

# Agopuntura

*neurofisiologia delle terapie fisiche basate sulla  
stimolazione sensoriale*



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*Institute of Translational Pharmacology  
CNR – National Research Council of Italy*

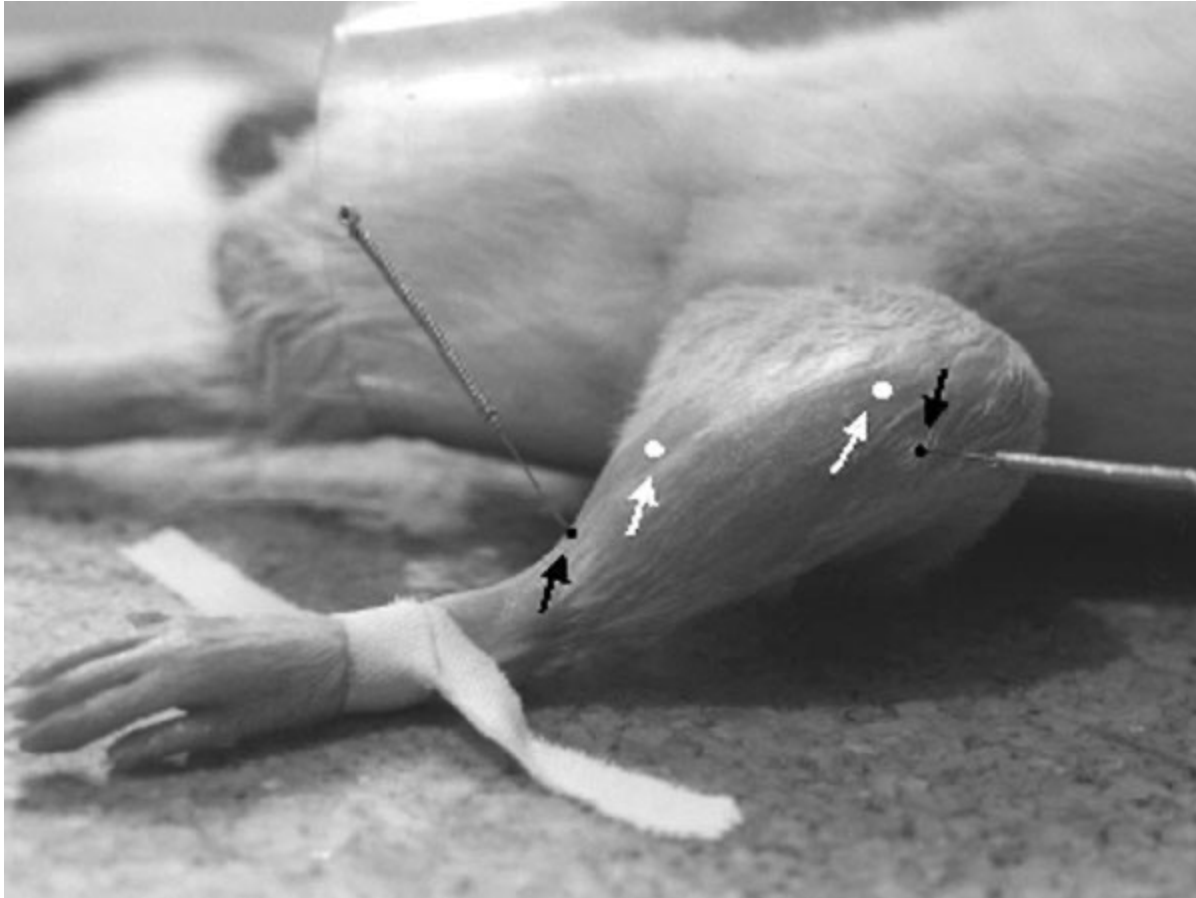
# Ricerca scientifica sull'agopuntura

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- Approccio scientifico per lo studio di una terapia che prevede l'inserzione e la stimolazione di aghi sulla superficie del corpo, sviluppata dalla Medicina Tradizionale Cinese (TCM).
- Differenze tra TCM e Medicina Occidentale:
  - Metodo di diagnosi
  - Perseguimento di un razionale scientifico per la terapia.

# Ricerca scientifica sull'agopuntura

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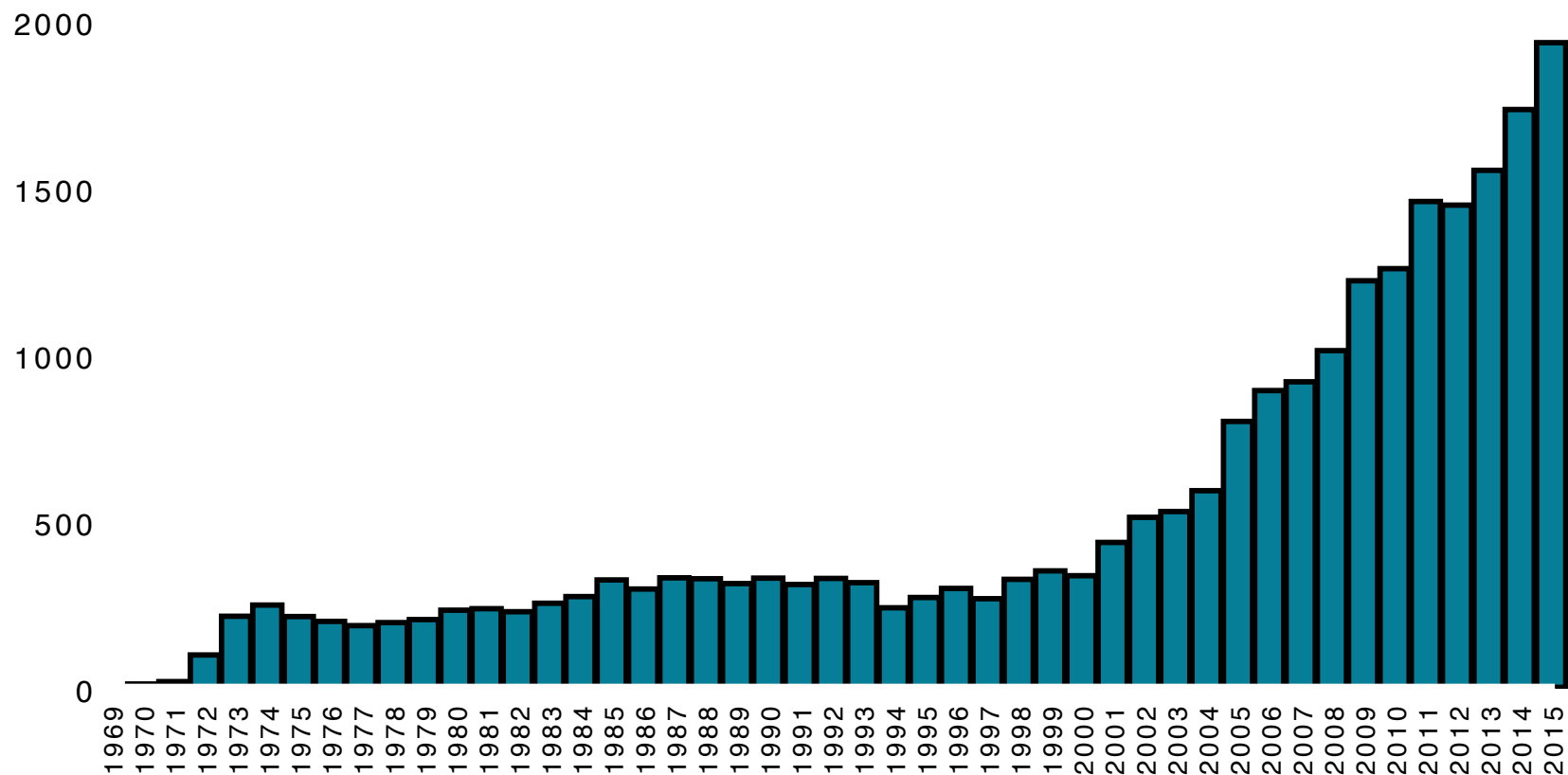
# Ricerca scientifica sull'agopuntura

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# Ricerca scientifica sull'agopuntura

# of PubMed Citations  
Search key: "acupuncture"



# Ricerca scientifica sull'agopuntura

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## **NIH Consensus Statement (1997)**

Addiction, Asthma, Carpal Tunnel Syndrome, Fibromyalgia, Headache, Low back pain, Menstrual cramps, Myofascial pain, Osteoarthritis, Postoperative dental pain, Stroke rehabilitation, Tennis elbow, Adult post-operative and chemotherapy nausea and vomiting.

