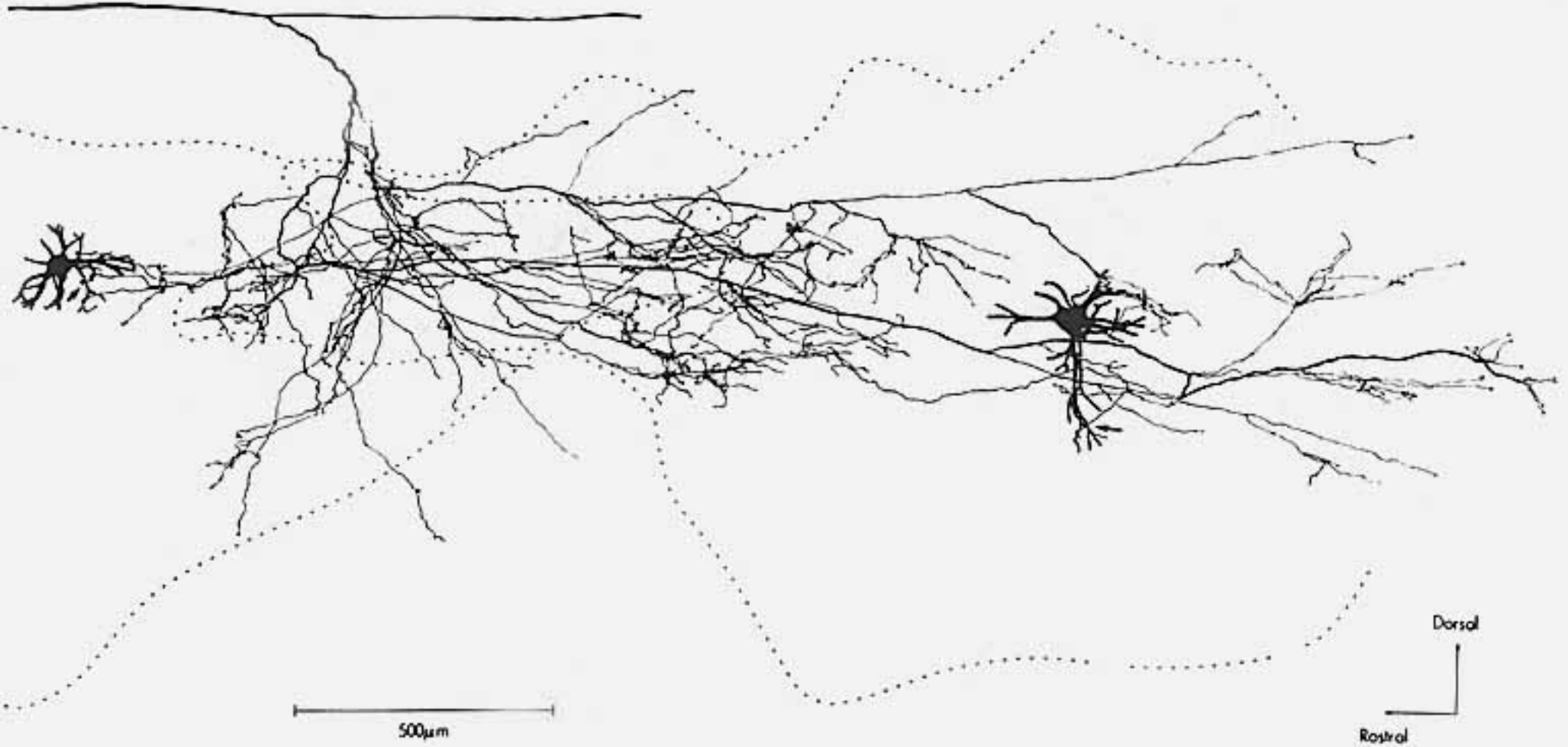
Large neurons innervate:

— many muscle fibers per neuron (large motoer units)

— fast-contacting larger, more powerful muscle cells (Type II muscle fibers)

Thus, the force of muscle output is related to the intensity of synpatic input to the neuron pool that innervates the muscle(s). Fatigue-resistant muscle fibers are naturally recruited first and most often; large muscle fibers are recruited subsequently as more strength is needed.


