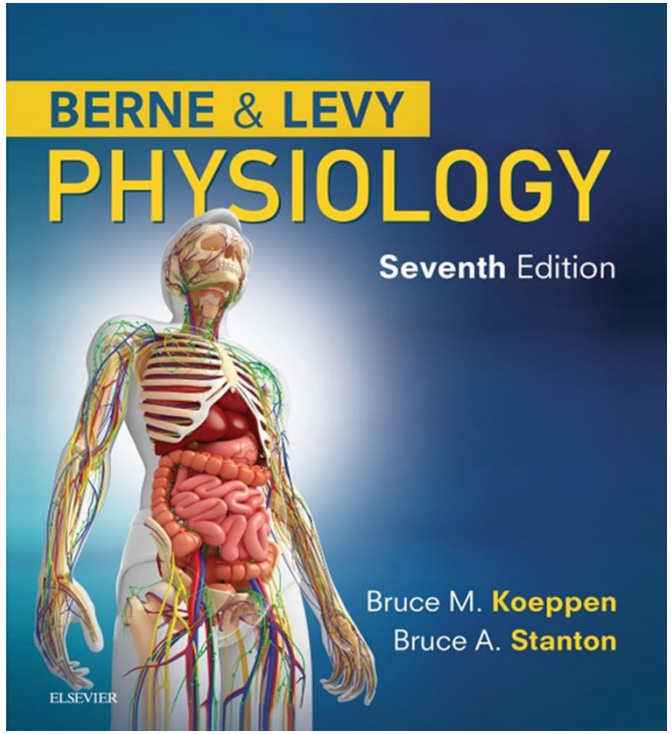
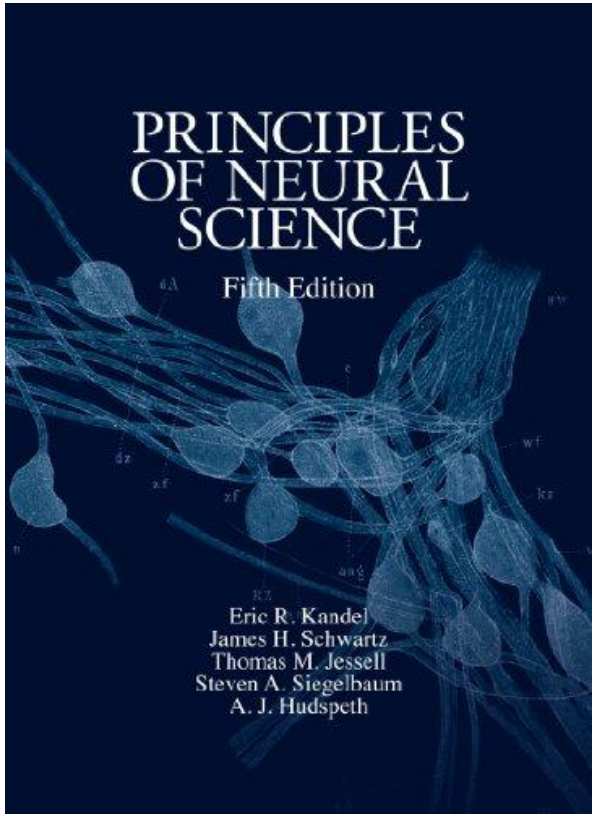
Sensory Receptors and General Sensibility



Chapters 7-8



Chapters 21-24, 32

Perception

The Greek philosopher Aristotle defined five senses—vision, hearing, touch, taste, and smell—each linked to specific sense organs in the body: the eyes, ears, skin, tongue, and nose. We now know that, beyond the classic five senses, there are other somatosensory modalities – sense of balance, thermal senses, pain and proprioception – that are all mediated by specialized receptors distributed throughout the body.

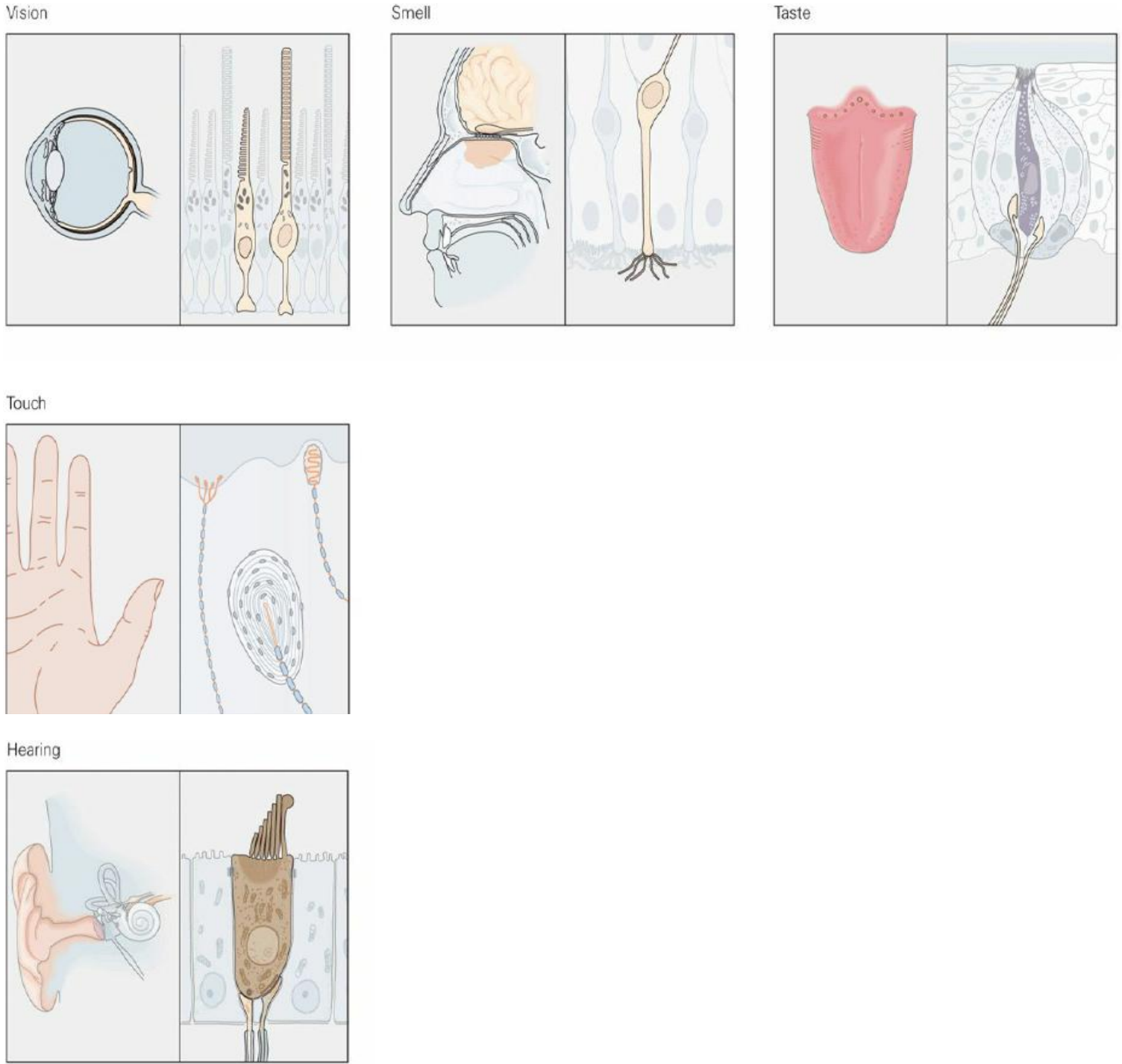


Fig. 21.1 Kandel

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Receptors provide the first neural representation of the external world. This information flows centrally to regions of the brain involved in cognition. The sensory pathways have both serial and parallel components, consisting of fiber tracts with thousands or millions of axons interrupted by synaptic relays comprising millions of neurons.

A specific type of stimulus energy is transformed into electrical signals by specialized receptors. The sensory information is transmitted to the central nervous system by trains of action potentials that represent particular aspects of the stimulus.

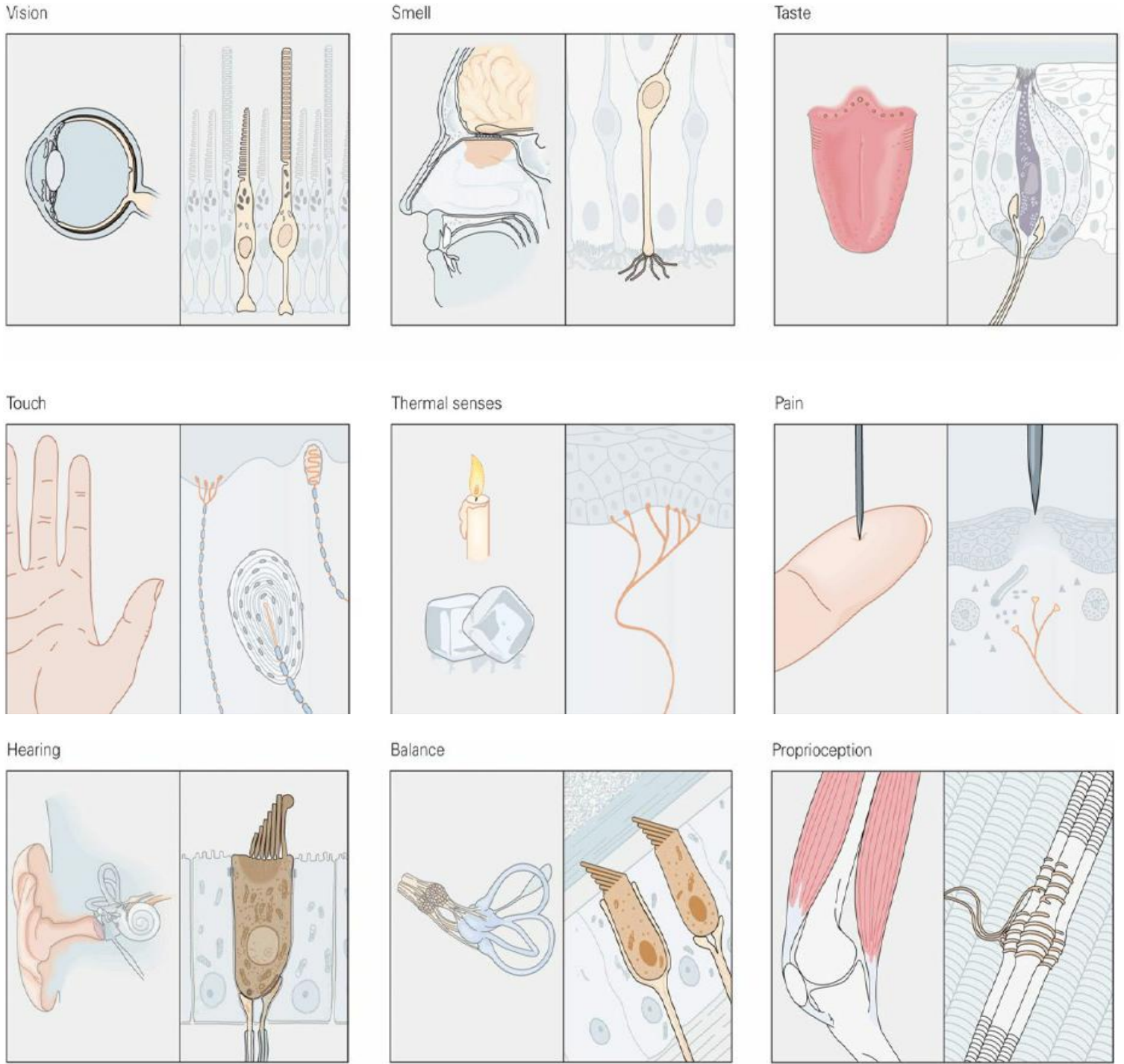

Fig. 21.1 Kandel

Physical Stimuli Are Represented in the Nervous System by Means of the Sensory Code

By recording neuronal activity at various stages of sensory processing, neuroscientists attempt to decipher the codes that convey information in peripheral nerves and in the brain, and analyze the transformation of signals along pathways in the cerebral cortex.

The nervous system extracts only certain pieces of information from each stimulus while ignoring others. It then interprets this information within the constraints of the brain's intrinsic structure and previous experience. Thus, we receive electromagnetic waves of different frequencies, but we see them as colors. We receive pressure waves from objects vibrating at different frequencies, but we hear sounds, words, and music. We encounter chemical compounds floating in the air or water, but we experience them as smells and tastes.

Colors, tones, smells, and tastes are mental creations constructed by the brain out of sensory experience. They do not exist as such outside the brain. We live in The Matrix!

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Sensory Receptors Are Responsive to a Single Type of Stimulus Energy

Each neuron performs a specific task, and the train of action potentials it produces has a specific functional significance for all postsynaptic neurons. This basic idea was expressed in the theory of specificity set forward by Charles Bell and Johannes Müller in the 19th century and remains one of the cornerstones of sensory neuroscience.

The richness of sensory experience begins with millions of highly specific sensory receptors. Each receptor responds to a specific kind of energy at specific locations on the body and sometimes only to energy with a particular temporal or spatial pattern.

The receptor transforms the stimulus energy into electrical energy, thus establishing a *common signalling mechanism in all sensory systems*.

The amplitude and duration of the electrical signal produced by the receptor, termed the **receptor potential**, are related to the intensity and time course of stimulation of the receptor.

The process by which specific stimulus energy is converted into an electrical signal is called **stimulus transduction**.

Sensory receptors are morphologically specialized to transduce specific forms of energy, and each receptor has a specialized anatomical region where stimulus transduction occurs. Most receptors are optimally selective for a single type of stimulus energy, a property termed **receptor specificity**.

Human sensory receptors are classified as mechanoreceptors, chemoreceptors, photoreceptors, or thermoreceptors

Sensory system	Modality	Stimulus	Receptor class	Receptor cells
Visual	Vision	Light (photons)	Photoreceptor	Rods and cones
Auditory	Hearing	Sound (pressure waves)	Mechanoreceptor	Hair cells in cochlea
Vestibular	Head motion	Gravity, acceleration, and head motion	Mechanoreceptor	Hair cells in vestibular labyrinths
Somatosensory				Cranial and dorsal root ganglion cells with receptors in:
	Touch	Skin deformation and motion	Mechanoreceptor	Skin
	Proprioception	Muscle length, muscle force, and joint angle	Mechanoreceptor	Muscle spindles and joint capsules
	Pain	Noxious stimuli (thermal, mechanical, and chemical stimuli)	Thermoreceptor, mechanoreceptor, and chemoreceptor	All tissues except central nervous system
	Itch	Histamine	Chemoreceptor	Skin
	Visceral (not painful)	Wide range (thermal, mechanical, and chemical stimuli)	Thermoreceptor, mechanoreceptor, and chemoreceptor	Gastrointestinal tract, urinary bladder, and lungs
Gustatory	Taste	Chemicals	Chemoreceptor	Taste buds
Olfactory	Smell	Odorants	Chemoreceptor	Olfactory sensory neurons

Table 21.1 Kandel

Vision is mediated by four kinds of photoreceptors in the retina. The light sensitivities of these receptors define the visible spectrum. The photopigments in rods and cones detect electromagnetic energy of wavelengths that span the range 390 to 670 nm. Unlike some other species, such as birds or reptiles, humans do not detect ultraviolet light or infrared radiation because we lack receptors that detect the appropriate short or long wavelengths. Similarly, radio waves and microwave energy bands are not perceived because humans have not evolved receptors for these frequencies.

Individual rod or cone photoreceptors are sensitive to a broad range of wavelengths (black and white curves), but each is most responsive to light in a particular spectral band. As a result, cone photoreceptors are classified as red, green, and blue types. The specific colors perceived result from the relative activation of the three cone types.

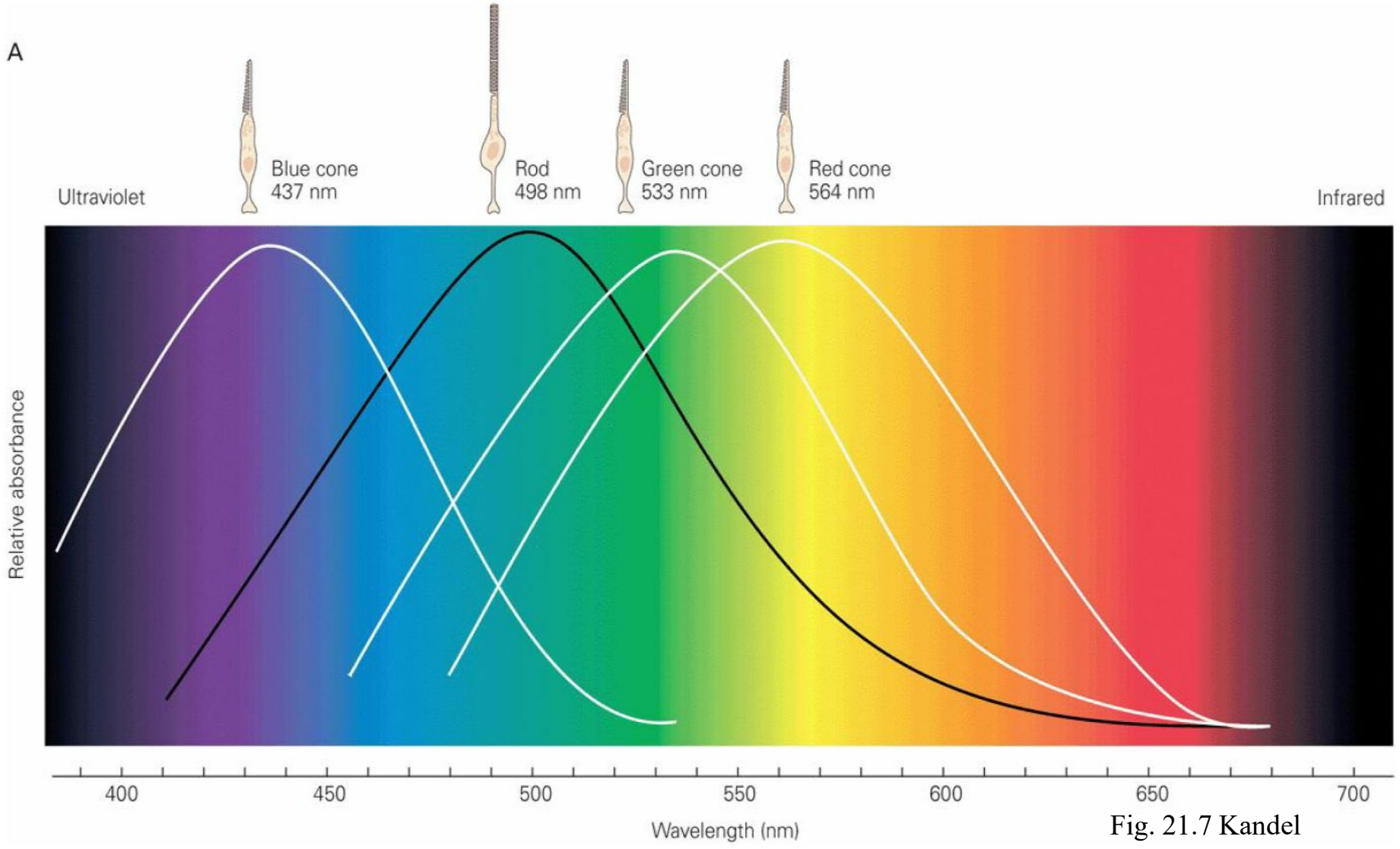


Fig. 21.7 Kandel

Where are they found?
Sensory receptors are found in specialized epithelia called sense organs, principally the eye, ear, nose, tongue, and skin.