Source: <http://odp.od.nih.gov/consensus/cons/107/107statement.htm>

## **WHO:**

Allergic rhinitis, Biliary colic, Depression, Dysentery, Dysmenorrhea, Primary Epigastralgia, Facial pain, Headache, Hypertension, Hypotension, Induction of labor, Knee pain, Leukopenia, Low back pain, Malposition of fetus, Morning sickness, Nausea and vomiting, Neck pain, Pain in dentistry, Periarthritis of shoulder, Postoperative pain, Renal colic, Rheumatoid arthritis, Sciatica, Sprain, Stroke, Tennis elbow, Adverse reactions to radiotherapy and/or chemotherapy

Source:

<http://216.239.41.104/u/who?qcache:k0eo2DnBw4J:www.who/int/medicines/library/trm>

# Ricerca scientifica sull'agopuntura



National Center for Complementary and Alternative Medicine (NCCAM)

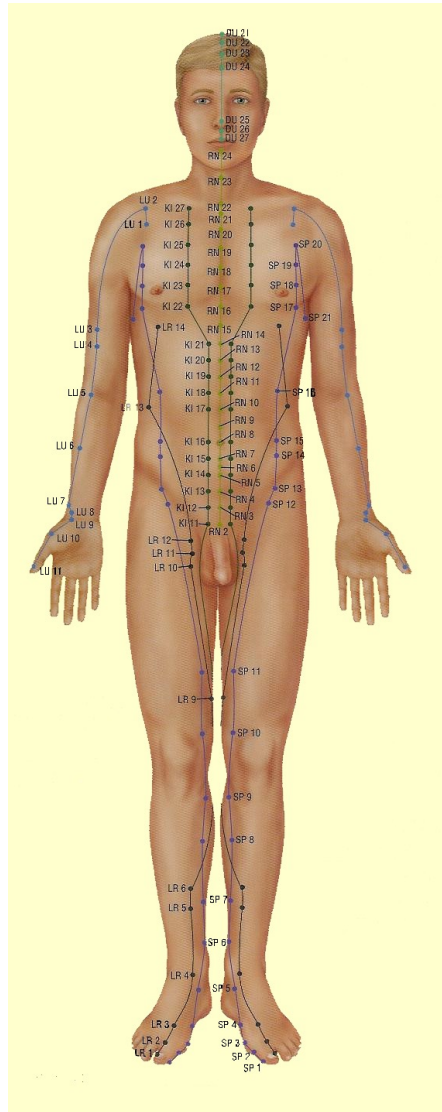
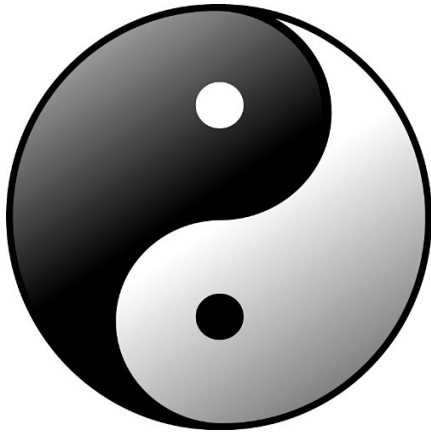
NIH is the Nation's medical research agency and is the largest source of funding for medical research in the world. In FY 2012, the entire NIH budget was approximately \$30.9 billion. NCCAM's overall budget that same year was about \$128 million, or 0.4 percent of the total NIH budget



The National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health (NIH) funds and conducts research to help answer important scientific and public health questions about complementary health approaches. NCCAM works to determine what is promising, what helps and why, what doesn't work, and what is safe.

<http://nccam.nih.gov/>

# Agopuntura





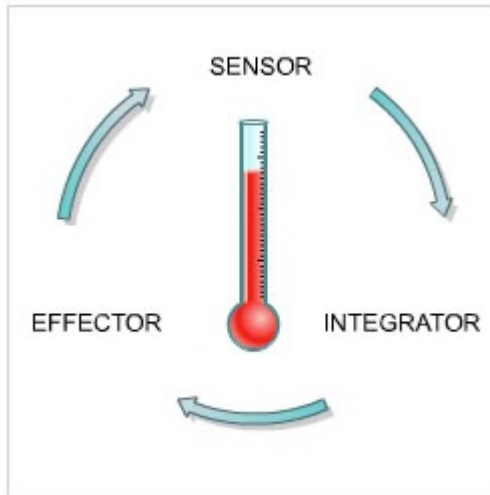
Regolazione dell'equilibrio tra  
Yin and Yang quando le potenzialità  
omeostatiche sono sopraffatte da stress  
acuto o cronico

# Agopuntura

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L'agopuntura è essenzialmente una tecnica usata per correggere disfunzioni reversibili in maniera fisiologica.

# Omeostasi



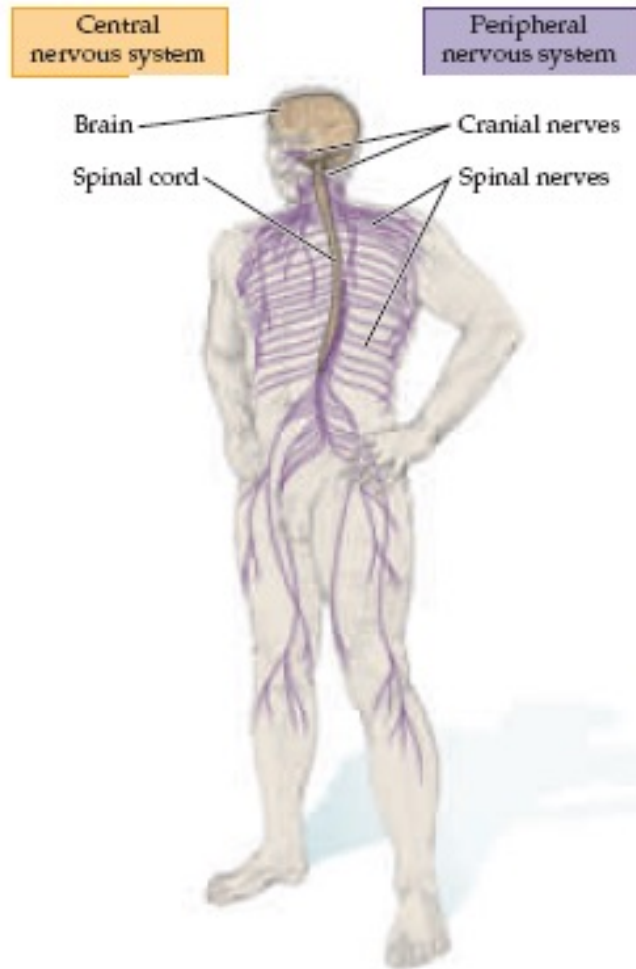
<b>Stimulus</b>	A change in the environment, such as an irritant, loss of blood or presence of a foreign chemical.
<b>Receptor</b>	The site within the body that detects or receives the stimulus, senses the change from normal, and sends signals to the control center.
<b>Control center</b>	The operational point, at which the signals are received, analyzed, and an appropriate response is determined. This is sometimes referred to as the integration center since it integrates the signals, and other information, to determine if a response is needed and the nature of a response.
<b>Effector</b>	The body site where a response is generated which counters the initial stimulus and thus attempts to maintain homeostasis.
<b>Feed back mechanisms</b>	Methods by which the body regulates the degree of response that has been elicited. A negative feed back depresses the stimulus to shut off or reduce the effector response whereas a positive feed back has the effect of increasing the effector response.