1mm
C8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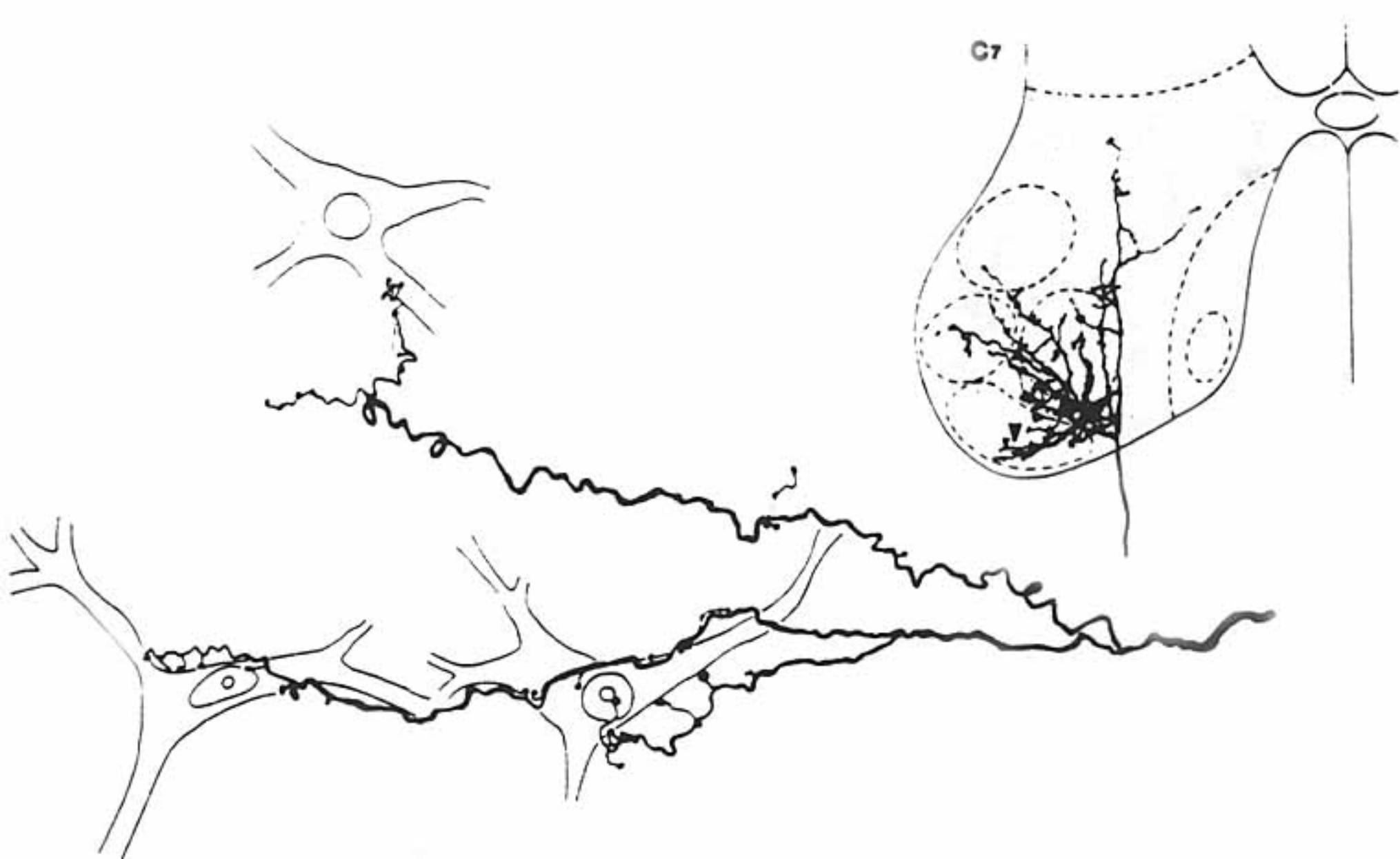
Dorsal
Rostral