Receptors as filters
Each major sensory system has several constituent qualities or *submodalities*. For example, taste can be sweet, sour, salty, or bitter. Submodalities exist because each class of receptors contains a variety of specialized receptors that respond to limited ranges of stimulus energies.

The receptor behaves as a filter for a narrow range or bandwidth of energy. For example, an individual photoreceptor is not sensitive to all wavelengths of light but only to a small part of the spectrum.

We say that a receptor is *tuned* to an optimal or best stimulus, the unique stimulus that activates the receptor at the lowest energy to evoke a response.

ADEQUATE STIMULUS
Stimulus to which a particular receptor responds effectively and gives rise to a characteristic sensation.

Photoreceptors → Light
Sound receptors → Sound (mechanical waves)
Pain receptors → nociceptive stimuli

Neural Firing Patterns Transmit Sensory Information to the Brain

The receptor potential generated by an adequate stimulus produces a local depolarization or hyperpolarization of the sensory receptor cell. The change in membrane potential produced by the sensory stimulus is transformed into action potentials that can be propagated over long distances.

Action potentials are generated in olfactory sensory neurons and dorsal root ganglion neurons of the somatosensory system whose axons project directly to the central nervous system. In the auditory, vestibular, and gustatory (taste) systems the receptor cells make synaptic contact with the peripheral branches of the sensory axons that form cranial nerves VIII, VII, and IX. The retina has the most elaborate neural network for processing sensory information. Photoreceptors send signals through a series of local interneurons to retinal ganglion cells that transform visual information into bursts of action potentials that travel to the brain through the optic nerve.

Sensory receptors encode the intensity of the stimulus in the amplitude of the receptor potential. This analog signal of intensity is transformed into a digital pulse code in which the frequency of action potentials is proportional to the intensity of the stimulus

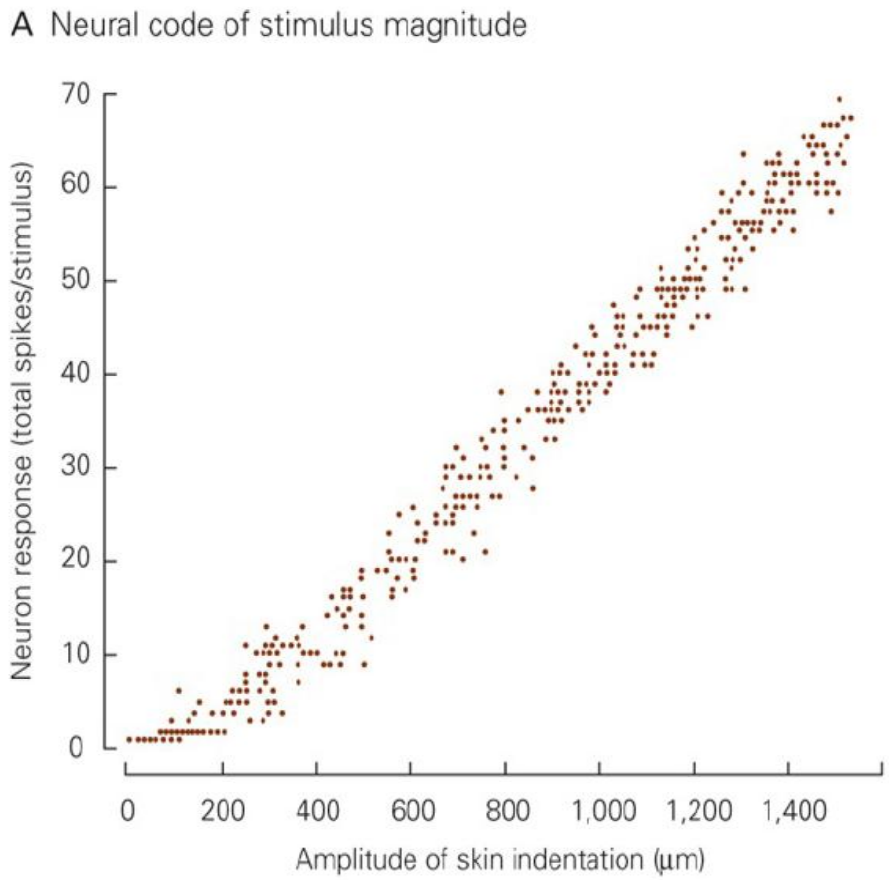


Fig. 21.3 Kandel

Neural Firing Patterns Transmit Sensory Information to the Brain

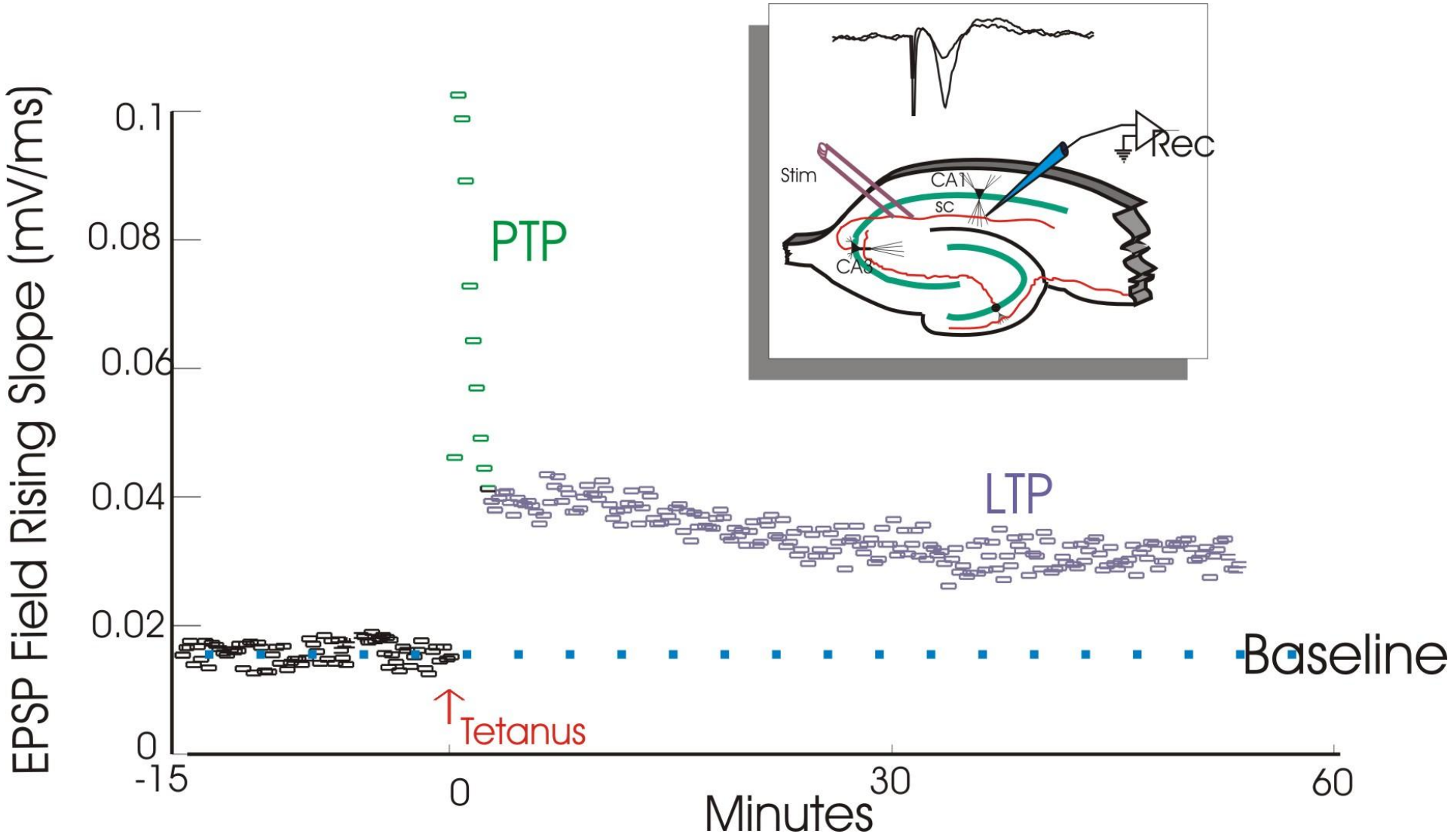
The intensity of a stimulus is also represented in the brain by the total number of active neurons in the receptor population. This type of *population code* depends on the fact that individual receptors in a sensory system differ in their sensory thresholds or in their affinity for particular molecules.

Most sensory systems have low- and high-threshold receptors. For example, rod cells in the retina are activated in very dim light but reach their maximal receptor potentials in daylight.

Cone cells do not respond in dim light but sense differences in brightness in daylight.

The timing of action potentials in the presynaptic cell can determine whether the postsynaptic cell fires. Two action potentials that arrive synchronously or nearly so will drive the postsynaptic neuron’s membrane potential much further toward or away from the threshold for an action potential than would asynchronous action potentials.

The timing of action potentials between neurons also has a profound effect on long-term potentiation and long-term depression at synapses


EPSP Field Rising Slope (mV/ms)
0.1
0.08
0.06
0.04
0.02
0
PTP
LTP
Baseline
Tetanus
-15
0
30
60
Minutes
Stim
Rec
CA1
SC
CA3

Neural Firing Patterns Transmit Sensory Information to the Brain

The temporal properties of a changing stimulus are encoded as changes in the pattern of sensory neuron activity. Many sensory neurons signal the rate at which stimulus intensity changes by rapidly altering their firing rates.

If a stimulus persists unchanged for several minutes without a change in position or amplitude, the neural response diminishes and sensation is lost, a condition called *receptor adaptation*.

Receptors that respond to prolonged and constant stimulation, known as slowly adapting receptors, encode stimulus duration by generating action potentials throughout the period of stimulation. In contrast, rapidly adapting receptors respond only at the beginning or end of a stimulus; they cease firing in response to constant amplitude stimulation and are active only when the stimulus intensity increases or decreases.

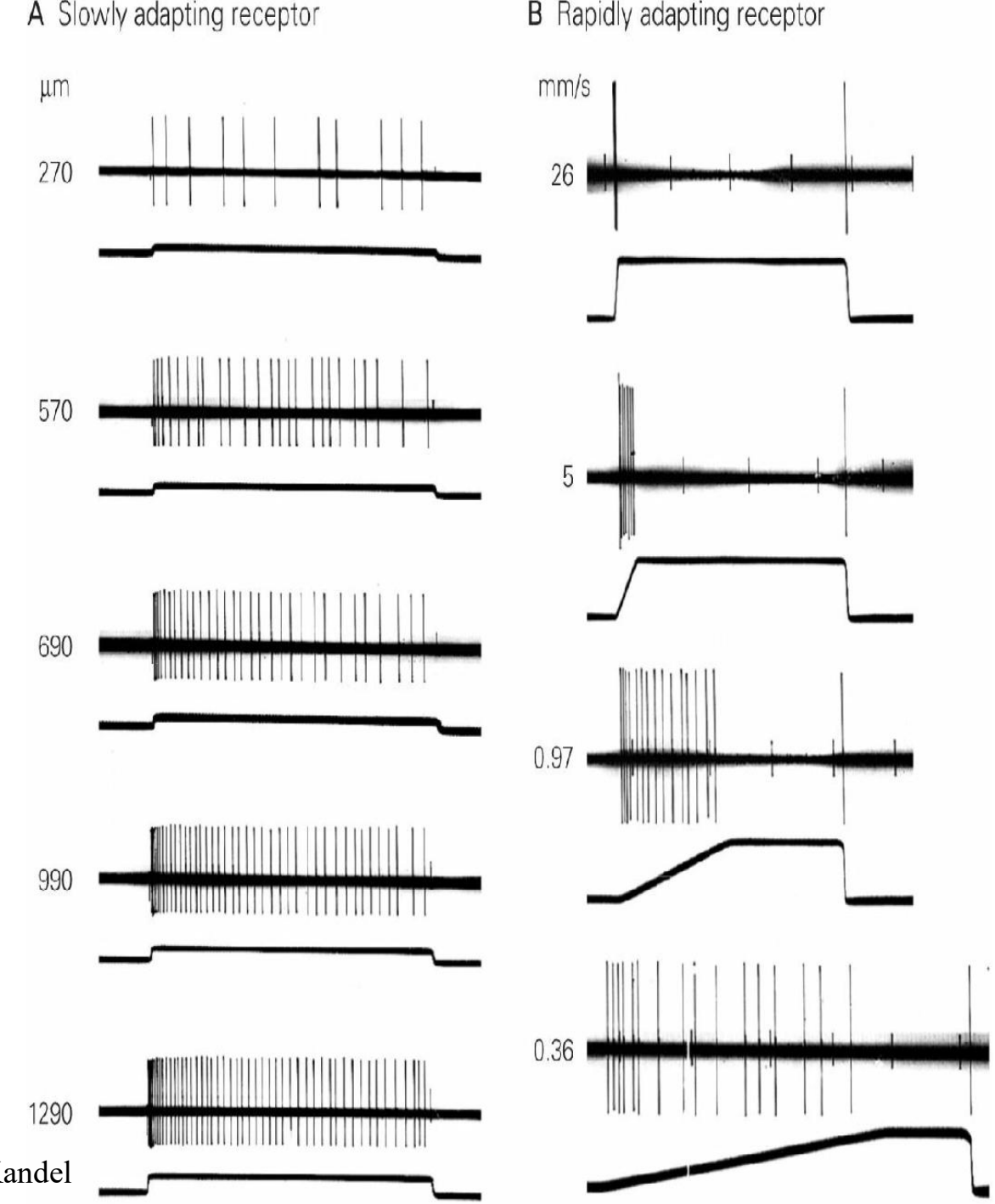


Fig. 21.8 Kandel

The Receptive Field of a Sensory Neuron Conveys Spatial Information

Populations of neurons are also important for conveying the spatial properties of stimuli in a variety of modalities.

The position of a sensory neuron in the sense organ is a major element of the specific information conveyed by that neuron. The skin area or region of space or tonal domain in which stimuli can activate a sensory neuron is called its *receptive field*. The skin area or region of space from which a sensation seems to arise is called the neuron's *perceptive field*. The two usually coincide.

The receptive field of a sensory neuron is the spatial domain in the sense organ where stimulation excites or inhibits the neuron. The receptive field of a touch-sensitive neuron denotes the region of skin where gentle tactile stimuli evoke action potentials in that neuron.

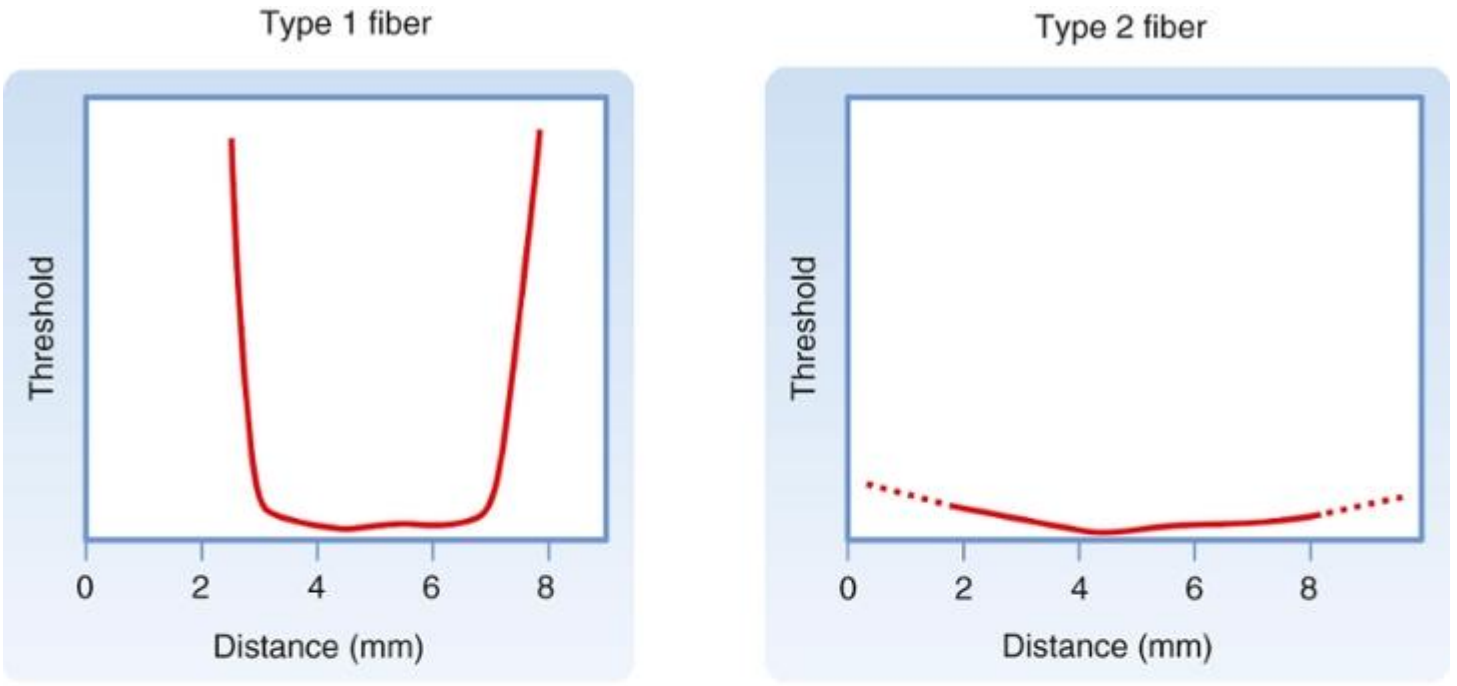


Fig. 7.3 Berne-Levy

The Receptive Field of a Sensory Neuron Conveys Spatial Information

Each receptor in the active population encodes the type of energy applied to the receptive field, the local stimulus magnitude, and its temporal properties.

The neural representation of an object or scene is therefore composed of a mosaic of individual receptors that collectively signal its size, contours, texture, color, and temperature.