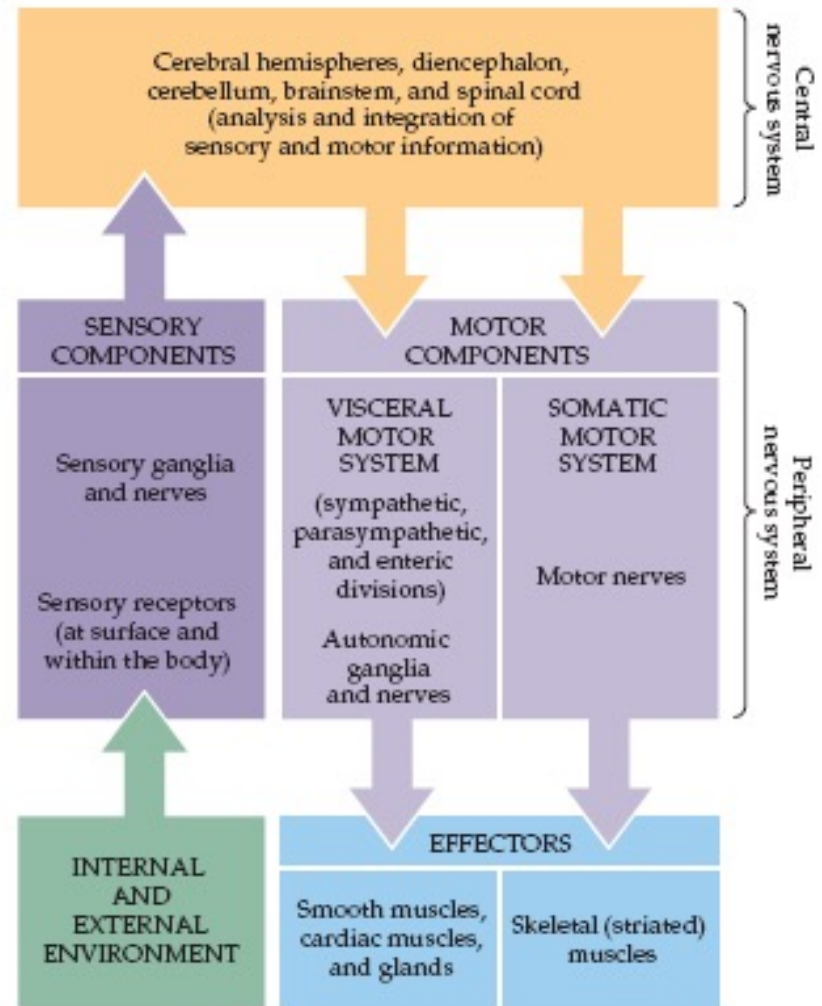
Awaiting allostasis (or grace), 2004, oil on canvas 76 x 76 cm

# Sistema nervoso

(A)



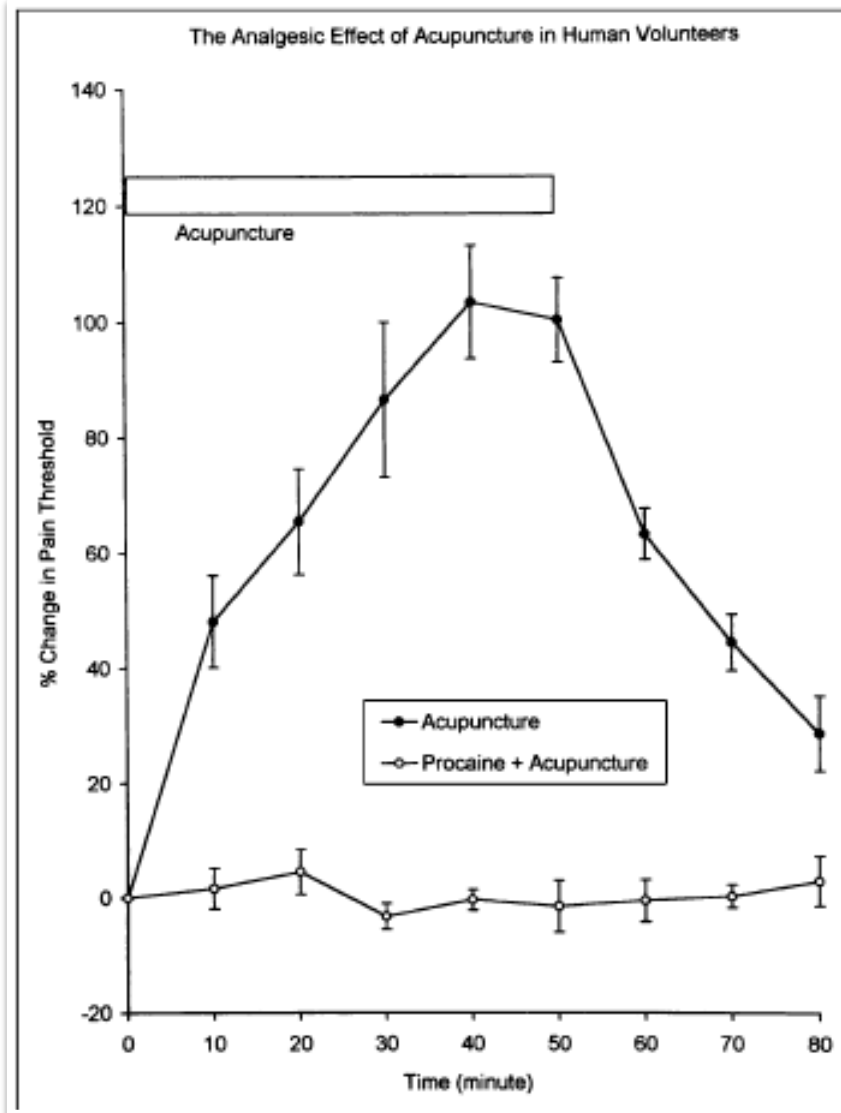
(B)



A fluorescence microscopy image of neural tissue. The image shows numerous cells with blue-stained nuclei and red-stained cytoplasm or specific organelles. The red staining is more prominent in a central region and along a fiber-like structure on the right side. The overall background is dark, highlighting the fluorescent structures.

# La Neurofisiologia dell'agopuntura

# Ricerca scientifica sull'agopuntura



1973: Increase of nociceptive threshold

Gradual changes: diffusible factors

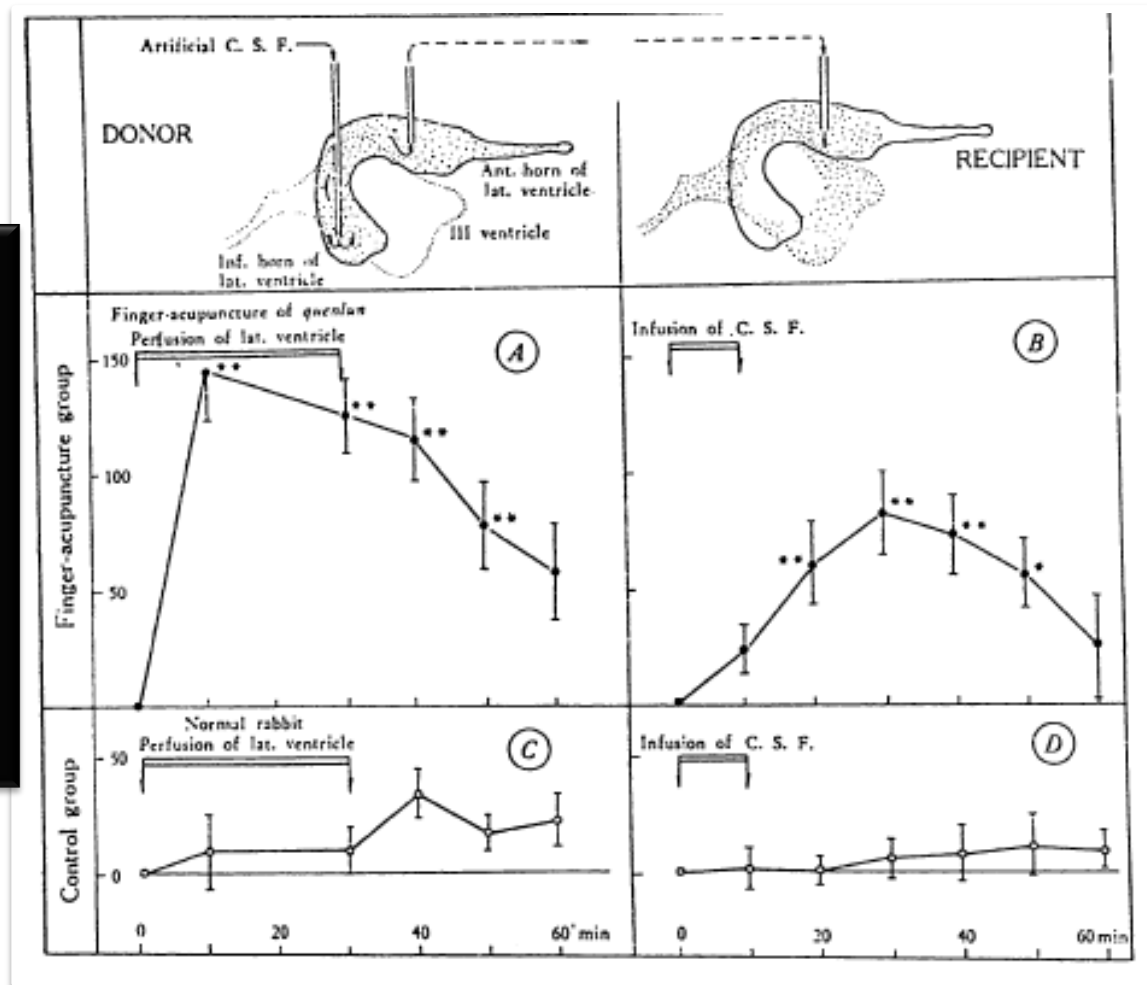
Blocked by procaine: sensory afferent

Chin Med J, 3:151; 1973

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1974: The analgesic action of acupuncture can be transferred between rabbits by transferring CSF.