C7

Excitatory vs Inhibitory synapses:

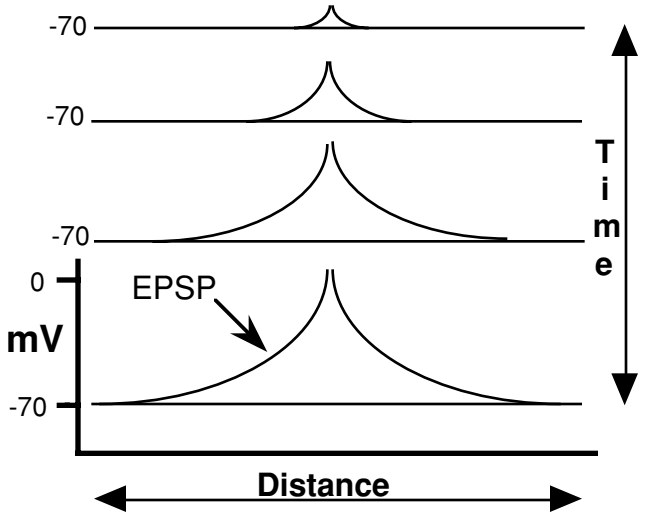
Excitatory synapses generate **EPSP**s which depolarize the postsynaptic region.

Inhibitory synapses generate **IPSP**s which hyperpolarize and cancel **EPSP**s.

The essential synaptic difference is the nature of the population of ligand-gated receptors situated in the postsynaptic membrane.

Generally excitatory and inhibitory synapse employ different neurotransmitters (e.g., GABA or glycine for inhibitory synapses & glutamate or aspartate for excitatory synapses). However, some neurotransmitters (e.g., norepinephrine or acetylcholine) are associated with both excitatory and inhibitory synapses, depending on which channels are present in the postsynaptic membrane.

Electrotonic Conduction



Additional Comments

- synaptic transmission is unidirectional (vesicles are located on only one side).
- synaptic transmission is slower than axonal conduction; each synapse introduces delay into a neural pathway (at least 0.5 msec/synapse).
- synapses are more susceptible to fatigue, hypoxia, and drug effects than are axons (generally pathways fail first at synapses).
- different kinds of drugs (tranquilizers, anesthetics, narcotics, anticonvulsants, muscle relaxants, etc.) work by modifying activity selectively among the different kinds of chemical synapses.
- certain diseases are manifestations of selective synaptic dysfunction; e.g., Parkinson's disease, tetanus, myasthenia gravis, various intoxications, etc.

Neuronal Integration

The dendritic zone of a typical multipolar neuron in the CNS may receive many thousands of synaptic inputs (excitatory/inhibitory; axosomatic/axodendritic; from interneurons/projection neurons; etc.). How does a neuron integrate all of its diverse input? How does it consolidate input signals in order to produce an appropriate output signal to pass on to other neurons in its circuit?

Neuronal input — is predominantly to dendrites & soma (receptive zone):

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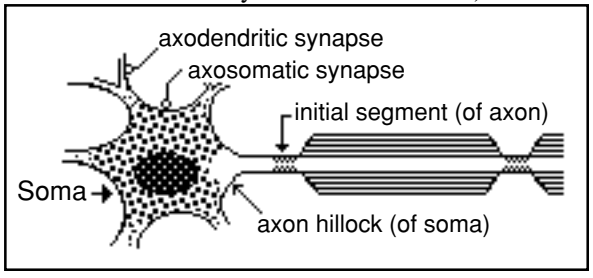


NOTE:

Inhibitory synapses behave like excitatory ones, except that they produce IPSPs that hyperpolarize the soma (cancel EPSPs).