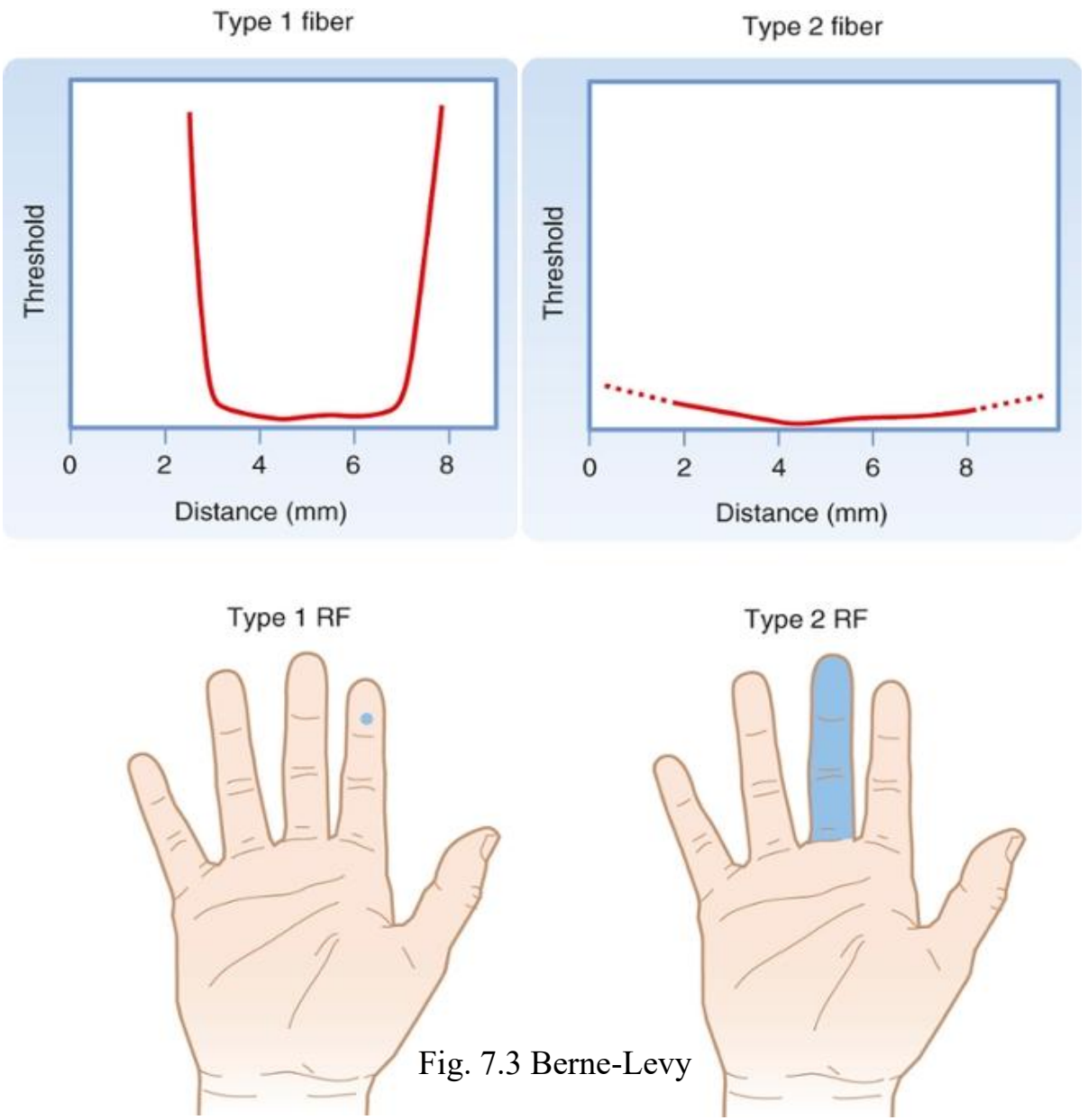
The spatial resolution of a sensory system is proportional to the total number of receptor neurons and how their receptive fields are apportioned within the population. Regions of a sense organ with a high density of receptors, such as the central retina (the fovea), have small receptive fields because the terminals of each sensory neuron are confined to a local cluster of receptors. But because there are so many of them, the population of cells in the fovea transmits a very detailed representation of the visual scene.

The Receptive Field of a Sensory Neuron Conveys Spatial Information

The part of tissue whose stimulation induces the discharge of a sensory neuron is called the receptive field of that neuron.

The precision with which we are able to locate the stimulation site (*acuity*) is not the same in all parts of our body.

The degree of perceptual acuity depends on numerous factors. 1) The size of the receptive fields of sensory neurons. 2) The degree of convergence along the ascending pathways to the cerebral cortex. 3) The degree of overlap of the receptor fields for adjacent sensory fibers.



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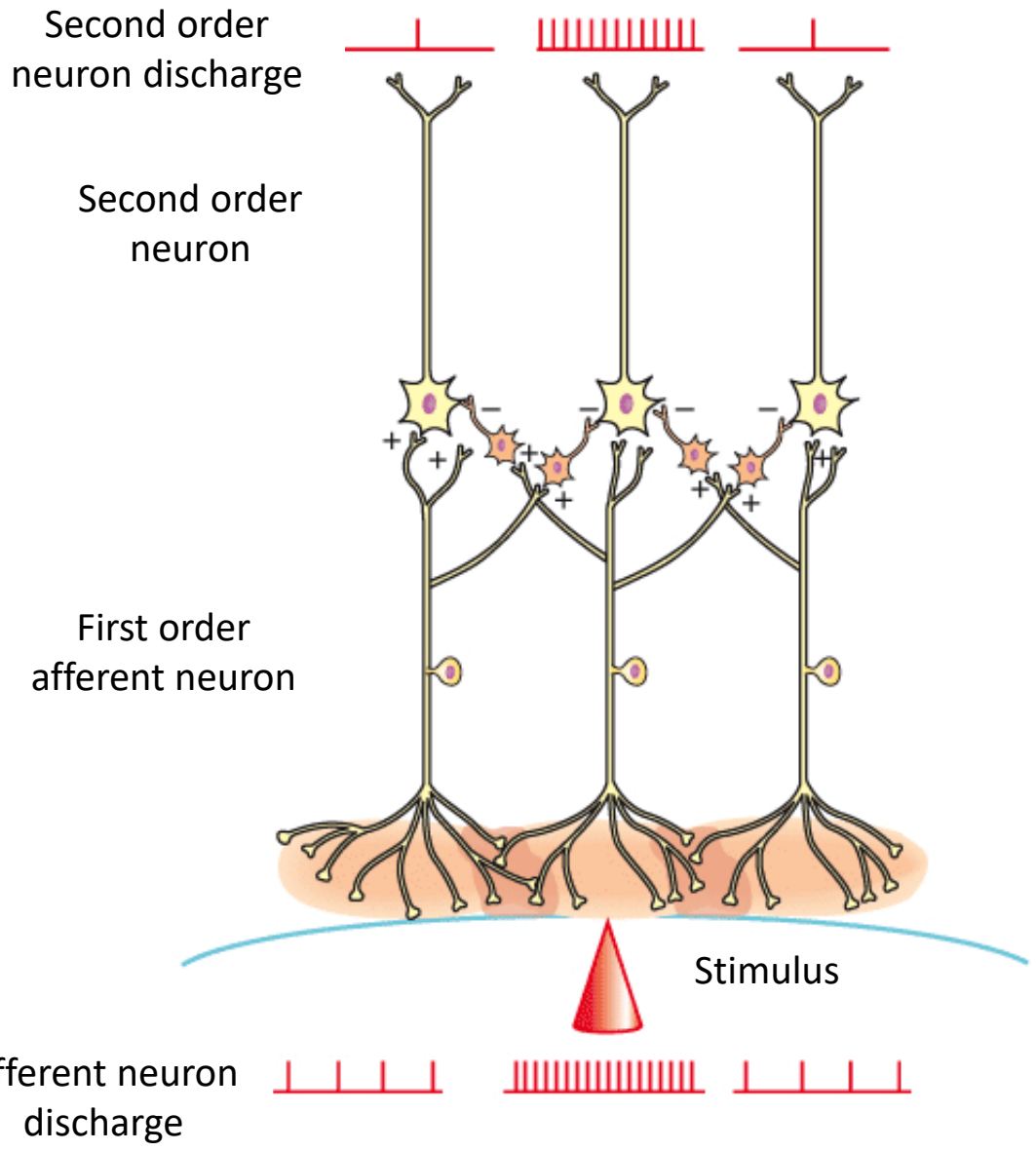
The fiber whose receptor field is stimulated in its central portion, richer in receptor terminations, will respond more lively than the adjacent fibers. This fact is exploited along the central pathways of the sensory systems to significantly improve acuity.



Lateral inhibition is the phenomenon whereby sensory information from the central area of the stimulation area is enhanced with respect to information from the edges.

Modality-Specific Pathways Extend to the Central Nervous System

Bell and Müller realized that the richness provided by the specificity of our receptors would be lost without connections to brain centers that are as rich and varied as the receptors themselves. A sensory neuron's action potentials have a specific effect on our sensory experience because of the neuron's central connections, not because of the stimulus that evokes the action potentials.

Synaptic relays in sensory pathways do more than simply pass on signals received. Each relay neuron receives convergent excitatory synaptic inputs from many neurons in the presynaptic pathway. Likewise, each receptor neuron excites a large number of postsynaptic neurons. In addition, inhibitory interneurons in the relay nucleus modulate the excitability of relay neurons, thereby regulating the amount of sensory information transmitted centrally to higher levels of the network

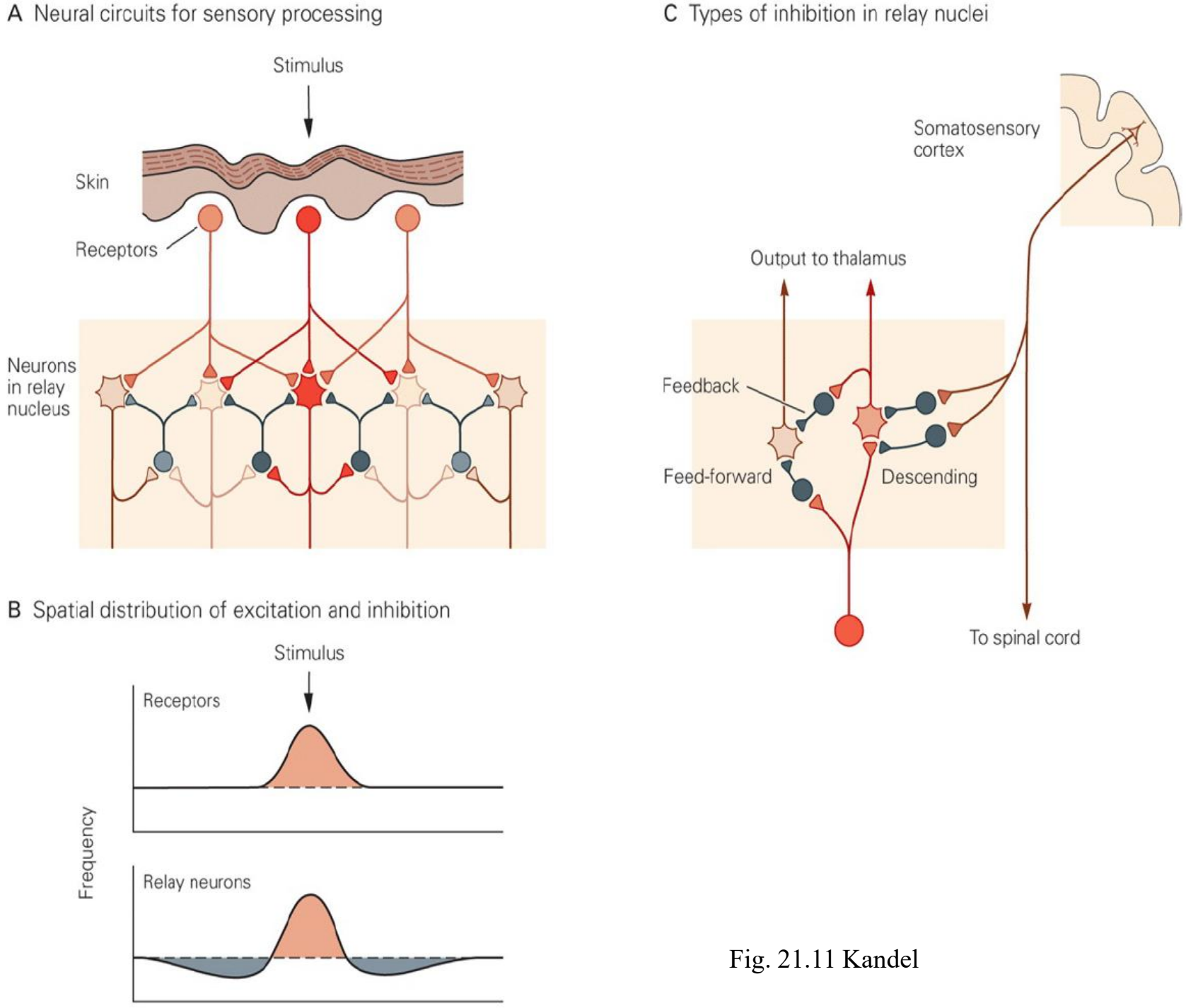


Fig. 21.11 Kandel

The somatosensory system

https://www.khanacademy.org/science/health-and-medicine/nervous-system-and-sensory-infor/sensory-perception-topic/v/somatosensation-1

The somatosensory system

Charles Sherrington, noted that the somatosensory system serves three major functions: ***proprioception, exteroception, and interoception***.

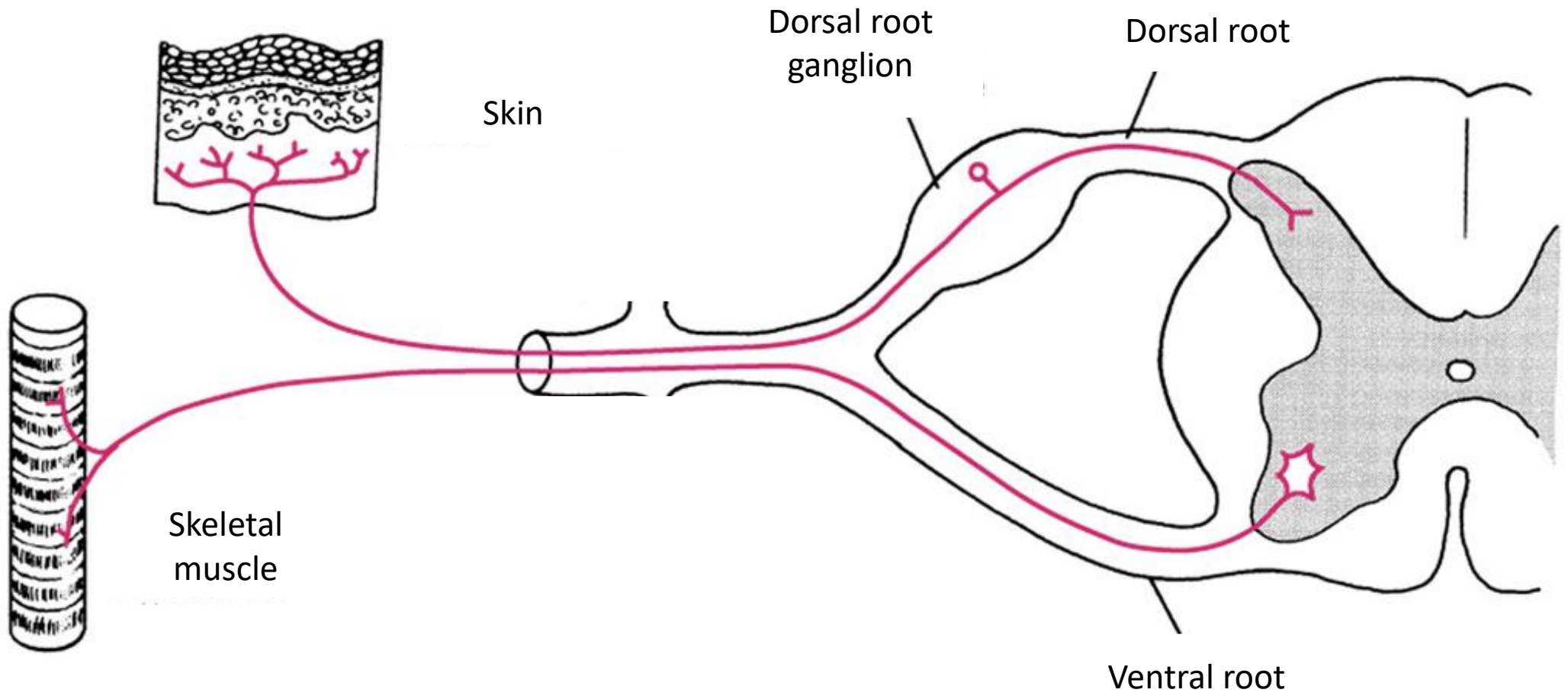
Proprioception is the sense of oneself. Receptors in skeletal muscle, joint capsules, and the skin enable us to have conscious awareness of the posture and movements of our own body, particularly the four limbs and the head.

Exteroception is the sense of direct interaction with the external world as it impacts on the body. The principal mode of exteroception is the sense of **touch**. Exteroception also includes the thermal senses of heat and cold. **Thermal sensations** are important controllers of behavior and homeostatic mechanisms needed to maintain the body temperature near 37°C. Finally, exteroception includes the sense of pain, or **nociception**, a response to external events that damage or harm the body. Nociception is a prime motivator of actions necessary for survival, such as withdrawal or combat.

The third component of somatic sensation, ***interoception***, is the sense of the function of the major organ systems of the body and its internal state. Although most of the events recorded by receptors in the viscera do not become conscious sensations, the information conveyed by these receptors is crucial for regulating autonomic functions, particularly in the cardiovascular, respiratory, digestive, and renal systems.

All the somatic senses are mediated by one class of sensory neurons: **the dorsal root ganglion neurons**. Individual neurons in a dorsal root ganglion respond selectively to specific types of stimuli because of morphological and molecular specialization of their peripheral terminals.

The Primary Sensory Neurons of the Somatosensory System Are Clustered in the Dorsal Root Ganglia



Somatosensory information from the skin, muscles, joint capsules, and viscera is conveyed by dorsal root ganglion neurons innervating the limbs and trunk or by trigeminal sensory neurons that innervate cranial structures. These sensory neurons perform two major functions: the transduction and encoding of stimuli into electrical signals and the transmission of those signals to the central nervous system.

Dorsal root ganglion neurons are a type of bipolar cell, called pseudo-unipolar cells. They are the **primary afferent fibers**.

The peripheral branches of these neurons differ in receptor morphology and stimulus selectivity.

The central branches terminate in the spinal cord or brain stem, forming the first synapses in somatosensory pathways.

Individual primary afferent fibers innervating a particular region of the body are grouped together into bundles or fascicles of axons forming the peripheral nerves. The peripheral nerves also include motor axons innervating nearby muscles, blood vessels, glands, or viscera.