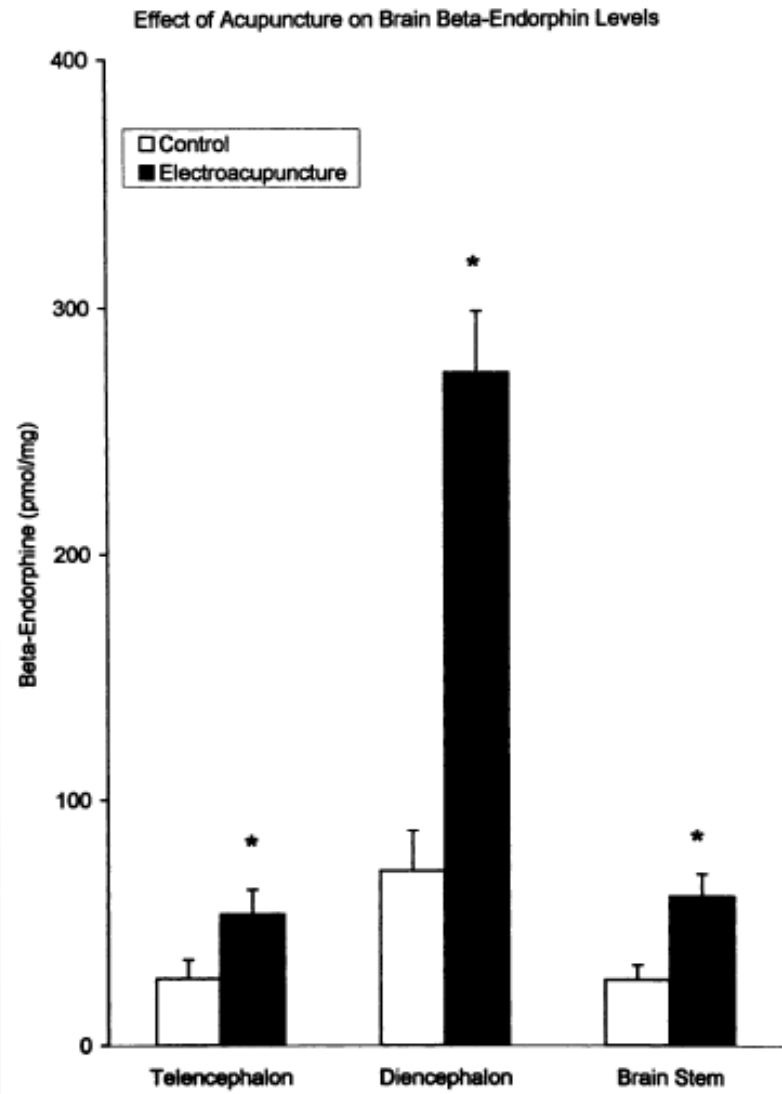
Scientia Sinica, 17:112; 1974



# Ricerca scientifica sull'agopuntura

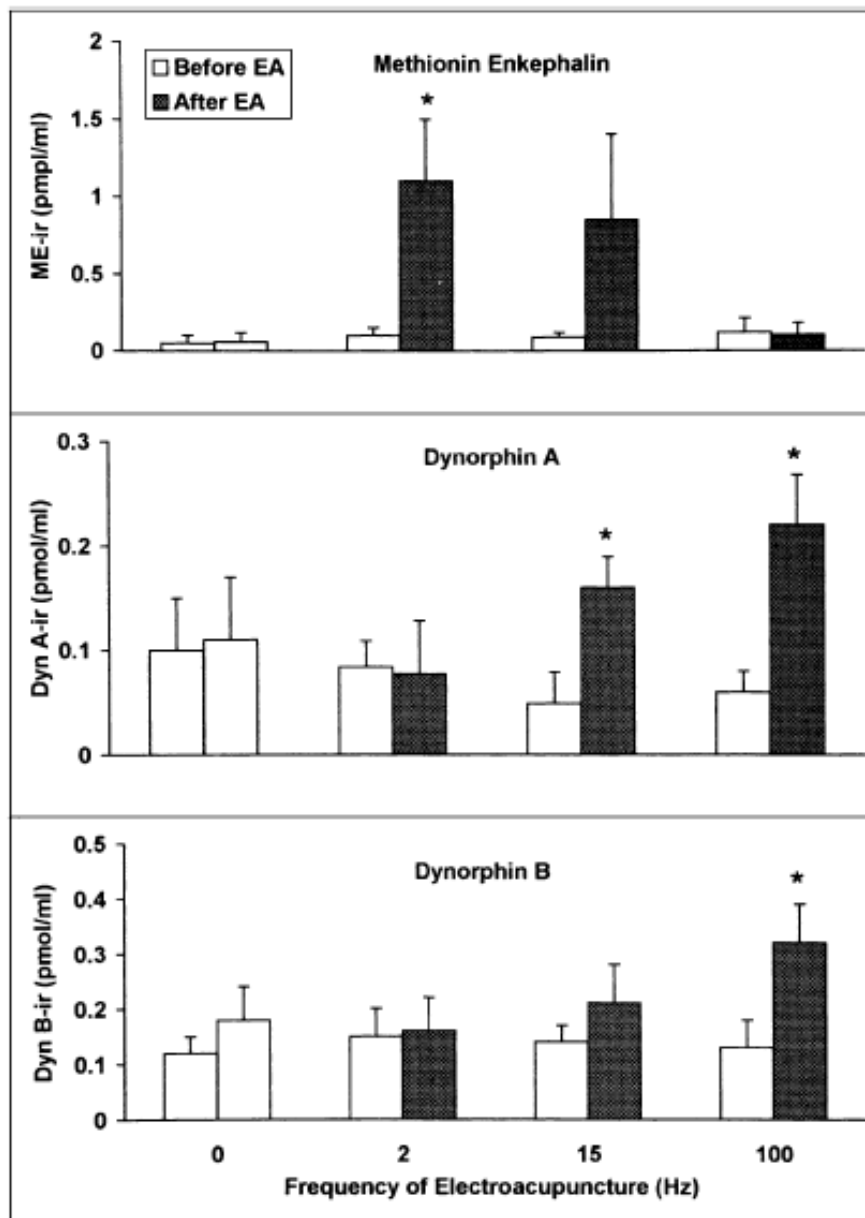
1983:  
Elettrocupuntura  
produce concomitante  
aumento della soglia  
del dolore e livelli  
cerebrali di beta-endorfina.