Synaptic Physiology . . .

Presynaptic events:

Neurotransmitter molecules are released in proportion to the amount of Ca^{++} influx, in turn proportional to the amount of presynaptic membrane depolarization, i.e.,

— in the resting state, the presynaptic membrane is polarized

— when an action potential arrives at the end of the axon, the adjacent presynaptic membrane is passively depolarized (toward zero transmembrane potential)

— voltage-gated Ca^{++} channels allow Ca^{++} influx (driven by $[Ca^{++}]$ gradient).

— elevated $[Ca^{++}]$ triggers vesicle mobilization and docking with the plasma membrane

— a number of vesicles fuse with presynaptic plasma membrane and release neurotransmitter molecules (about 5,000 per vesicle) by exocytosis.

— transmitter molecules diffuse across the cleft & bind with postsynaptic receptor proteins

— neurotransmitter molecules are eliminated from synaptic clefts via pinocytotic uptake by presynaptic or glial processes and/or via enzymatic degradation at the postsynaptic membrane. The molecules are recycled.

— subsequently, presynaptic plasma membrane repolarizes (due to K^+ channel conductance).

Postsynaptic events:

Neurotransmitter binding results in a proportional ion flux across the postsynaptic membrane. The particular excitability effect depends on the nature of the ion flux which depends on the nature of the ion channels in the particular postsynaptic membrane, i.e.,

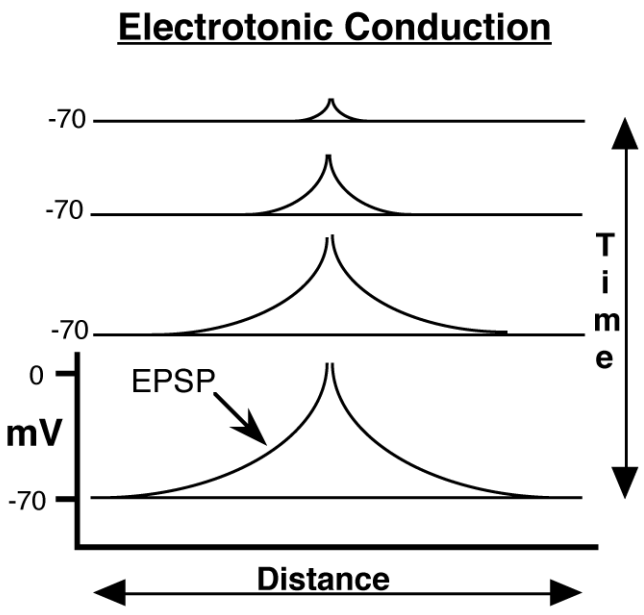
— in the resting state, postsynaptic plasma membrane is polarized
(voltage activated K^+ channels dominate conductance)

— arriving neurotransmitter molecules bind briefly/repeatedly to ligand-gated receptors, which opens ion channels directly or by means of second messengers
activation of $[Na^+$ & $K^+]$ channels —> leads to depolarization toward zero potential;
activation of Cl^- or K^+ channels —> hyperpolarization of postsynaptic membrane.

— a postsynaptic potential (**PSP**) results from the altered membrane conductance
EPSP = Excitatory PSP = depolarization toward zero potential, excites the postsynaptic cell
IPSP = Inhibitory PSP = hyperpolarization (serves to cancel EPSPs), inhibits the postsynaptic cell

— following the removal/degradation of neurotransmitter molecules, the postsynaptic membrane is re-polarized (K^+ channel conductance again dominates.)

Note: **PSP**s constitute *electrotonic conduction*, a passive voltage spread (in contrast to the regenerative conduction of which axons are capable). **PSP**s decay exponentially, over distance and with time. The magnitude of a **PSP** depends on the number of open ion channels which, in turn, depends on the amount of neurotransmitter released.



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