Peripheral Somatosensory Nerve Fibers Conduct Action Potentials at Different Rates

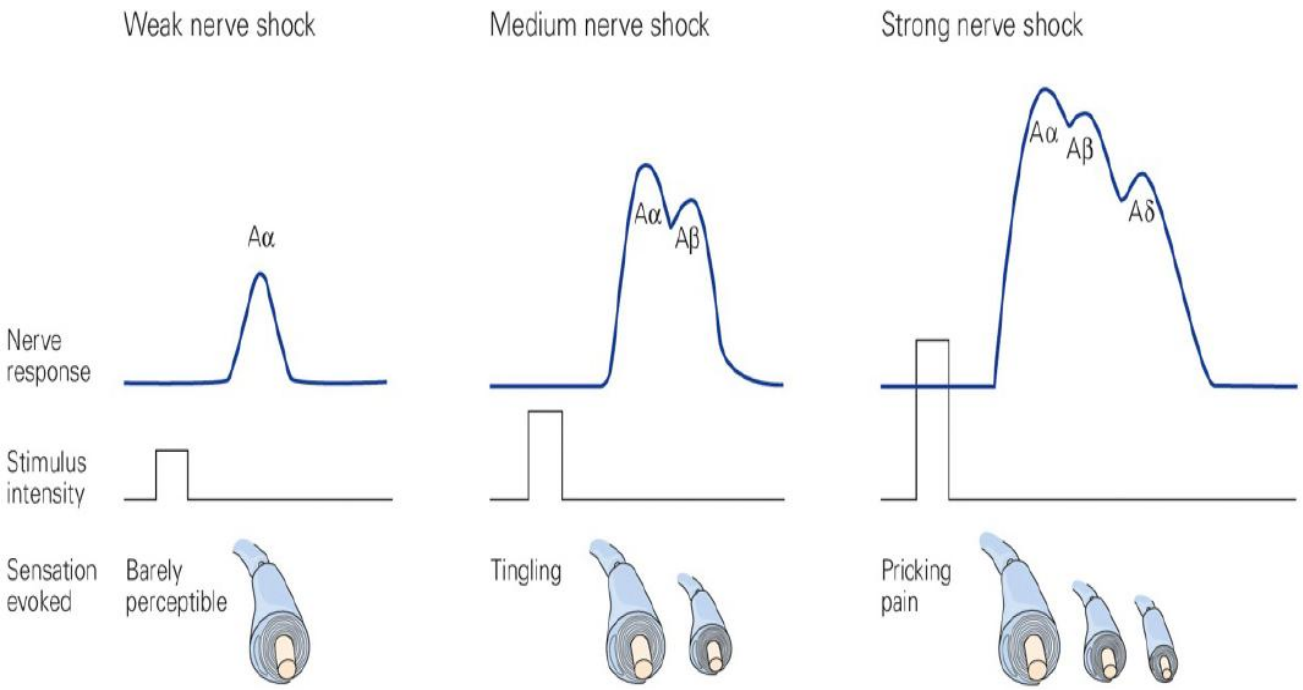
The diverse modalities of somatic sensation are mediated by peripheral nerve fibers that differ in diameter and conduction velocity. Mechanoreceptors for touch and proprioception are innervated by dorsal root ganglion neurons with large-diameter, myelinated axons that conduct action potentials rapidly. Thermal receptors, nociceptors, and other chemoreceptors have small-diameter axons that are either unmyelinated or thinly myelinated; these nerves conduct impulses more slowly.

Large-diameter fibers conduct action potentials more rapidly because the internal resistance to current flow along the axon is low, and the nodes of Ranvier are widely spaced along its length

	Muscle nerve	Cutaneous nerve[2]	Fiber diameter (μm)	Conduction velocity (m/s)
Myelinated				
Large diameter	I	Aα	12–20	72–120
Medium diameter	II	Aβ	6–12	36–72
Small diameter	III	Aδ	1–6	4–36
Unmyelinated	IV	C	0.2–1.5	0.4–2.0

[1]Sensory fibers from muscle are classified according to their diameter, whereas those from the skin are classified by conduction velocity.

Table 22.1 Kandel



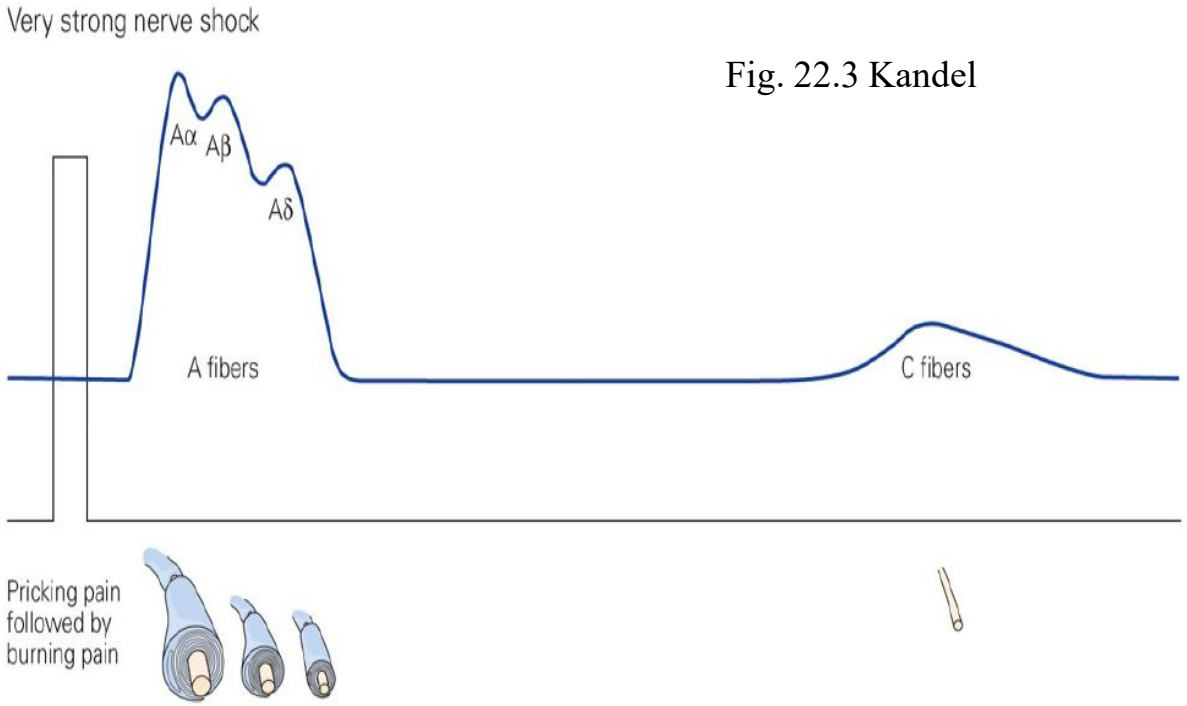


Fig. 22.3 Kandel

At higher voltages, when axons in the smaller Aδ range are recruited, the stimulus becomes painful, resembling an electric shock produced by static electricity. Voltages sufficient to activate unmyelinated C fibers evoke sensations of burning pain.

Rapid conduction in a peripheral nerve provides the prompt sensory feedback required for motor control. The greatest velocities are in the afferent fibers from muscle that signal muscle length, contraction velocity, and force. Any delay in the feedback signal would cause instability, which probably explains why the fibers innervating spindles have the greatest diameters among peripheral axons.

In C fibers delays range from 0.8 s to 1.8 s, the mean delay is about 1.3 s, and the spike arrival times are distributed over about 1 s; thus events occurring more often than once per second are smeared together. In Aα fibers delays range from 7.5 ms to 12.5 ms, the mean delay is 10 ms, and the arrival times vary by only 5 ms; events can therefore occur as often as 200 per second without smearing. The comparable limits for Aδ and Aβ fibers are approximately 8 Hz and 80 Hz.

Somato-sensory receptors

Receptor type	Fiber group[1]	Fiber name	Modality
Cutaneous and subcutaneous mechanoreceptors			Touch
Meissner corpuscle	Aα,β	RA1	Stroking, flutter
Merkel disk receptor	Aα,β	SA1	Pressure, texture
Pacinian corpuscle[2]	Aα,β	RA2	Vibration
Ruffini ending	Aα,β	SA2	Skin stretch
Hair-tylotrich, hair-guard	Aα,β	G1, G2	Stroking, fluttering
Hair-down	Aδ	D	Light stroking
Field	Aα,β	F	Skin stretch
C mechanoreceptor	C		Stroking, erotic touch
Thermal receptors			Temperature
Cool receptors	Aδ	III	Skin cooling (<25°C [77°F])
Warm receptors	C	IV	Skin warming (>35°C [95°F])
Heat nociceptors	Aδ	III	Hot temperature (>45°C [113°F])
Cold nociceptors	C	IV	Cold temperature (<5°C [41°F])
Nociceptors			Pain
Mechanical	Aδ	III	Sharp, pricking pain
Thermal-mechanical (heat)	Aδ	III	Burning pain
Thermal-mechanical (cold)	C	IV	Freezing pain
Polymodal	C	IV	Slow, burning pain
Muscle and skeletal mechanoreceptors			Limb proprioception
Muscle spindle primary	Aα	Ia	Muscle length and speed
Muscle spindle secondary	Aβ	II	Muscle stretch
Golgi tendon organ	Aα	Ib	Muscle contraction
Joint capsule receptors	Aβ	II	Joint angle
Stretch-sensitive free endings	Aδ	III	Excess stretch or force

Table 22.2 Kandel

Mechanoreceptors

Mechanoreceptors sense physical deformation of the tissue in which they reside.

Mechanical stimulation deforms the receptor protein, thus opening stretch-sensitive ion channels and increasing Na+, and Ca2+ conductances that depolarize the receptor neuron.

A. Channels can be directly activated by forces conveyed through lipid tension in the cell membrane, such as osmotic swelling.

B. Forces conveyed through structural proteins linked to the ion channel can also directly activate channels. The linking proteins may be either extracellular (attached to the surrounding tissue) or intracellular (bound to the cytoskeleton) or both.

C. Channels can be indirectly activated by forces conveyed to a force sensor (a separate protein) in the membrane. An internal second messenger carries the sensory signal from the mechanosensitive protein to the channel (TRP channels).

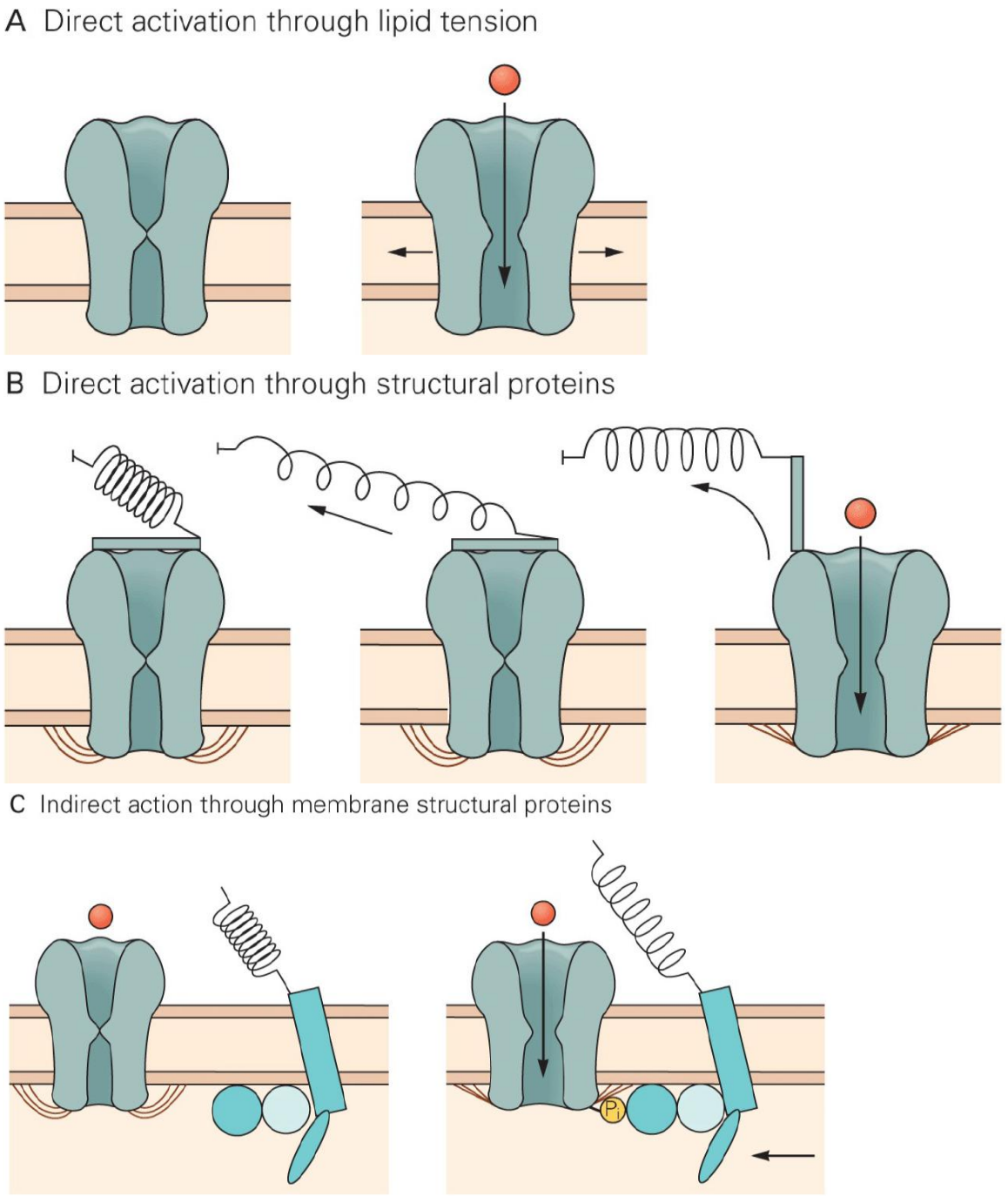


Fig. 22.4 Kandel

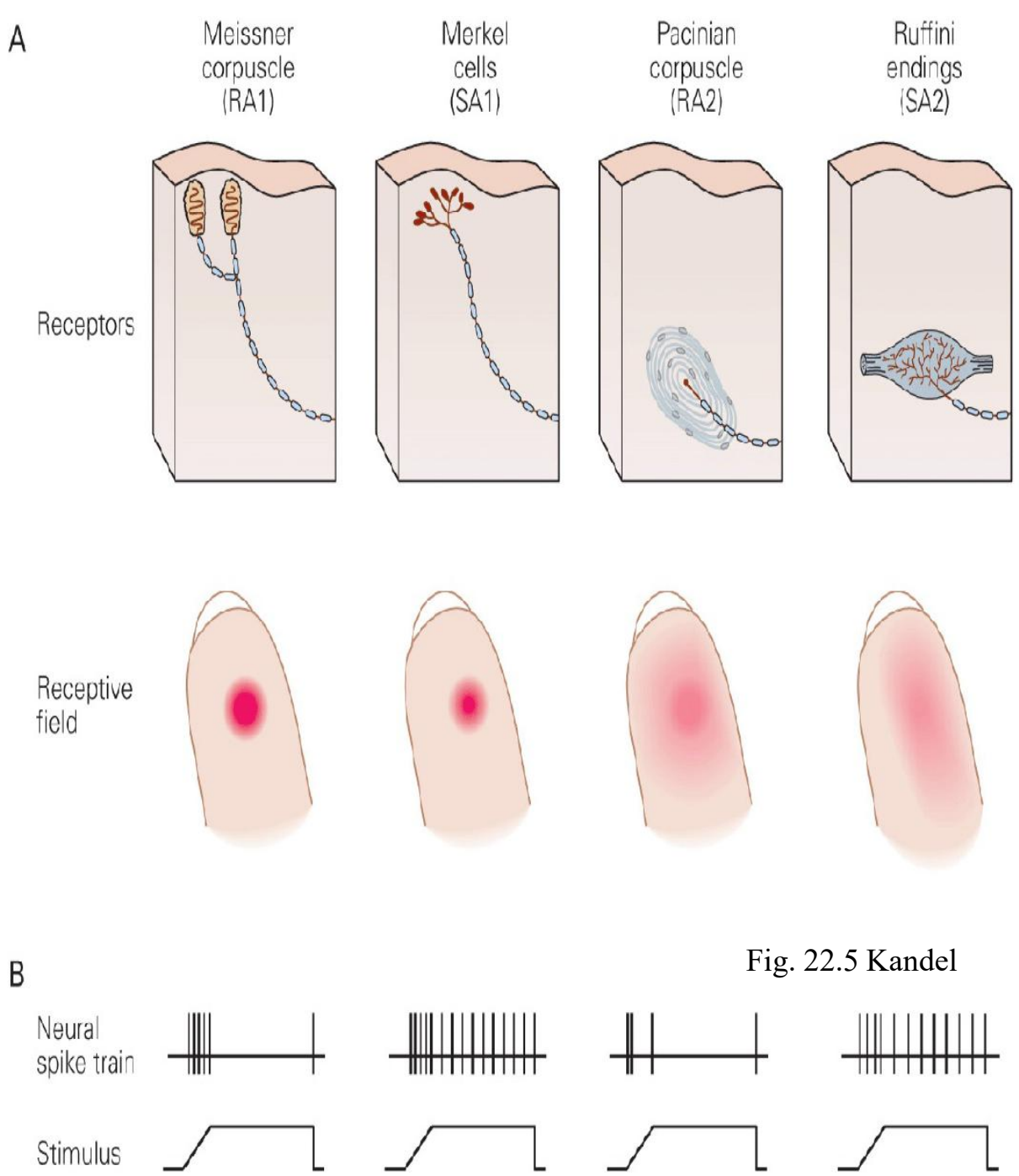


Fig. 22.5 Kandel

The skin has eight types of mechanoreceptors that are responsible for the sense of touch – 4 of these are in the glabrous skin.

Merkel cells are innervated by slowly adapting type 1 (SA1) fibers. They signal the amount of pressure applied to the skin and are particularly sensitive to edges, corners, and points.

The **Ruffini endings** are innervated by slowly adapting type 2 (SA2) fibers.

Meissner corpuscles are innervated by rapidly adapting type 1 (RA1) fibers.

The **Pacinian corpuscles** are innervated by rapidly adapting type 2 (RA2) fibers. The receptor is a large, onion-like capsule that surrounds the axon terminal.

The general hairy skin includes all of the mechanoreceptor organs of the glabrous skin except the Meissner corpuscle.

Proprioceptors

Specific class of mechanoreceptors that convey information about the posture and movements of the body and thereby play an important role in motor control. These receptors include two types of muscle-length sensors, the type Ia and II muscle-spindle endings; one muscle force sensor, the Golgi tendon organ; and joint-capsule receptors, which transduce tension in the joint capsule.

Nociceptors

Receptors that respond selectively to stimuli that can damage tissue. They respond directly to mechanical and thermal stimuli, and indirectly to other stimuli by means of chemicals released from cells in the traumatized tissue. Nociceptors signal impending tissue injury and, more importantly, they provide a constant reminder of tissues that are already injured and must be protected. Nociceptors innervated by Aδ fibers produce short-latency pain that is described as sharp and pricking. Nociceptors innervated by C fibers produce dull, burning pain that is diffusely localized and poorly tolerated. In the viscera nociceptors are activated by distension or swelling, producing sensations of intense pain.

Thermal receptors

Although the size, shape, and texture of objects held in the hand can be apprehended visually as well as by touch, the thermal qualities of objects are uniquely somatosensory. Humans recognize four distinct types of thermal sensation: cold, cool, warm, and hot. Although we are exquisitely sensitive to sudden changes in skin temperature, we are normally unaware of the wide gradual swings in skin temperature that occur as our cutaneous blood vessels open and close to discharge or conserve body heat. Because of their characteristics, humans are more sensible to cooling than warming. Recent studies by David Julius and his colleagues revealed that thermal stimuli activate specific classes of TRP ion channels in the membrane. These nonselective cation receptor-channels are similar in structure to voltage-gated channels.