Kexue Tonga 28:312; 1983





# Ricerca scientifica sull'agopuntura

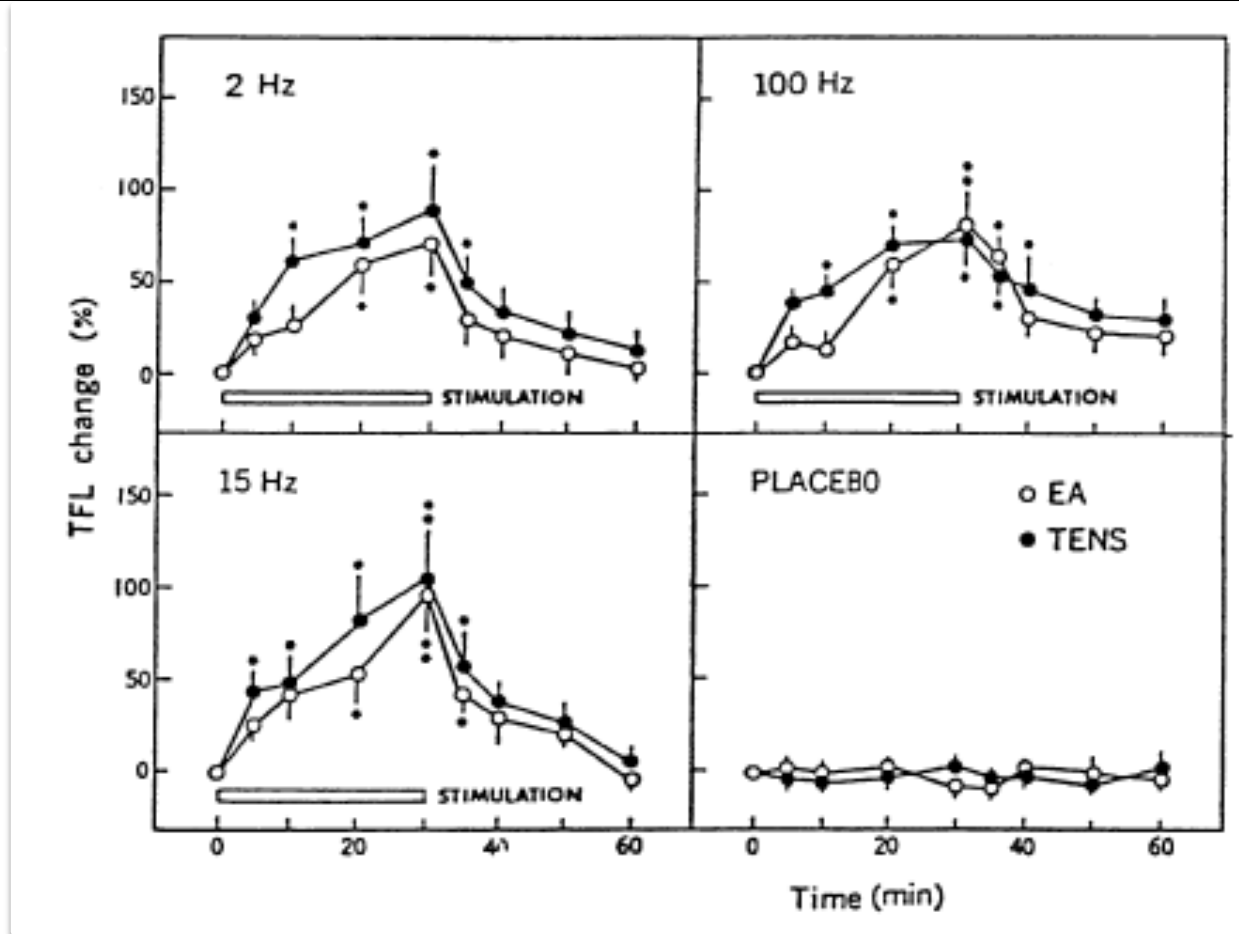


1986: Elettrocupuntura at low and high frequencies releases different types of endogenous opioids from the CNS.

Kexue Tongbo 31: 1512; 1986

# Ricerca scientifica sull'agopuntura

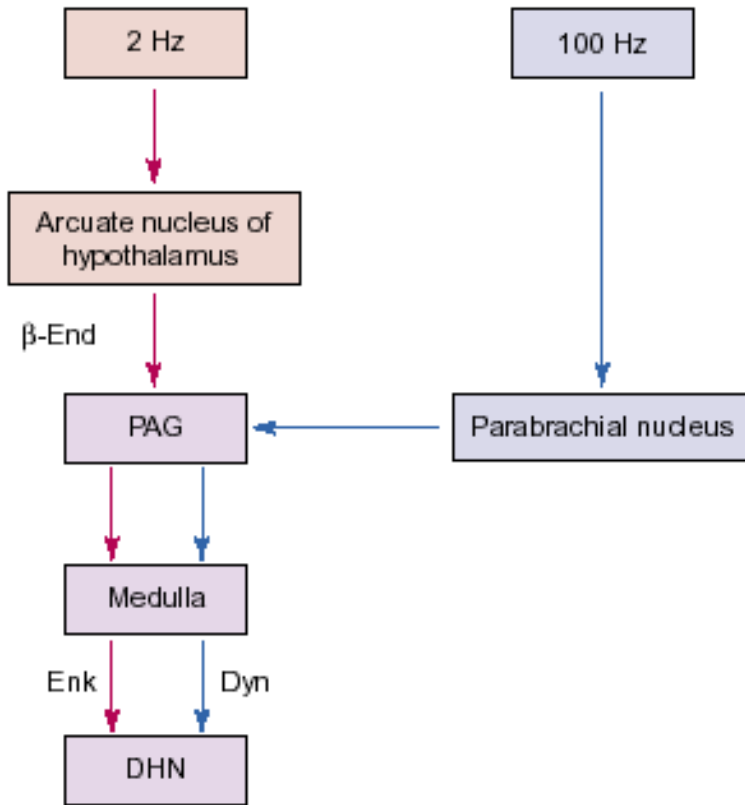
1992: EA and TENS at acupoints produce similar analgesic



Int J Neurosci 65:117; 1992

# Ricerca scientifica sull'agopuntura

## Frequency of Stimulation



(a)

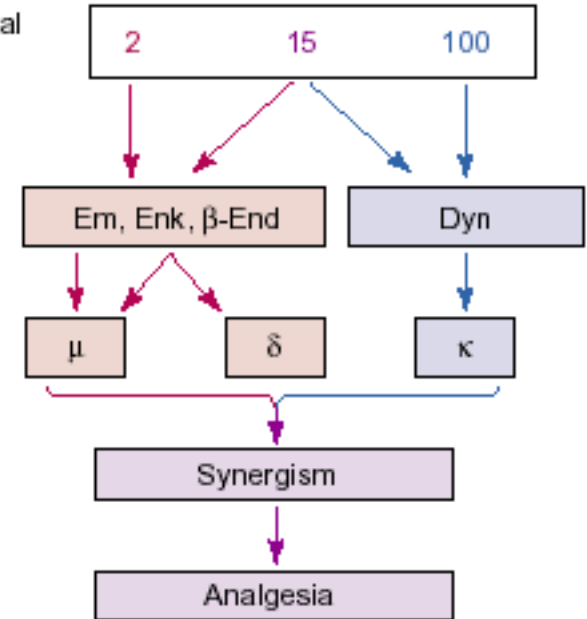
Frequency of electrical stimulation (Hz)