Itch is a common sensory experience that is confined to the skin, the ocular conjunctiva, and the mucosa. Itch can be induced either by the injection of histamine or by procedures that release endogenous histamine, which suggests that the transducers are coupled to histamine receptors. Itch appears to be mediated by a recently discovered class of C fibers with very slow conduction velocities (0.5 m/s)

Visceral Sensations Represent the Status of Various Internal Organs

Visceral sensations are important physiologically because they drive several types of behavior that are critical for survival, such as respiration, hunger, thirst, sexual arousal, and copulation. Thirst and hunger, for instance, provide the motivation to drink and eat; they come to dominate our behavior when we have been without water or food for periods that threaten our survival.

There are peripheral and central sensors.

Sensations associated with the need to breathe, for example, arise from partial pressure of oxygen (PO_2) and partial pressure of carbon dioxide (PCO_2) sensors in the carotid bodies associated with the carotid arteries and from PCO_2 receptors in the respiratory centers of the medulla and hypothalamus.

Nausea, which teaches animals—including us—which foods are unsafe to eat, depends on vagal serotonin receptors in the gut as well as the area postrema in the brain stem. Neurons within the area postrema are able to sense toxins in the blood and cerebrospinal fluid because the area lacks a bloodbrain barrier

Somatosensory Information Flows from the Spinal Cord to the Thalamus Through Parallel Pathways

The spinal gray matter is further subdivided into 10 laminae (or layers), numbered I to X from dorsal to ventral, based on differences in cell and fiber composition. Lamina I consists of a thin layer of neurons capping the dorsal horn of the spinal cord and pars caudalis of the spinal trigeminal nucleus. Individual neurons of lamina I receive monosynaptic inputs from small myelinated fibers (Aδ) or unmyelinated C fibers of a single type.

Neurons in laminae II and III are interneurons that receive inputs from Aδ and C fibers, and make excitatory or inhibitory connections to neurons in lamina I, IV, and V that project to higher brain centers. The dendrites of neurons in laminae III to V are the main targets of the large myelinated sensory (Aβ) fibers from cutaneous mechanoreceptors.

Neurons in lamina V typically respond to more than one modality—low-threshold mechanical stimuli, visceral stimuli, or noxious stimuli—and have therefore been named wide-dynamic-range neurons.

Visceral C fibers have widespread projections in the spinal cord that terminate ipsilaterally in laminae I, II, V, and X; some also cross the midline and terminate in lamina V and X of the contralateral gray matter.

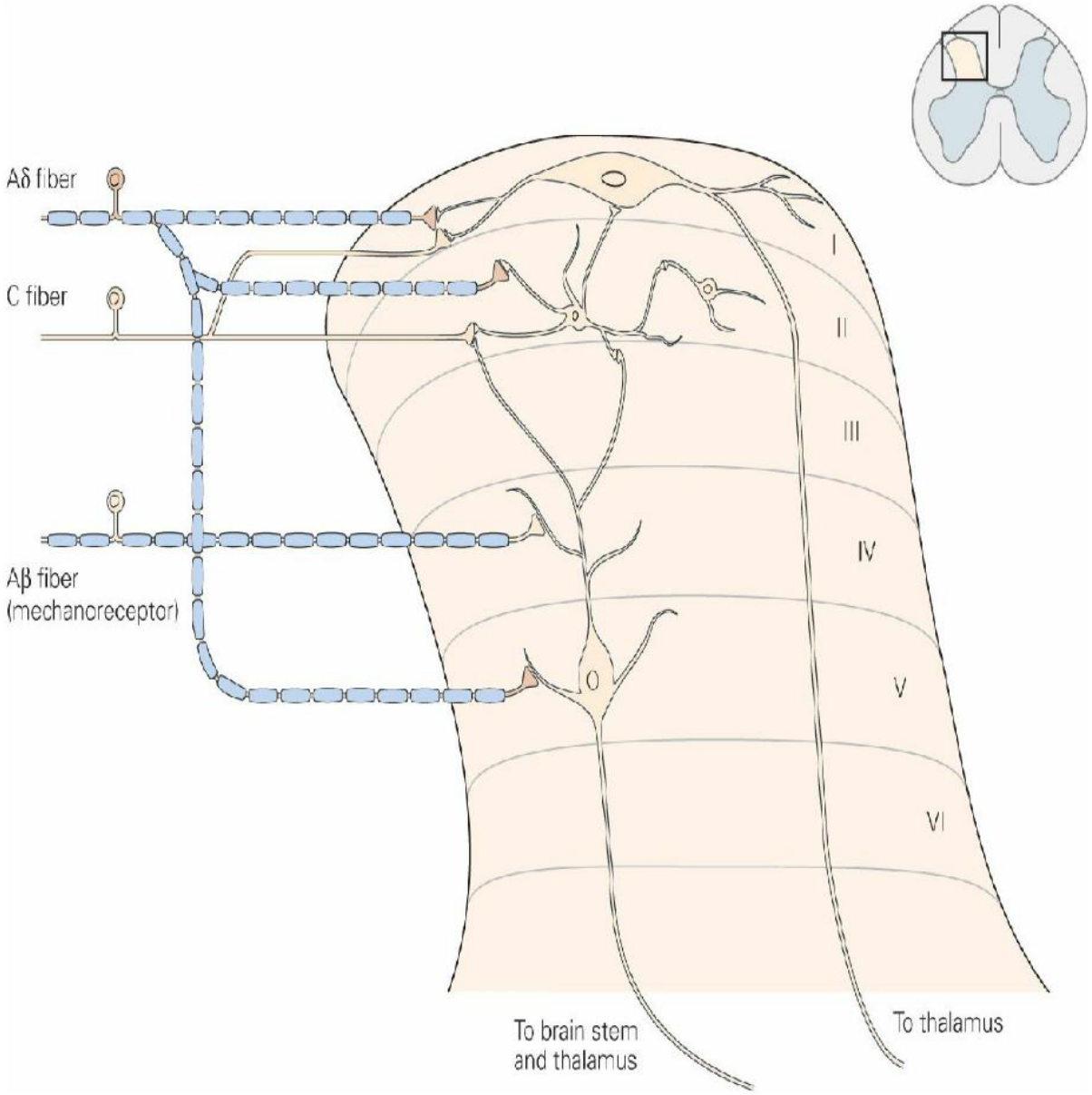


Fig. 22.10 Kandel

Pain

Pain describes the unpleasant sensory and emotional experiences associated with actual or potential tissue damage.

Pain serves an important protective function, alerting us to injuries that require evasion or treatment. It has both affective and emotional components.

The perception of pain is subjective and is influenced by many factors. An identical sensory stimulus can elicit quite distinct responses in the same individual under different conditions. Pain is not the direct expression of a sensory event but rather the product of elaborate processing by the brain of a variety of neural signals.

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When pain is experienced it can be acute, persistent, or in extreme cases chronic. Persistent pain characterizes many clinical conditions and is usually the reason that patients seek medical attention. In contrast, chronic pain appears to have no useful purpose

Noxious Insults Activate Nociceptors

Nociceptors are specialized sensory receptors that are activated by noxious insults. Most of these nociceptors are simply the free nerve endings of primary sensory neurons. There are three main classes of nociceptors widely distributed in skin and deep tissues often coactivated: thermal, mechanical, and polymodal. There is also a more enigmatic fourth class, termed silent nociceptors.

Thermal nociceptors: activated by extremes in temperatures. Aδ fibers (5-30 m/s).

Mechanical nociceptors: activated by intense pressure. Aδ fibers

Polymodal nociceptors: activated by high intensity mechanical, thermal or chemical stimuli. C fibers (1 m/s)

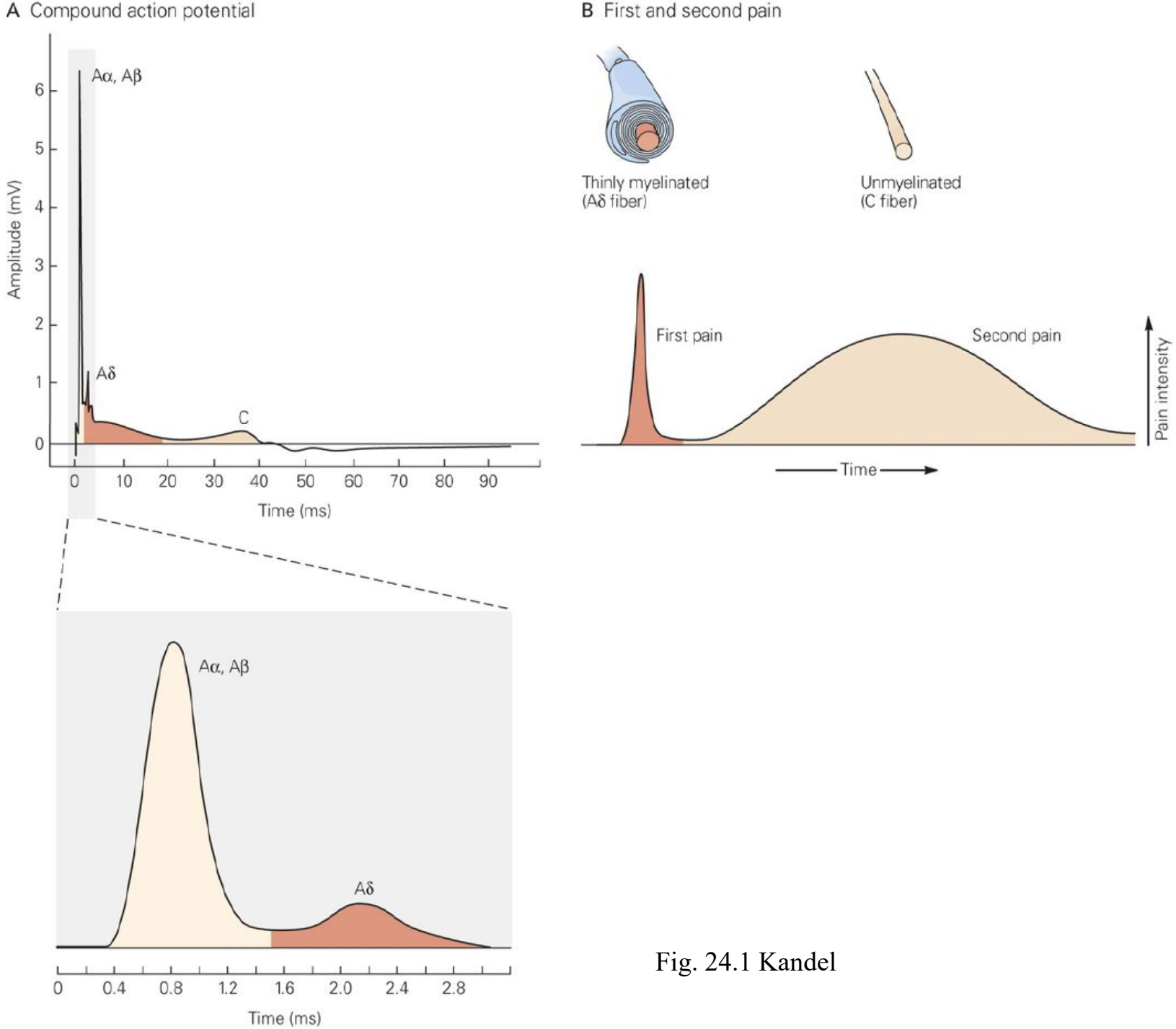

Fig. 24.1 Kandel

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Silent nociceptors are found in the viscera. This class of receptors is not normally activated by noxious stimulation; instead, inflammation and various chemical agents dramatically reduce their firing threshold.

The membrane of the nociceptor contains receptors that convert the thermal, mechanical, or chemical energy of noxious stimuli into a depolarizing electrical potential. One such protein is a member of a large family of so-called **transient receptor potential (TRP) ion channels**. TRPV1 is expressed selectively by nociceptive neurons and mediates the pain-producing actions of capsaicin

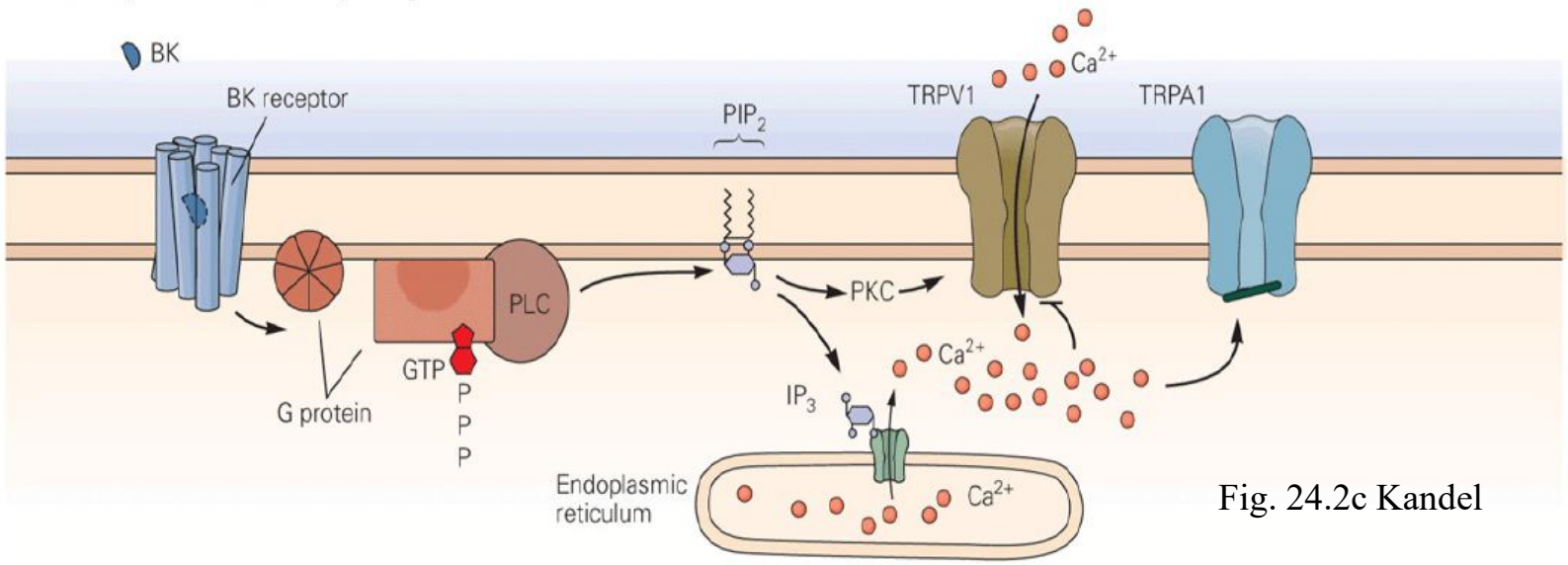


Fig. 24.2c Kandel

Other receptors and ion channels are involved. Nociceptors selectively express **tetrodotoxin-resistant Na+ channels**. One Na+ channel (**SCN9A**, also called Nav1.7) plays a key role in the perception of pain in humans, as revealed by the rare pain-insensitive individuals who possess mutations in the corresponding gene.

Nociceptors also express an ionotropic purinergic receptor, PTX3, that is activated by ATP released from peripheral cells after tissue damage.

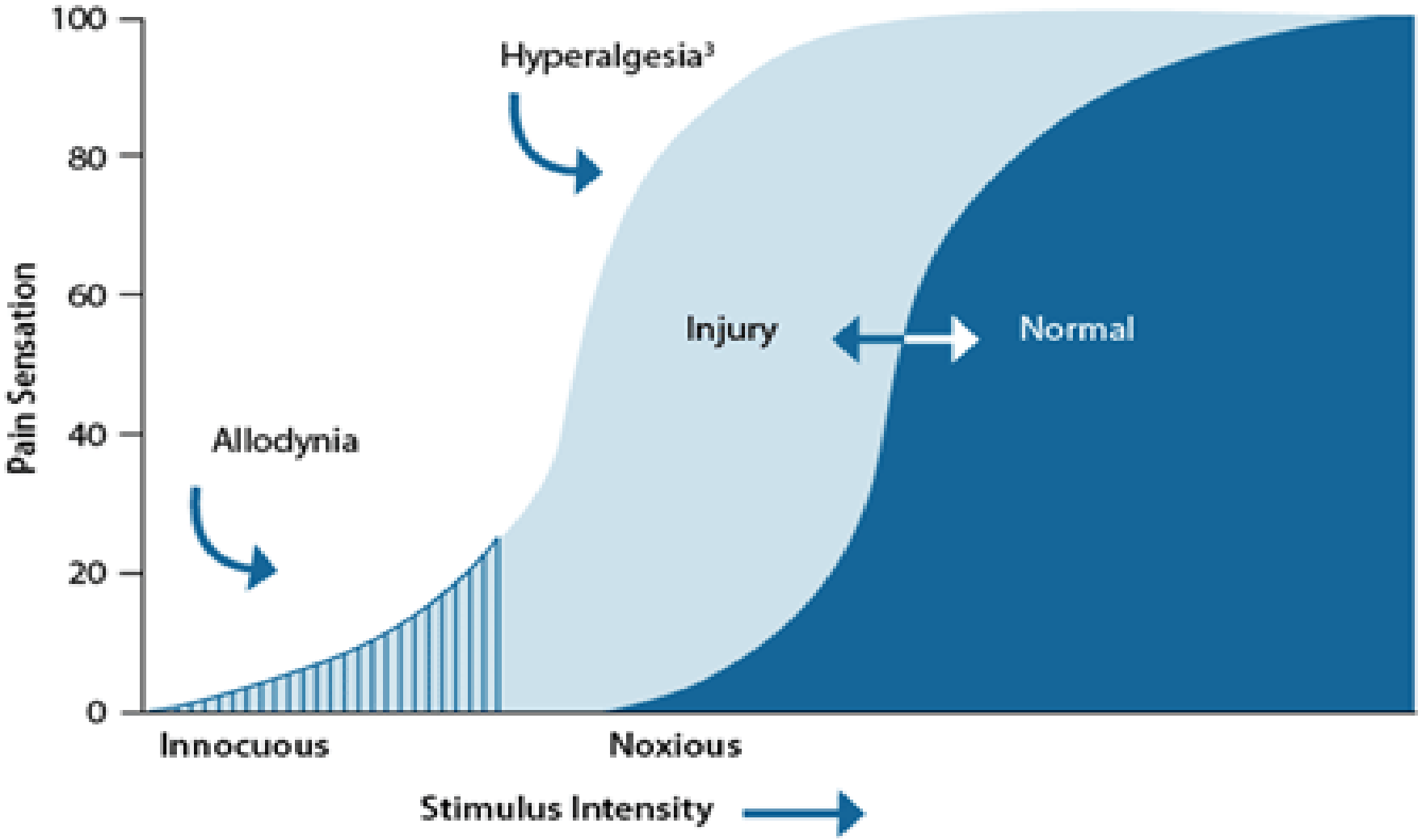
The uncontrolled activation of nociceptors is associated with several pathological conditions. **Allodynia** and **hyperalgesia** are two common pain states that reflect changes in nociceptor activity.

Allodynia: pain due to a stimulus that does not usually provoke pain.

Hyperalgesia: increased pain from a stimulus that usually provokes pain.

Patients with allodynia do not feel pain constantly; in the absence of a peripheral stimulus there is no pain. Patients with hyperalgesia typically report persistent pain in the absence of sensory stimulation.

Allodynia vs Hyperalgesia



Medscape

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Persistent pain can be subdivided into two broad classes, **nociceptive and neuropathic**.

Nociceptive pain results from the activation of nociceptors in the skin or soft tissue in response to tissue injury, and it usually arises from an accompanying inflammation.

Neuropathic pain results from direct injury to nerves in the peripheral or central nervous system and is often accompanied by a burning or electric sensation.

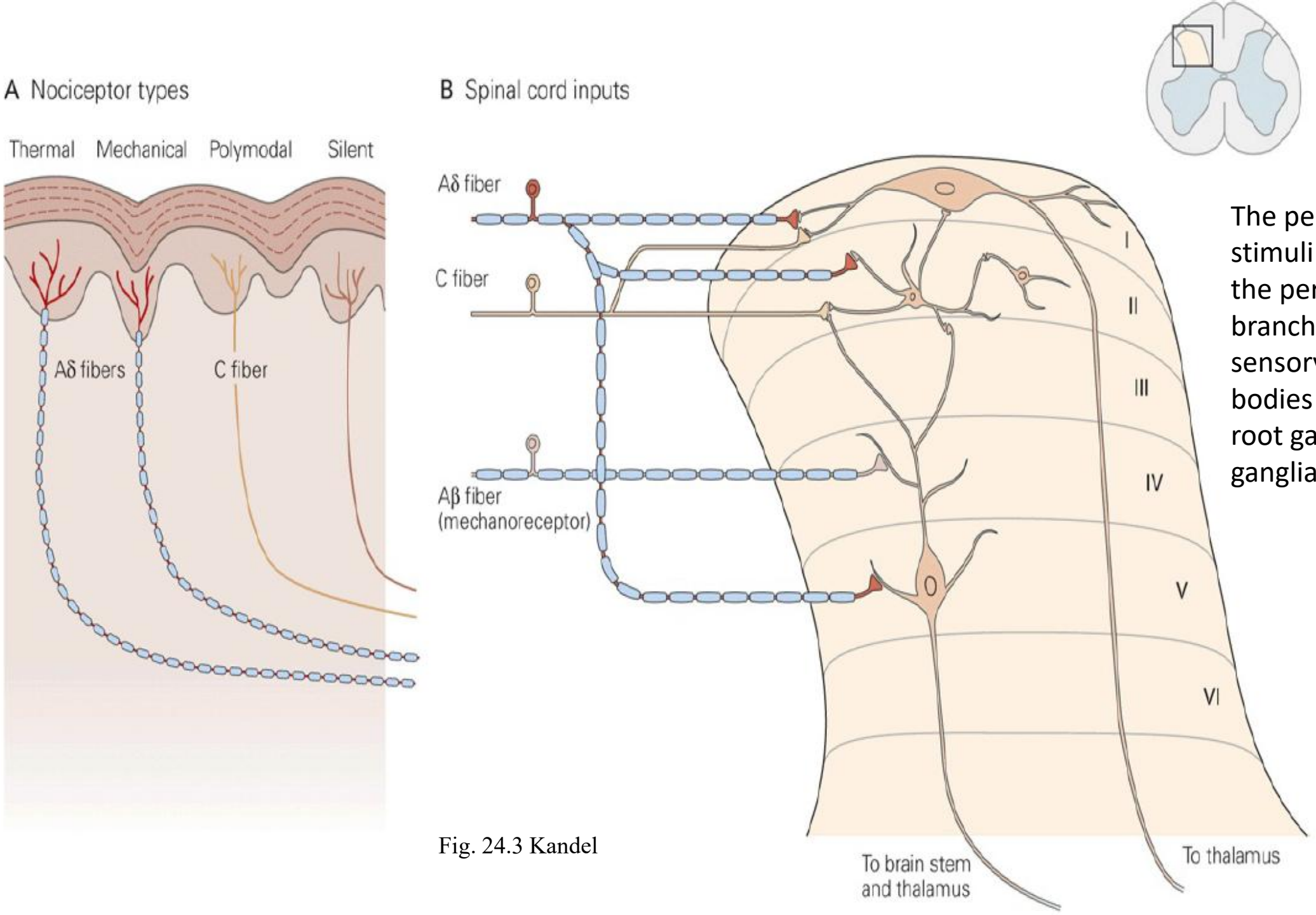


Fig. 24.3 Kandel

The perception of noxious stimuli arises from signals in the peripheral axonal branches of nociceptive sensory neurons whose cell bodies are located in dorsal root ganglia or the trigeminal ganglia.

Nociceptive sensory neurons that activate neurons in the dorsal horn of the spinal cord release two major classes of neurotransmitters. **Glutamate** is the primary neurotransmitter of all primary sensory neurons, regardless of sensory modality.

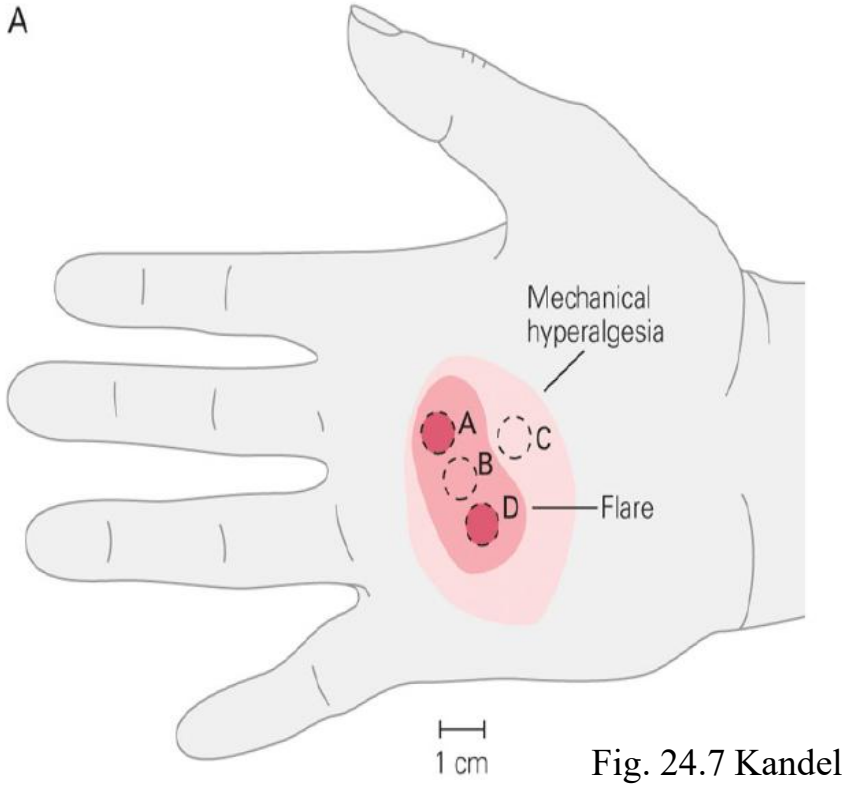
Neuropeptides are released as co-transmitters: substance P, calcitonin gene-related peptide (CGRP), somatostatin, and galanin

Substance P is released from the central terminals of nociceptive afferents in response to tissue injury or after intense stimulation of peripheral nerves. Its interaction with neurokinin receptors on dorsal horn neurons elicits slow excitatory postsynaptic potentials that prolong the depolarization elicited by glutamate.

Infusion of substance P coupled to a neurotoxin into the dorsal horn of experimental animals results in selective destruction of neurons that express neurokinin receptors. Animals treated in this way fail to develop the central sensitization that is normally associated with peripheral injury.

Hyperalgesia – peripheral origin

The normal process of sensory signaling can be dramatically altered when peripheral tissue is damaged, resulting in an increase in pain sensitivity or hyperalgesia. This condition can be elicited by sensitizing peripheral nociceptors through repetitive exposure to noxious mechanical stimuli



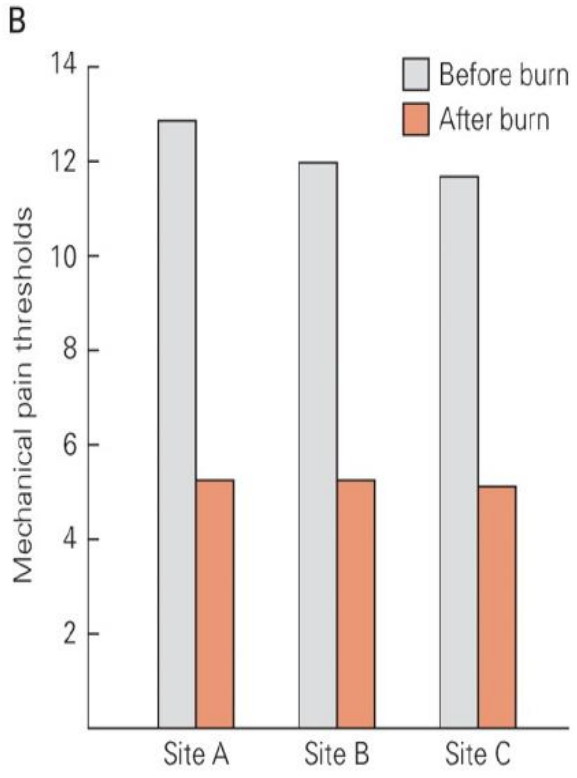


Fig. 24.7 Kandel

The sensitization is triggered by a complex mix of chemicals released from damaged cells that accumulate at the site of tissue injury. This cocktail contains peptides and proteins such as bradykinin, substance P, and nerve growth factor, as well as molecules such as ATP, histamine, serotonin, prostaglandins, leukotrienes, and acetylcholine.

Many of these chemical mediators are released from distinct cell types, but together they act to decrease the threshold of nociceptor activation.

Bradykinin is one of the most active pain-producing agents.

Damaged cells also release prostaglandins, through the activity of cyclooxygenase (COX) enzymes that cleave arachidonic acid.

Hyperalgesia – central origin

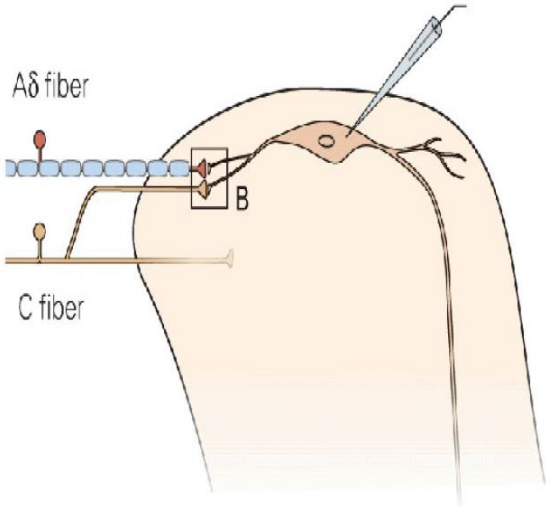
Neurotrophins are causative agents in pain.

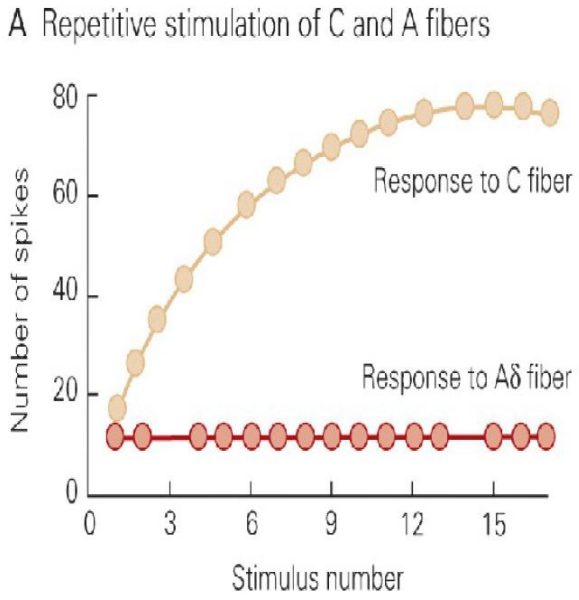
Nerve growth factor (NGF) is upregulated in many inflamed peripheral tissues. NGF-neutralizing molecules are effective analgesic agents in animal models of persistent pain.

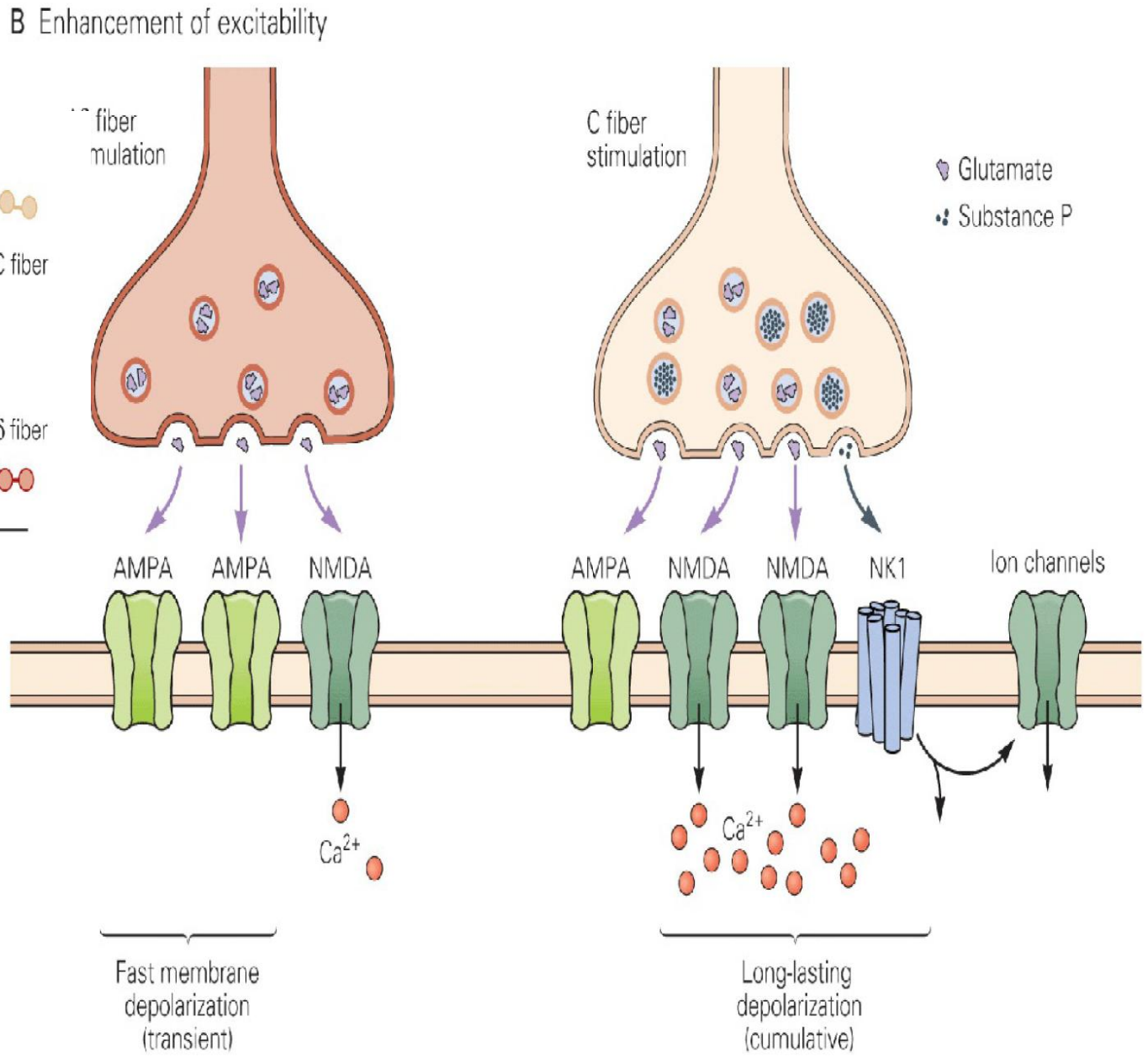
The expression of brain derived neurotrophic factor (**BDNF**) is also elevated in nociceptive neurons under conditions of inflammatory and neuropathic pain. BDNF is transported to the central terminals of the primary afferents in the spinal dorsal horn, where its release enhances the response of dorsal horn neurons to painful stimuli. Drugs that block BDNF expression in nociceptive neurons may therefore be useful as analgesics.

Under conditions of persistent injury C fibers fire repetitively and the response of dorsal horn neurons increases progressively. The gradual enhancement in the excitability of dorsal horn neurons has been termed “wind-up” and is thought to involve N-methyl-D-aspartate (NMDA)-type glutamate receptors.

Hyperalgesia – central origin







Typical responses of a dorsal horn neuron in the rat to electrical stimuli delivered transcutaneously at a frequency of 1 Hz. With repetitive stimulation, the long-latency component evoked by a C fiber increases gradually, whereas the short-latency component evoked by an A fiber remains constant.

Fig. 24.10 Kandel

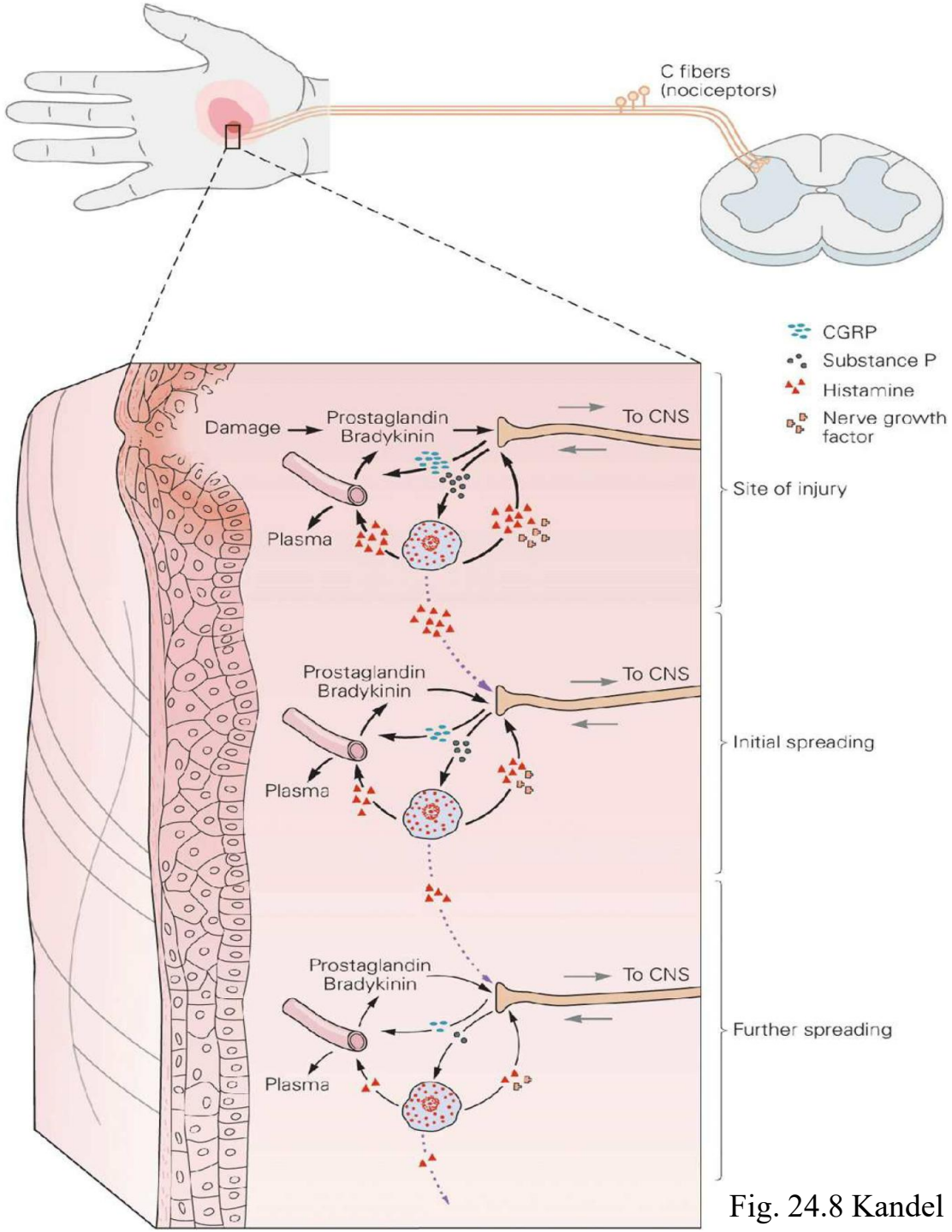


Fig. 24.8 Kandel

Neurogenic inflammation - Central origin

Neurogenic inflammation. Injury or tissue damage releases bradykinin and prostaglandins, which activate or sensitize nociceptors. Activation of nociceptors leads to the release of substance P and CGRP (calcitonin gene-related peptide). Substance P acts on mast cells in the vicinity of sensory endings to evoke degranulation and the release of histamine, which directly excites nociceptors. Substance P produces plasma extravasation, and CGRP produces dilation of peripheral blood vessels: the resultant edema causes additional liberation of bradykinin.