Opioid peptides

Opioid receptors

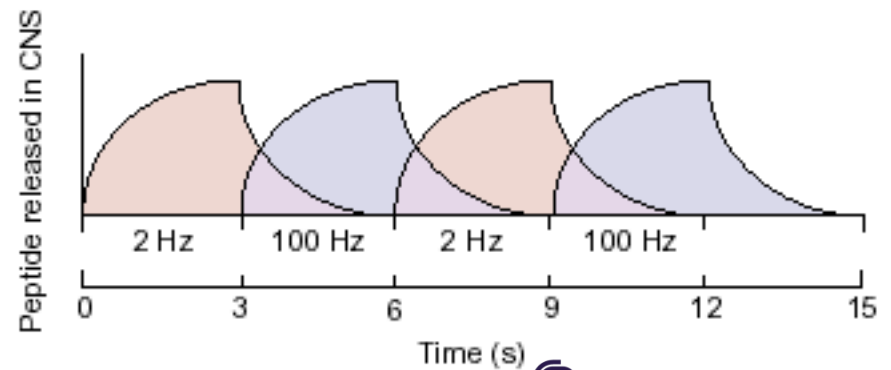
Interaction

Physiological effects



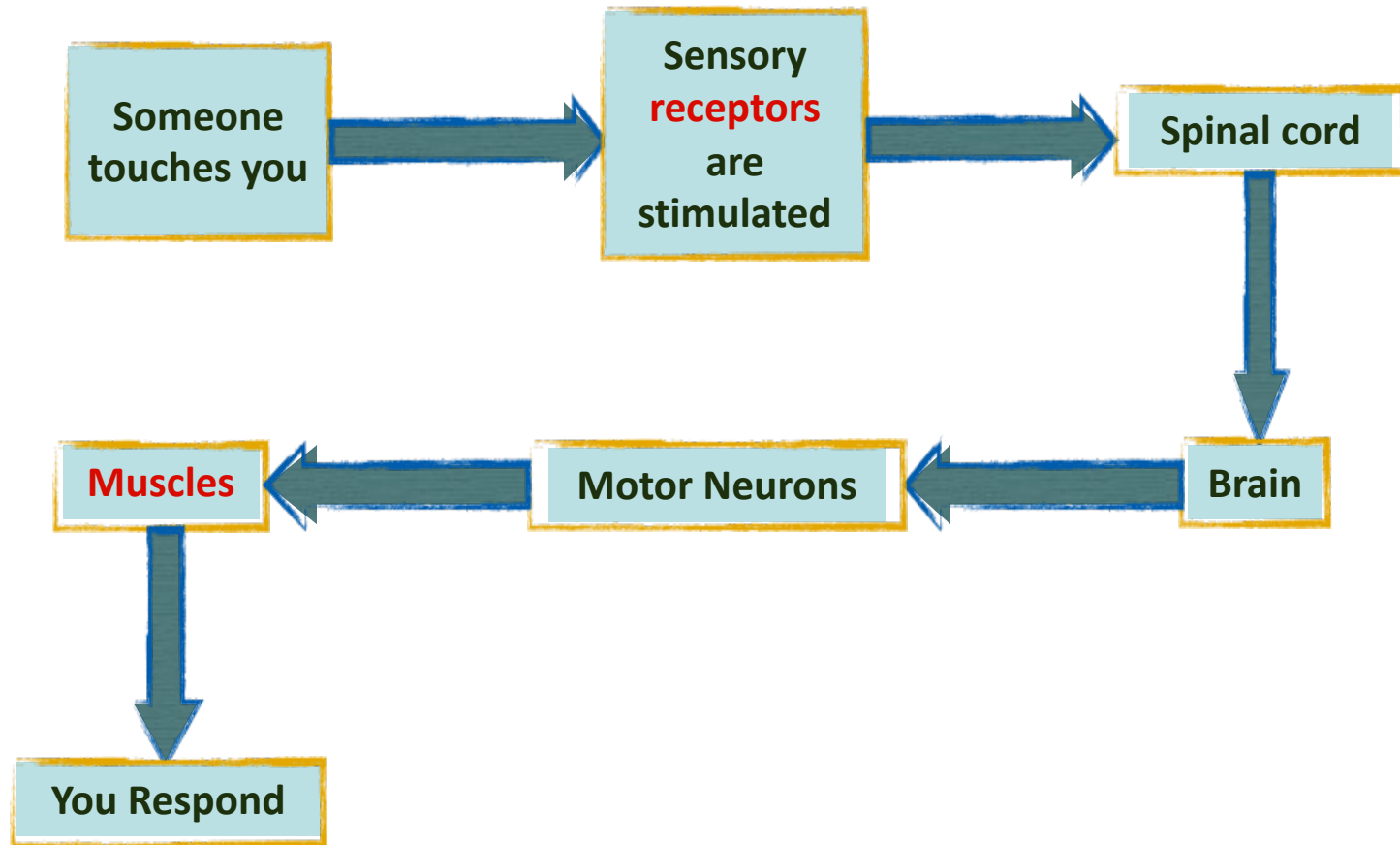
(b)