These mechanisms also occur in healthy tissue, where they cause secondary or spreading hyperalgesia.

The gate-control theory of nociception

Many projection neurons in the dorsal horn of the spinal cord respond selectively to noxious inputs, but others receive convergent inputs from both nociceptive and non-nociceptive afferents. The relative balance of activity in nociceptive and non-nociceptive afferents influences the transmission and perception of pain.

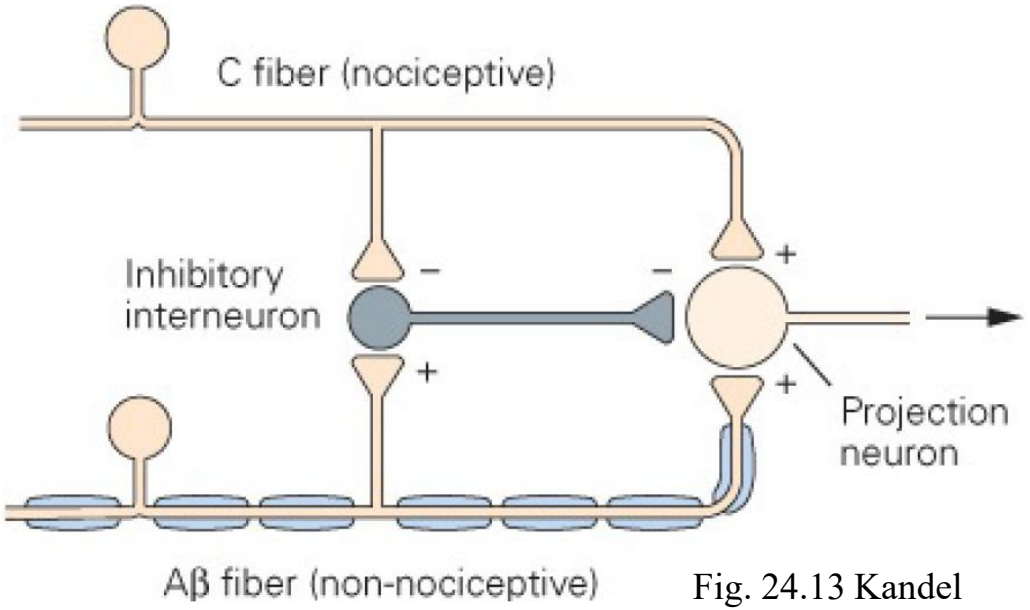


Fig. 24.13 Kandel

Such interactions can also occur at many supraspinal relay centers.

The idea of convergence also helped to promote the use of transcutaneous electrical nerve stimulation (TENS) and dorsal column stimulation for the relief of pain. With TENS, stimulating electrodes placed at peripheral locations activate large-diameter afferent fibers that overlap the area of injury and pain.

Opioids

Since discovery by the Sumerians in 3300 BC, the opium poppy and its active ingredients, opiates such as morphine and codeine, have been recognized as powerful analgesic agents.

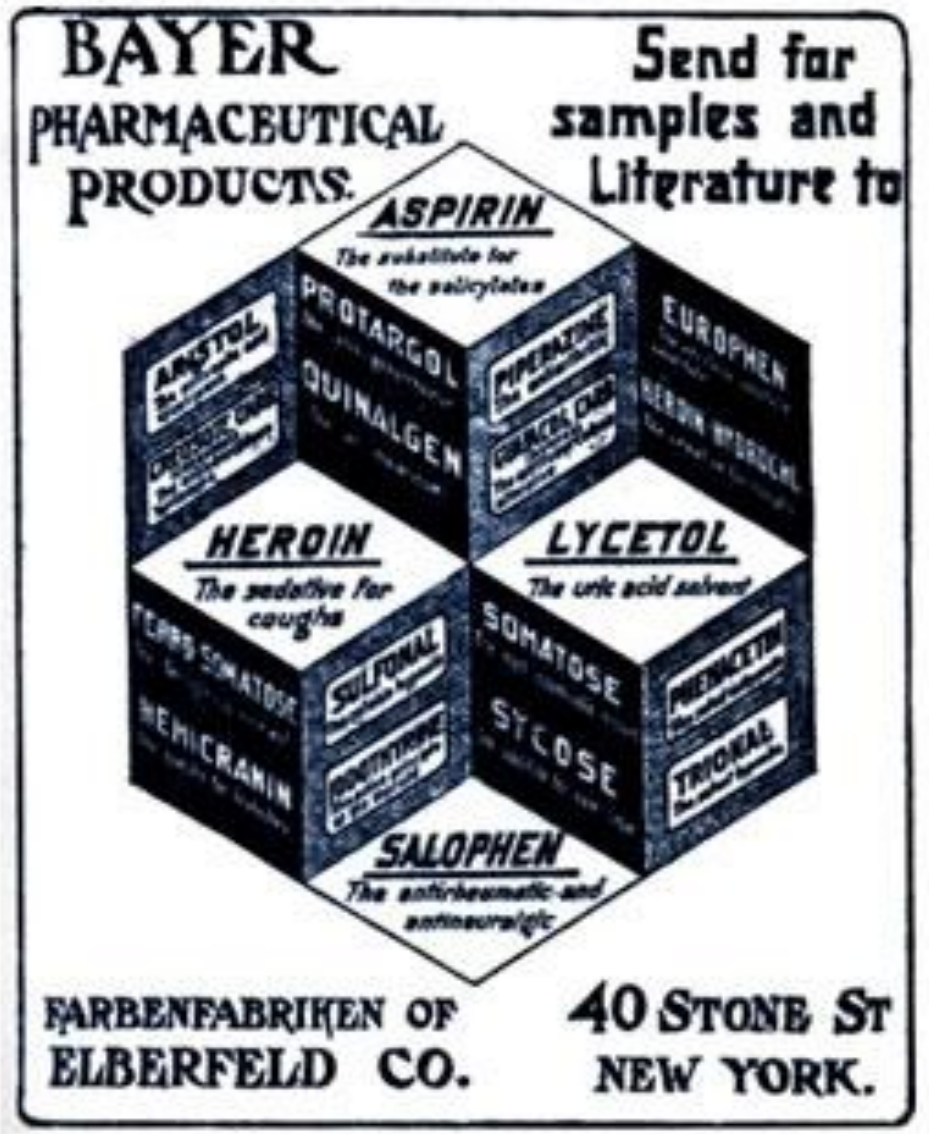
Opium poppy is a flowering plant (Papaver somniferum) of the family Papaveraceae(70–100 species) native to Turkey.

Opium, morphine, codeine, and heroin are all derived from the milky fluid found in its unripe seed capsule.

A common garden annual, some opium poppy bears blue-purple or white flowers 5 in. (13 cm) wide on plants about 3–16 ft (1–5 m) tall, with lobed or toothed silver-green foliage.

Opium poppy is also grown for its tiny non-narcotic ripe seeds, which are kidney-shaped and grayish blue to dark blue; the seeds are used in bakery products and for seasoning, oil, and birdseed.

The poppy flower flourishes in dry, warm climates about three months after seeds are planted: brightly-colored flowers bloom at the tips of greenish, tubular stems. As the petals fall away, they expose an egg-shaped seed pod. Inside the pod is an opaque, milky sap. This is opium in its crudest form. The sap is extracted by slitting the pod vertically in parallel strokes with a special curved knife. As the sap oozes out, it turns darker and thicker, forming a brownish-black gum. A farmer collects the gum with a scraping knife, bundles it into bricks, cakes or balls and wraps them in a simple material such as plastic or leaves. Then the opium enters the black market.



Heroin is prepared from equal quantities of morphine and acetic anhydride, heated in a glass or enamel-lined container to form impure diacetylmorphine; water and chloroform are added to the solution to precipitate impurities; the solution is drained and sodium carbonate added to make the heroin solidify and sink; the heroin is filtered out of the sodium carbonate solution with activated charcoal and purified with alcohol, which is gently heated to evaporate the alcohol and leave heroin.

It was synthesized in 1897 by **Felix Hoffmann** and commercialized by **Baye**r in the following year

Opioids

rabbit immunoglobulin), whereas L cells treated with normal rabbit serum showed no fluorescence (6). Further immunofluorescence studies showed the presence of cell-bound rabbit immunoglobulin with all of the cell-antiserum combinations with which stimulation occurs.

Other studies (6) indicate that the large increases in radioactive nucleoside uptake may be due in part to increased nucleoside transport, but it is clear from the measurements of cell number that cell proliferation is also being stimulated. There is a close analogy here to the stimulatory effects of lectins on lymphocyte cell growth, in which there are marked increases in radioactive [^{3}H]dT uptake with smaller increases in cell number and total cellular DNA content.

Our tentative conclusions are that antibodies specific for cell surface antigens can induce the cell to undergo DNA synthesis and cell division and that the antigenic determinants involved may be similar on the several different cell lines that show immunologic cross-reactivity. One of these cell lines, L-929, was transformed by a chemical carcinogen, methylcholanthrene, yet shows cross-stimulation with antiserums against two human cancers that have no known transforming agent. In cell lines stimulated by the same antiserums, the cross-stimulation we see could be due to the presence of common, tumor-related glycopeptides, but the possibility of viral or mycoplasmal infection of our cultures should also be considered. Viral infection is highly unlikely because we have obtained comparable immune stimulation with fresh cell lines in another laboratory with different equipment. Mycoplasma-free and mycoplasma-infected cell lines yield similar immune stimulation.

This is, to our knowledge, the first direct evidence that antibodies can stimulate the growth of transformed, nonlymphocytic cell lines. While the mechanism is unclear, there has been considerable speculation about the possible role of increased transport of essential nutrients into the cell during accelerated cell growth. In this connection, it is of interest that stimulation of active transport of potassium has been demonstrated in sheep LK red blood cells after incubation with sheep antibody against the L determinant (7). The possible relevance of these observations to blocking effects of antiserum on cell-mediated immunity in

(C. Pert et al. Science, 182: 1359-1361, 1973)

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9. The HT-29 cells were supplied by J. Fogh, Sloan-Kettering Institute; and MOPC-315 cells were supplied by R. Lynch, Washington University. We thank B. Moore for technical assistance. Supported in part by PHS special research fellowship 1F03-AI53856 (W.T.S.) and by NIH grant 5R01 CA 12626.

30 July 1973

Opiate Agonists and Antagonists Discriminated by Receptor Binding in Brain

Abstract. *Receptor binding of opiate agonists and antagonists can be differentiated in vivo and in vitro. Administration of either rapidly elevates stereospecific [^{3}H]dihydromorphine binding to mouse brain extracts by 40 to 100 percent, but antagonists are 10 to 1000 times more potent than agonists; as little as 0.02 milligram of naloxone per kilogram of body weight significantly enhances opiate receptor binding. Sodium enhances antagonist binding in vitro but decreases agonist binding, a qualitative difference that may be relevant to the divergent pharmacological properties of opiate agonists and antagonists.*

Opiate antagonists are thought to occupy opiate receptor sites, preventing the access of opiates but not themselves eliciting analgesia or euphoria. Potent, long-lasting, and "pure" antagonists may provide an effective treatment for addiction, while drugs combining opiate agonist and antagonist activities offer promise as nonaddicting analgesics (1).

We described opiate binding in animal nervous tissue (2) which we attributed to specific opiate receptor sites on the basis of the stereospecificity of binding (3) and the close parallel between affinity for binding sites and pharmacological potency. These results have been confirmed (4, 5). Of 40 monkey brain regions examined, binding is most enriched in the anterior amygdala, hypothalamus, periaqueductal gray, and caudate head (6). Selective destruction of specific catecholamine, serotonin, and acetylcholine neural pathways in the brain does not alter binding (6). Receptor binding is degraded by trypsin, chymotrypsin, and phospholipase A in concentrations of less than 0.5 μg/ml and by 0.01 percent concentrations of the detergents Triton-X 100, deoxycholate, and sodium dodecyl sulfate, results suggesting that protein and lipid are important constituents of the opiate-receptor complex (7). The receptor is present in all vertebrate brains examined, including mammals, birds, reptiles, amphibia, and teleost fish, but cannot be detected in invertebrates such as arthropods and platyhelminths (8). We now report differential receptor interactions of opiate agonists and antagonists in vivo and in vitro.

Homogenates of mouse or rat brain (150 ml per gram) were incubated in triplicate in the dark for 30 minutes at 25°C in the presence of $10^{-7}M$ levorphanol or $10^{-7}M$ dextrorphan after the addition of the appropriate isotopically labeled opiate or antagonist. Samples were filtered (2) and washed with two 5-ml portions of tris(hydroxymethyl)-aminomethane (tris) buffer at 4°C. After extraction, the filters were counted by liquid scintillation (2). Specific opiate receptor activity was calculated by subtracting binding of the ^{3}H-labeled ligand in the presence of $10^{-7}M$ levorphanol from binding in the presence of $10^{-7}M$ dextrorphan, its analgeti-

In 1973 Candace Pert, Gavril Pasternak and Solomon Snyder demonstrated the unequivocal existence of opioid receptors in the nervous system.

In 1975, John Hughes, Terry Smith, Hans Kosterliz, Linda Fotherghill, Barry Morgan and Howard Morris identified, in the nervous tissue, the presence of 2 peptides of 5aa each, that acted as potent agonists for opioid receptors. They termed these neuropeptides enkephalins.

Opioids

Since discovery by the Sumerians in 3300 BC, the opium poppy and its active ingredients, opiates such as morphine and codeine, have been recognized as powerful analgesic agents.

Morphine and other opiates interact with specific receptors on neurons in the spinal cord and brain. The brain synthesizes endogenous neuropeptides with opiate-like activities at these receptors.

Table 24.1 Kandel

Propeptide	Peptide(s)	Preferential receptor
POMC	β-endorphin	μ/δ
	Endomorphin-1	μ
	Endomorphin-2	μ
Proenkephalin	Met-enkephalin	δ
	Leu-enkephalin	δ
Prodynorphin	Dynorphin A	κ
	Dynorphin B	κ
Pro-orphanin FQ	Orphanin FQ	Orphan receptor

Opioid receptors fall into four major classes: mu (μ), delta (δ), kappa (κ), and orphan. The opioid receptors were originally defined on the basis of the binding affinity of different agonist compounds.

Morphine and other opioid alkaloids are potent agonists at μ receptors. The μ receptors are highly concentrated in the superficial dorsal horn of the spinal cord, the ventral medulla, and the periaqueductal gray matter. Their widespread distribution explains why systemically administered morphine influences many physiological processes in addition to the perception of pain.

Neuronal cell bodies and axon terminals containing enkephalin and dynorphin are found in the dorsal horn of the spinal cord, particularly in laminae I and II, as well as in the rostral ventral medulla and the periaqueductal gray matter.

Neurons that synthesize β-endorphin are confined primarily to the hypothalamus; their axons terminate in the periaqueductal gray region and on noradrenergic neurons in the brain stem.

Opioids

Microinjection of low doses of morphine or other opiates directly into specific regions of the rat brain produces a powerful analgesia. Morphine-induced analgesia can be blocked by injection of the opiate antagonist naloxone into the periaqueductal gray region or the nucleus raphe magnus.

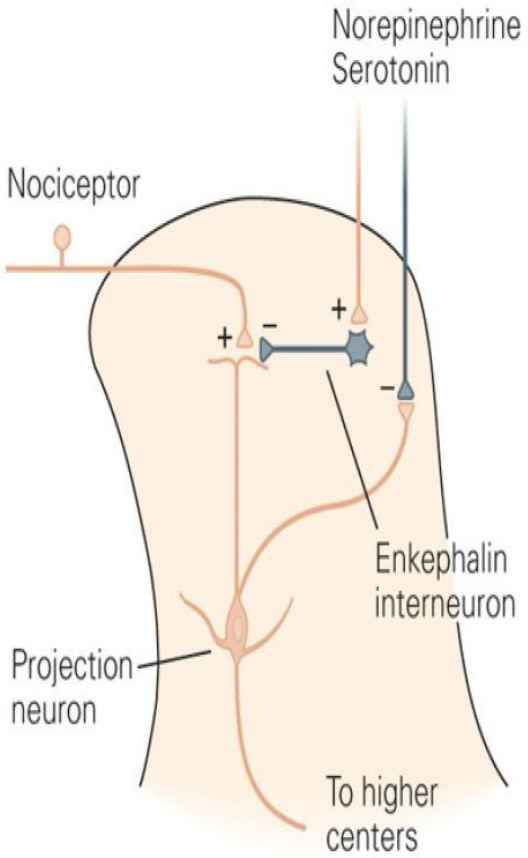
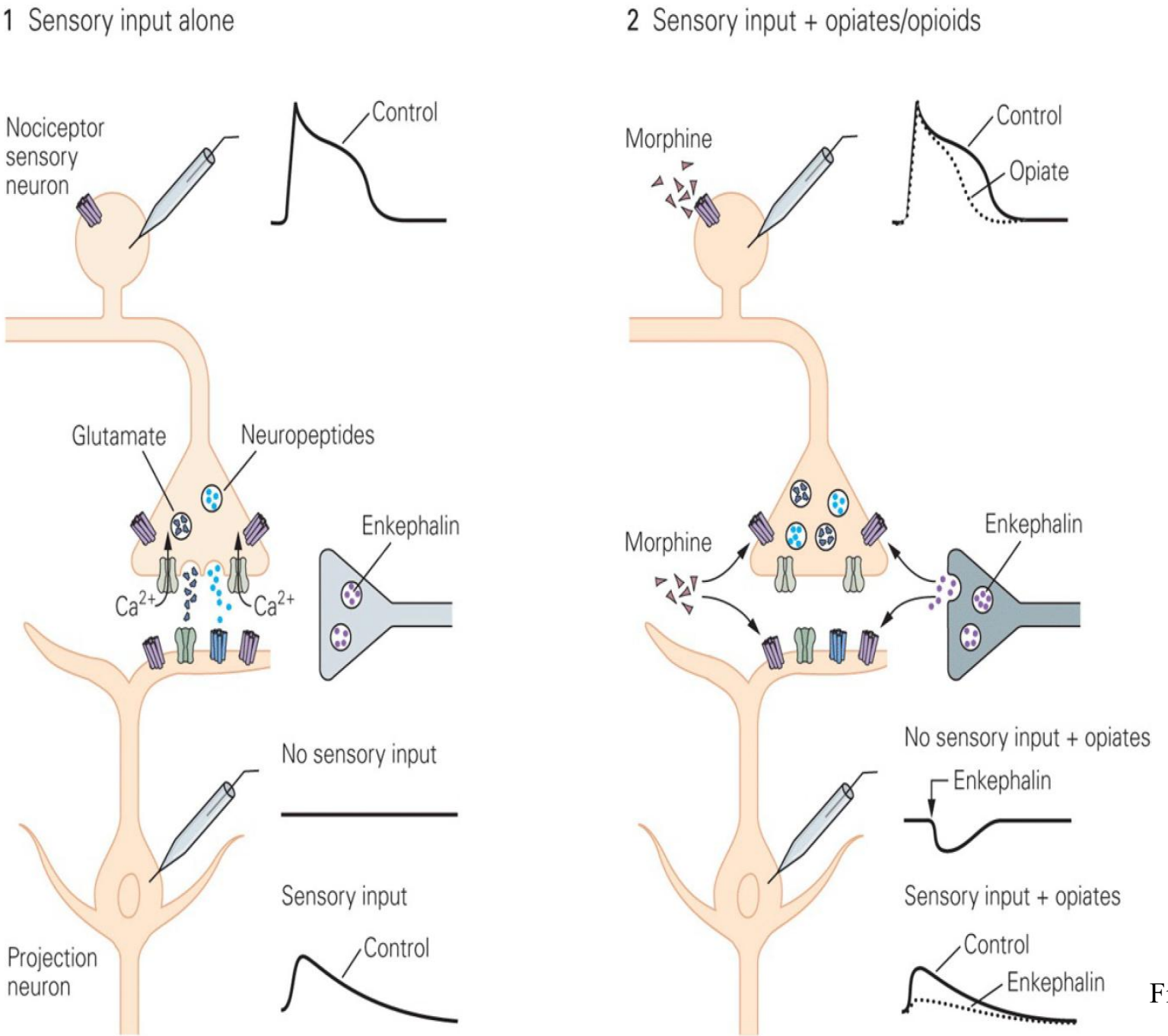


Fig. 24.17 Kandel

The superficial dorsal horn of the spinal cord contains interneurons that express enkephalin and dynorphin, and the terminals of these neurons lie close to synapses formed by nociceptive sensory neurons and spinal projection neurons

Opioids



Opiates regulate nociceptive transmission at synapses in the dorsal horn through two main mechanisms:

1) they open K+ channels in the dorsal horn neurons, hyperpolarizing the neurons and thus increasing the threshold for activation.
2) by binding to receptors on presynaptic sensory terminals opiates inhibit Ca2+ entry into the sensory nerve terminal.

Fig. 24.17 Kandel

Opioids

Many of the side effects of opiates are caused by the activation of opiate receptors within the brain and periphery.

Opiate receptors are expressed by muscles of the bowel and anal sphincter; their activation contributes to constipation. The activation of opiate receptors in the nucleus of the solitary tract is responsible for respiratory depression and cardiovascular side effects. Confining drug administration to the spinal cord or to the periphery can minimize the side effects of systemic opiates.

The release of endogenous opioid peptides from chromaffin cells of the adrenal medulla or from immune cells that migrate into injury sites may normally be involved in regulating the activation of nociceptors.

The chronic use of morphine produces major problems, most notably tolerance and addiction. Resistance to the analgesic effects of the drug, with the consequence that progressively higher drug doses are required to achieve the same therapeutic effect, is common.

One theory holds that tolerance results from uncoupling of the opioid receptor from its G protein transducer. Nevertheless, the binding of naloxone to μ opiate receptors can precipitate withdrawal symptoms in tolerant subjects, suggesting that the opioid receptor is still active in the tolerant state. Addiction and tolerance are different phenomena with different mechanisms.

CANNABIS

Modern medicine meets ancient medicine

Cannabis

The Cannabis plant produces a resin containing psychoactive compounds called cannabinoids.

The highest concentration of cannabinoids is found in the flowers of the plant and only feminine cannabis plants produce flower heads.

Cannabis is a plant belonging to the family Cannabaceae of the nettle order (Urticales). By some classifications, the genus Cannabis comprises a single species, hemp (Cannabis sativa) a stout, aromatic, erect annual herb that originated in Central Asia and is now cultivated worldwide, including in Europe, southern Asia, the Middle East, India, Africa, and the Americas.

A tall, cane-like variety is raised for the production of hemp fibre, while the female plant of a short, more branchy variety is prized as the more abundant source of the psychoactive substance tetrahydrocannabinol (THC), the active ingredient of marijuana.

Morphological differences in wild and cultivated forms of cannabis have introduced taxonomic uncertainties. Hence, in addition to Cannabis sativa, some scientists consider the genus as including a second species, Cannabis indica, or even a third, Cannabis ruderalis.

(Nature, 346: 561-564, 1990)

Structure of a cannabinoid receptor and functional expression of the cloned cDNA

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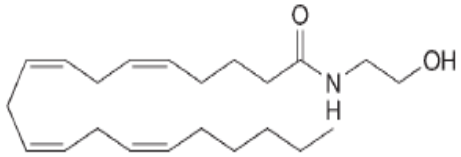
MARIJUANA and many of its constituent cannabinoids influence the central nervous system (CNS) in a complex and dose-dependent manner[1,2]. Although CNS depression and analgesia are well documented effects of the cannabinoids, the mechanisms responsible for these and other cannabinoid-induced effects are not so far known[3]. The hydrophobic nature of these substances has suggested that cannabinoids resemble anaesthetic agents in their action, that is, they nonspecifically disrupt cellular membranes. Recent evidence, however, has supported a mechanism involving a G protein-coupled receptor found in brain and neural cell lines, and which inhibits adenylate cyclase activity in a dose-dependent, stereoselective and pertussis toxin-sensitive manner[4–7]. Also, the receptor is more responsive to psychoactive cannabinoids than to non-psychoactive cannabinoids[8]. Here we report the cloning and expression of a complementary DNA that encodes a G protein-coupled receptor with all of these properties. Its messenger RNA is found in cell lines and regions of the brain that have cannabinoid receptors. These findings suggest that this protein is involved in cannabinoid-induced CNS effects (including alterations in mood and cognition) experienced by users of marijuana.

bradykinin, substance P, neuropeptide Y, neurotensin, vasopressin and other ligands at 1 or 10 μM. Although this strategy for selecting candidate ligands is beset with limitations, the critical findings, which prompted us to examine cannabinoids as ligands for SKR6, included the presence of both cannabinoid receptors[5,11] and SKR6 mRNA in the same cell lines (Fig. 2*a*) and the localization of both the receptor[12,13] and SKR6 mRNA in similar brain areas (Fig. 2*b*; data not shown).

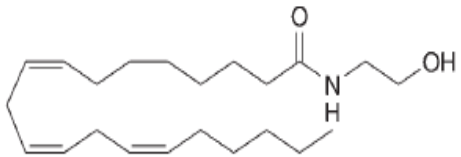
In Chinese hamster ovary K1 cells stably transfected with SKR6, expression of a cannabinoid-responsive, G protein-coupled receptor was obtained. The major psychoactive cannabinoid found in marijuana (Δ^9-tetrahydrocannabinol, Δ^9-THC) and a synthetic analogue with potent analgesic properties (CP 55940) inhibited forskolin-stimulated accumulation of cAMP in a dose-dependent manner (Fig. 3*a*). In addition, the dose–response curves for the opposite (+) enantiomeric forms of these two cannabinoids indicated this effect was stereoselective. The effector concentration for half-maximum response (EC_{50}) of CP 55940 compared with that of its (+) enantiomer (CP 56667) revealed a >100-fold difference in potencies between these compounds. By contrast, the difference in EC_{50} observed between (+) and (−) Δ^9-THC was only 50-fold. These data are in general agreement with data for N18TG-2 cell membranes, that is, that the degree of stereoselectivity between various cannabinoid analogues is greater with more potent compounds (such as CP 55940 compared with CP 56667) (ref. 14). As observed in neuroblastomas[8,14], none of the cannabinoids inhibited cAMP accumulation by 100 per cent but CP 55940 inhibited the accumulation of cAMP more than Δ^9-THC. In addition, (−) Δ^8-THC was less potent than (−) Δ^9-THC yet affected cAMP to a similar extent (inhibition of 36 versus 39 per cent). Finally, in transfected cells, cannabinol produced only a slight effect on cAMP accumulation, whereas the non-psycho-

The discovery of cannabinoid receptor (termed CB1) in the CNS

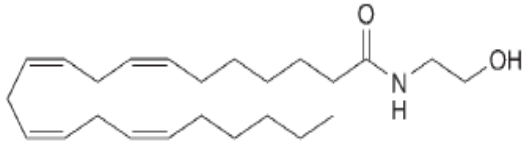
ENDOCANNABINOIDS



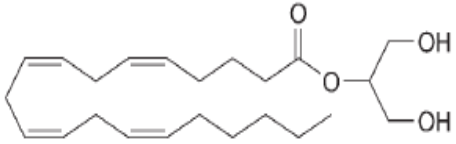
Anandamide
[54]



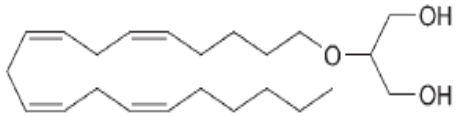
homo-γ-Linolenoylethanolamide
[55]



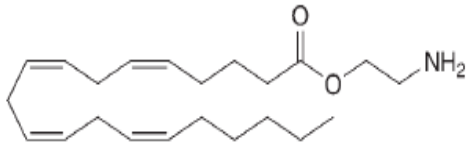
7,10,13,16-Docosatetraenoylethanolamide
[55]



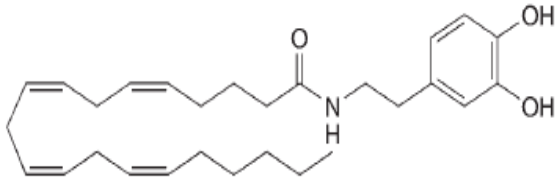
2-Arachidonoylglycerol
[59]



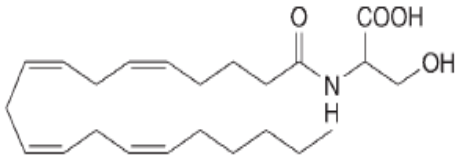
Noladin ether
[61]



Virodhamine
[62]



Arachidonoyldopamine
(NADA) [63]



N-Arachidonoylserine
[64]

The observation, made for the opioid system, that receptors would not have been selected by evolution merely to be activated by a plant product, was applied by Raphael Mechoulam and his group in Jerusalem, who also believed that the CB1 receptor, which was showing to be one of the most abundant G protein coupled receptors (GPCR) in the mammalian brain, had to be activated by some endogenous agonists.

The lipophilic nature of the first endogenous ligand of CB1 receptors (anandamide) retarded for a while its isolation and chemical identification.

Anandamide, also known as N-arachidonoylethanolamine or AEA, was named from the Sanskrit word ananda, which means "bliss, delight", and amide.

Synthetic delta-9-tetrahydrocannabinol (dronabinol) was licensed, in 1986, for the treatment of chemotherapy-associated nausea and vomiting and in, 1992, as an appetite stimulant for HIV / AIDS patients.

Understanding the mechanism of cannabinoid-induced analgesia has been increased through the study of cannabinoid receptors, endocannabinoids, and synthetic agonists and antagonists. The CB1 receptor is found in both the central nervous system (CNS) and in peripheral nerve terminals.

Similar to opioid receptors, high levels of the CB1 receptor are found in regions of the brain that regulate nociceptive processing. CB2 receptors, located predominantly in peripheral tissue, exist at very low levels in the CNS.

With the development of receptor-specific antagonists, additional information about the roles of the receptors and endogenous cannabinoids in the modulation of pain has been obtained: cannabinoids may also contribute to pain modulation through an anti-inflammatory mechanism; a CB2 effect with cannabinoids acting on mast cell receptors to attenuate the release of inflammatory agents, such as histamine and serotonin, and on keratinocytes to enhance the release of analgesic opioids has been described.

ANALGESIA

Without pharmaceutical treatment

THE PLACEBO EFFECT

Placebo analgesia is the most studied and understood type of placebo response, since it has been known for a very long time that many psychosocial factors tune very finely pain perception.

Also, modern placebo research has been influenced by the work by Henry K Beecher, an anesthesiologist who, as an army doctor during the Second World War, faced the problem of the lack of strong analgesics on the battlefield by treating many of the wounded just with saline solutions.

He noticed that many had a pain relief that appeared strongly dependent on his convincing attitude. In 1955 Becher published a seminal paper that is considered the beginning of a systematic approach to the placebo effect.

J.A.M.A., Dec. 24, 1955

THE POWERFUL PLACEBO

Henry K. Beecher, M.D., Boston

In humans, expectation and conditioning are not necessarily mutually exclusive, as they may represent two sides of the same coin. In other words, a conditioning procedure might lead to placebo responses through a mechanism of "reinforced expectations."

Indeed, in humans conditioning does not depend merely on the pairing of conditioned and unconditioned stimuli, but on the cognitive information of the conditioned stimulus. Therefore, a conditioning procedure would lead to the expectation that a given event will follow another event.

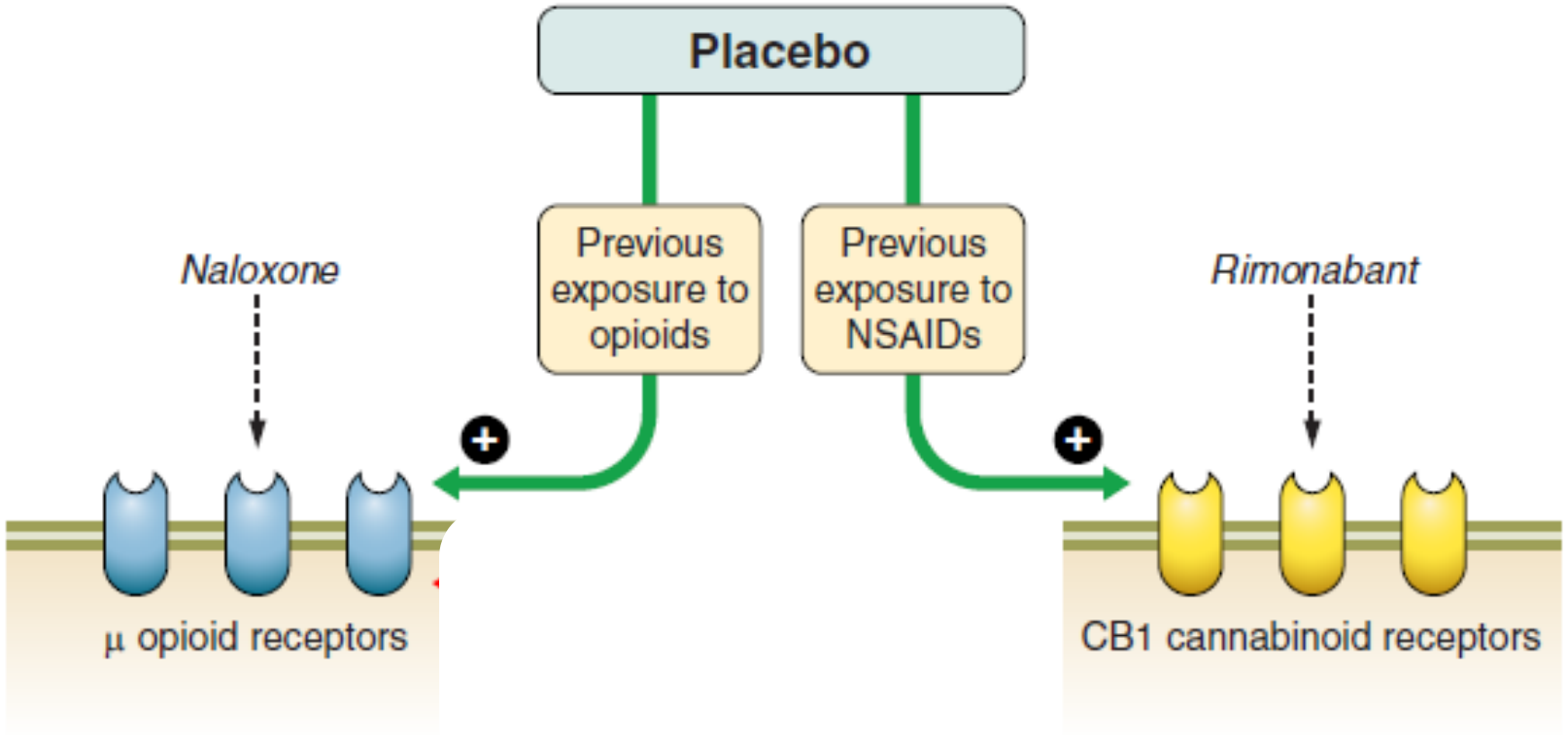
If a placebo is given after repeated administrations of morphine (preconditioning procedure), the placebo response can be blocked by NALOXONE (NALOXONE SENSITIVE).

Conversely, if the placebo response is induced by means of prior conditioning with a nonopioid drug, such as nonsteroid anti-inflammatory drugs (NSAIDs), it is NALOXONE INSENSITIVE.

On the basis of these findings, Benedetti and collaborators (2011) induced opioid or nonopioid placebo analgesic responses and assessed the effects of the CB1 cannabinoid receptor antagonist rimonabant. Differently from naloxone, rimonabant had no effect on opioid-induced placebo analgesia following morphine preconditioning, whereas it completely blocked placebo analgesia following nonopioid preconditioning with the NSAID ketorolac.

These findings indicate that those placebo analgesic responses that are elicited by NSAID conditioning are mediated by CB1 cannabinoid receptors (NSAID SENSITIVE ? CANNABINOID SENSITIVE ?)

(F Benedetti, 2013)



The mechanism of the placebo analgesic response depends on the previous exposure to different pharmacological agents, thus suggesting a memory for drug action. The previous exposure to opioids leads to opioid-mediated placebo responses, whereas the prior exposure to nonsteroid anti-inflammatory drugs (NSAIDs) leads to cannabinoid-mediated placebo responses.