Enk Dyn Enk + Dyn



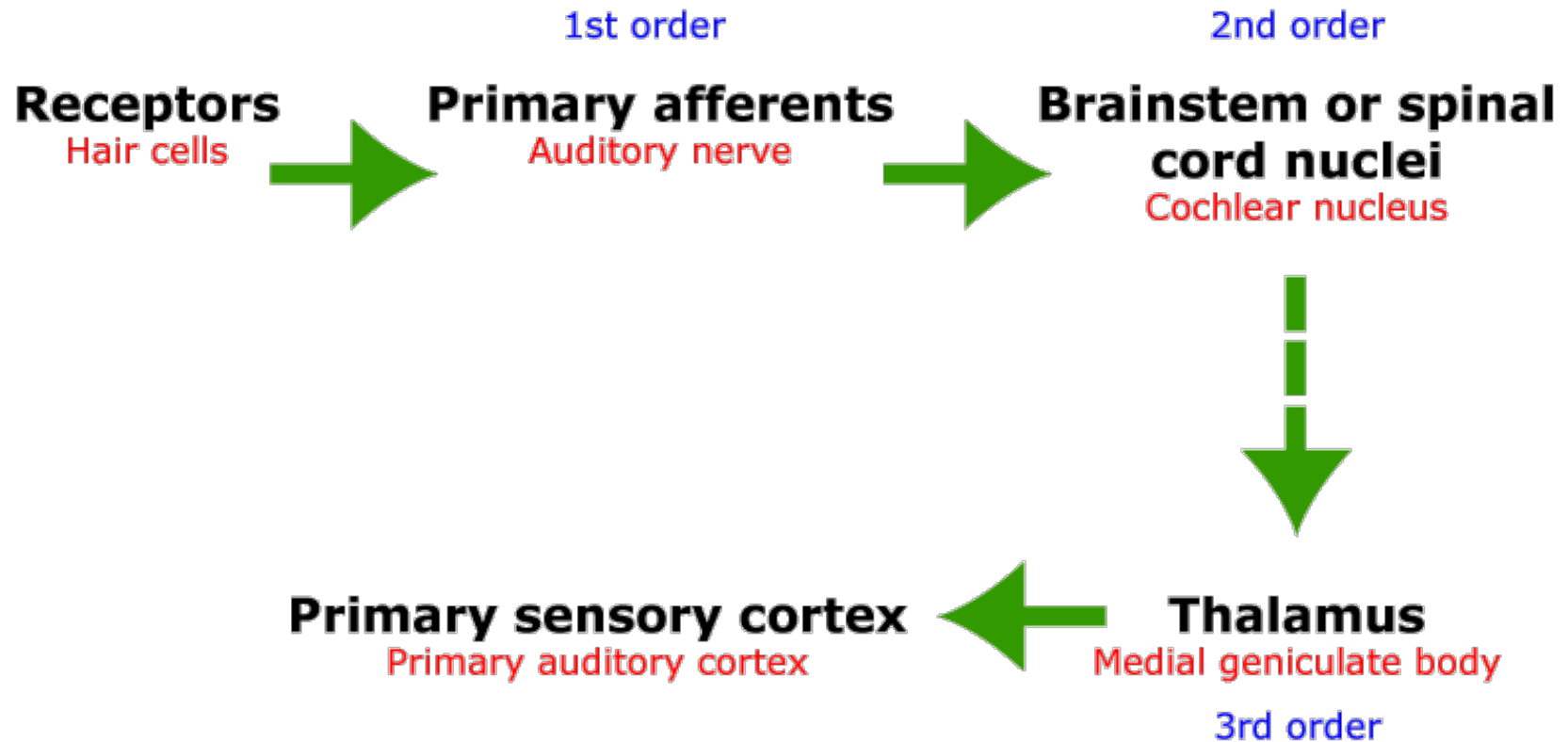
# Relaying an impulse

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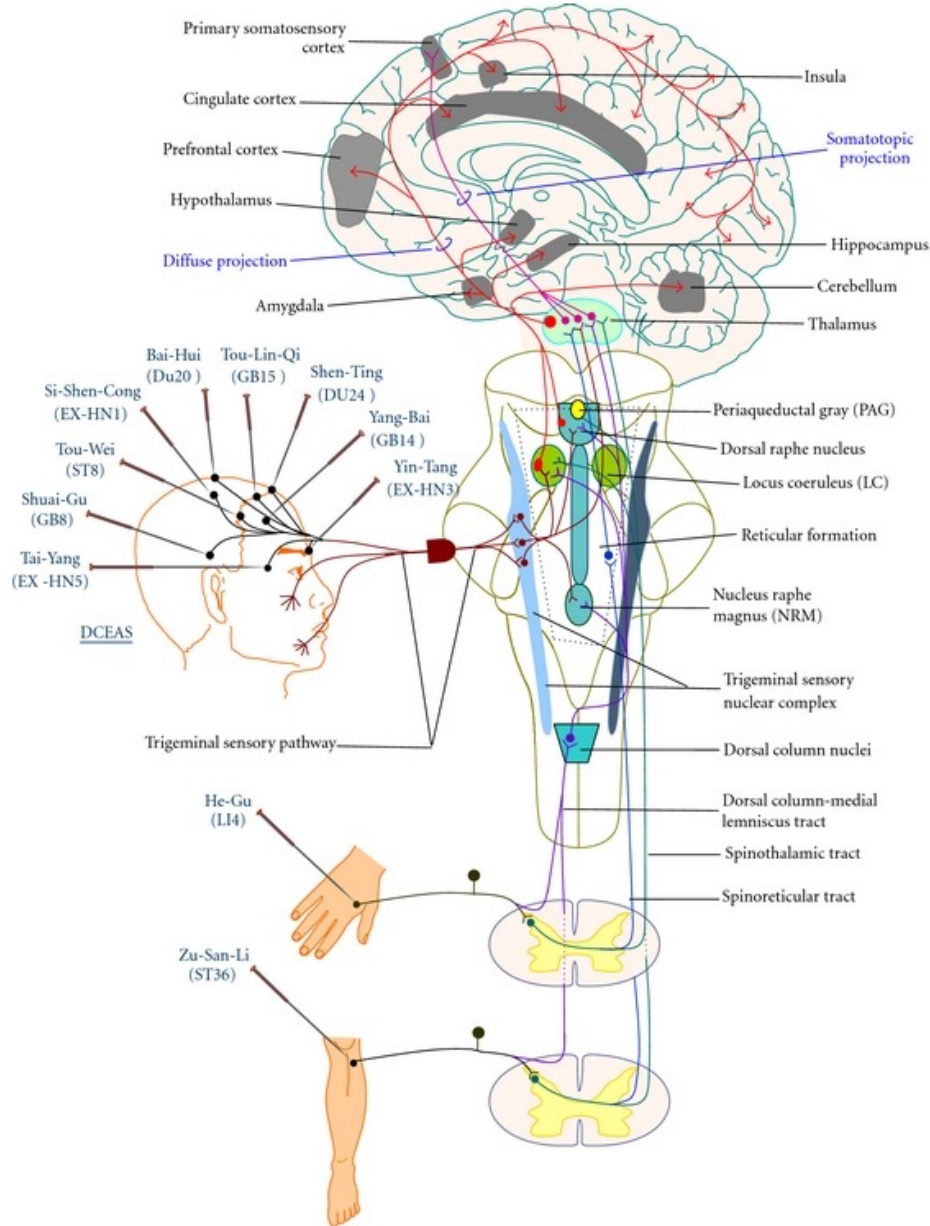


# Relaying an impulse

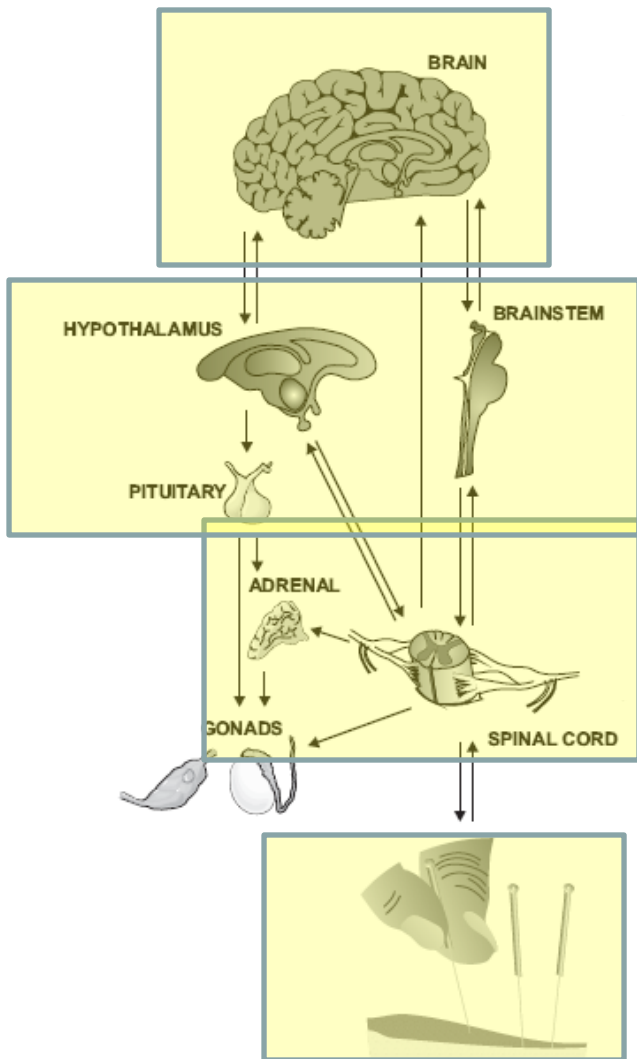
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# Neurofisiologia dell'agopuntura



# Neurofisiologia dell'agopuntura



## **CENTRAL NERVOUS SYSTEM LEVEL**

Possible effects on higher brain functions (mood, depression, anxiety). Feedback/descending regulation of pain, autonomic activity and hormonal milieu.

## **CENTRAL NERVOUS SYSTEM LEVEL**

Action on autonomic activity and pain descending control system. Control of sympatho-adrenal and hypothalamus-pituitaryadrenal /gonadal axis.

Mediators: Endorphins, ACTH, MSH, LH, FSH, etc., Neurotransmitters (5-HT, NE), Neuropeptides (Oxitocyn, Vasopressin, PACAP, etc.), Growth Factors. Cannabinoids.

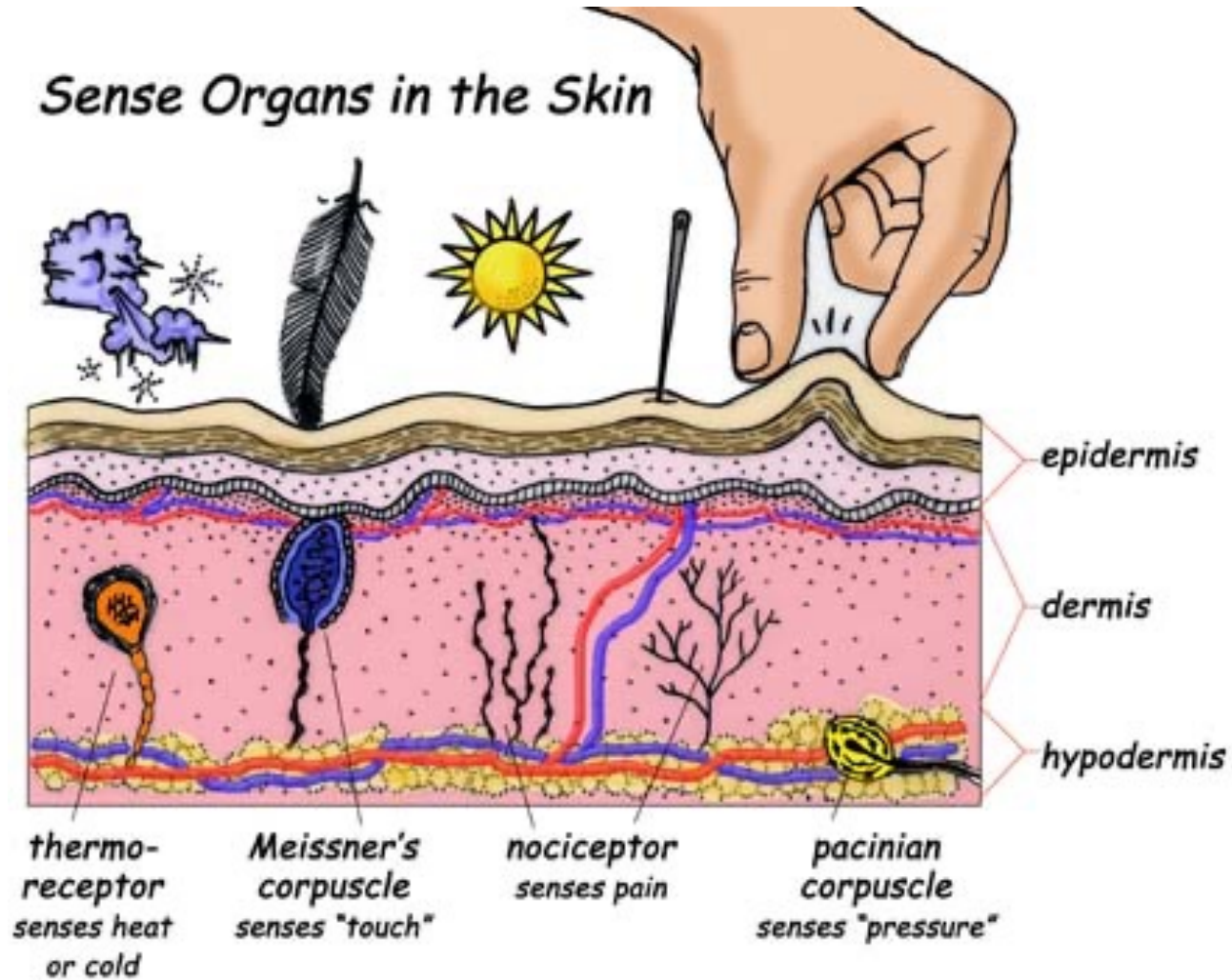
## **SPINAL / SEGMENTAL LEVEL**

Reflexive modulation of visceral organ function mediated by autonomic nervous system.

## **LOCAL LEVEL**

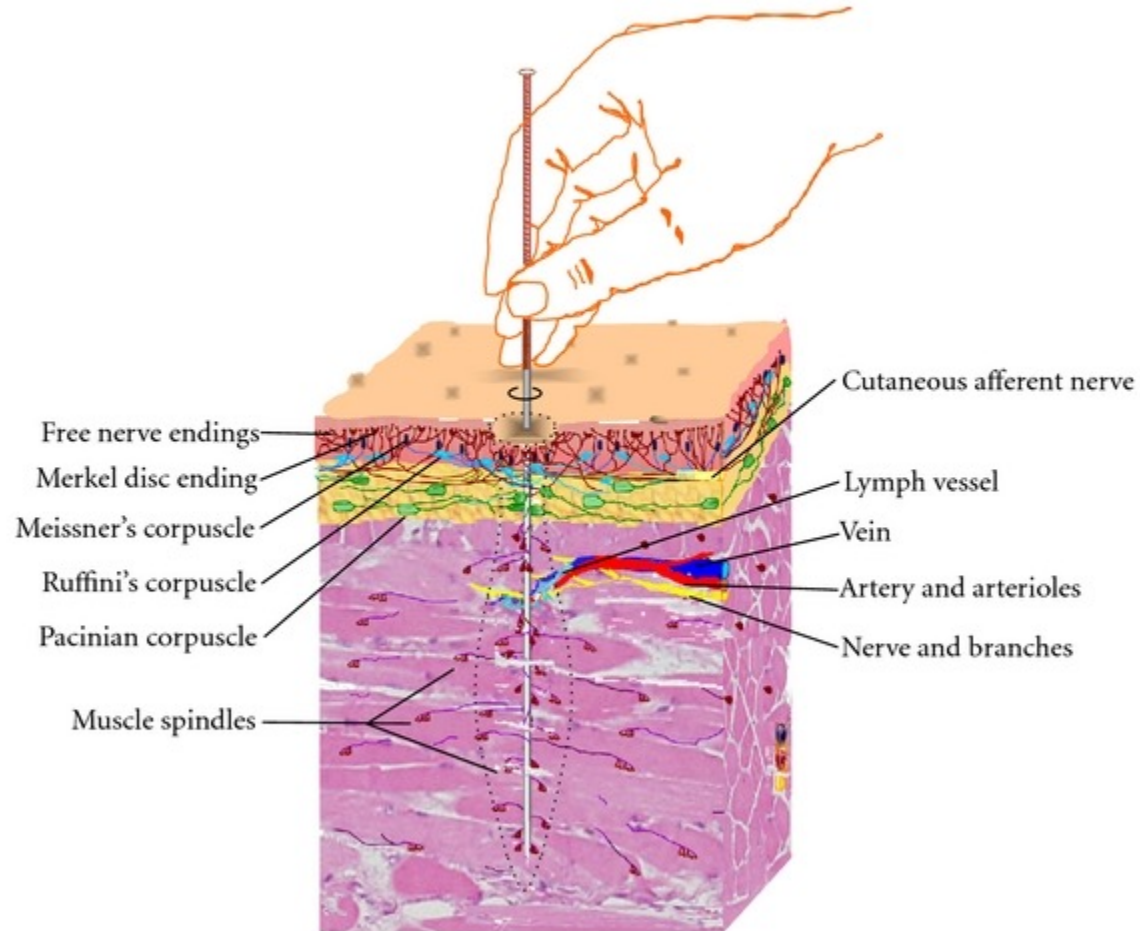
Afferent nerve activation. Local reaction mediated by: Neuropeptides, Prostaglandins, histamin Growth Factors (NGF), Adenosin. Cannabinoids.

# Somatosensory system: Detection of stimuli

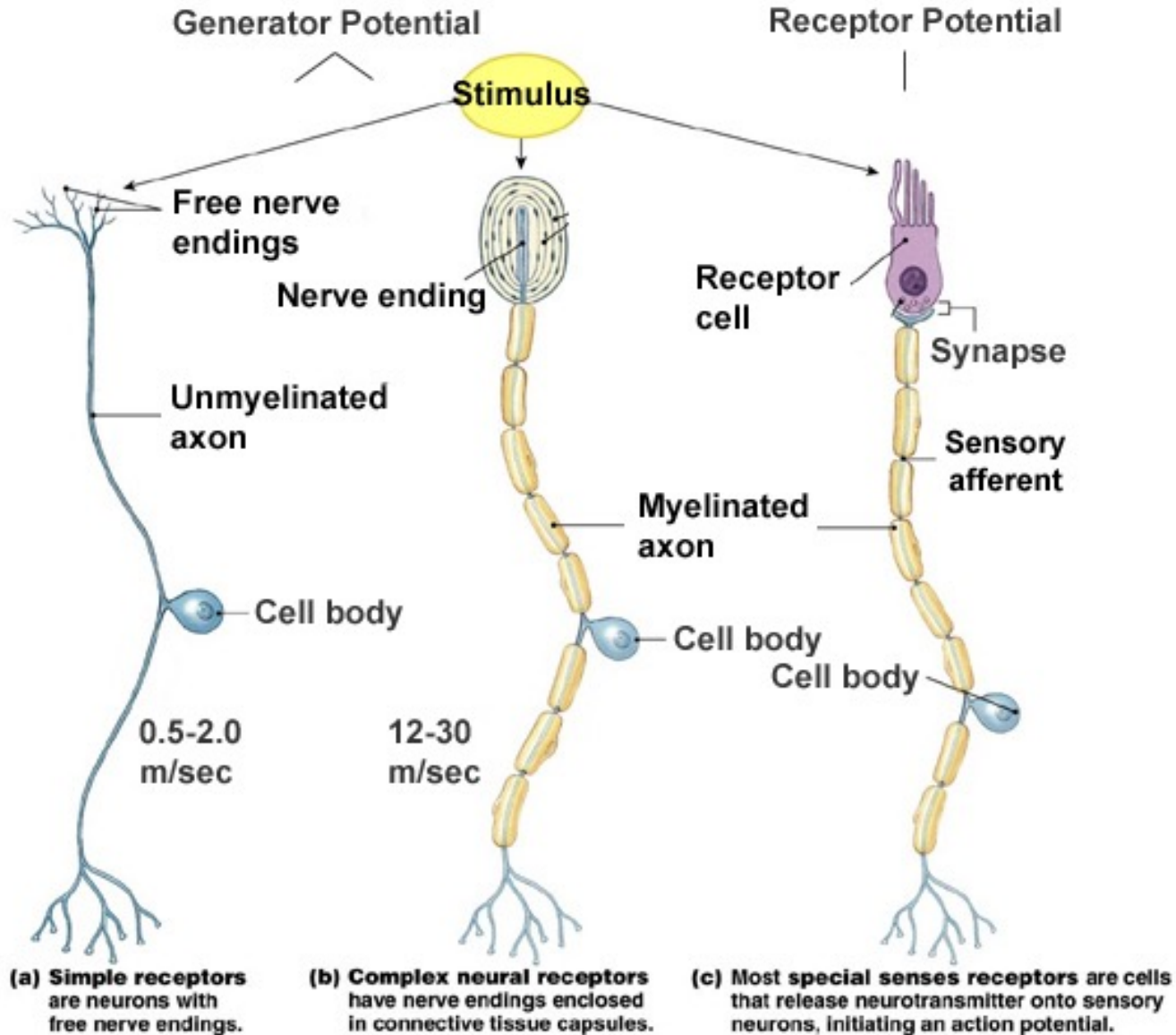




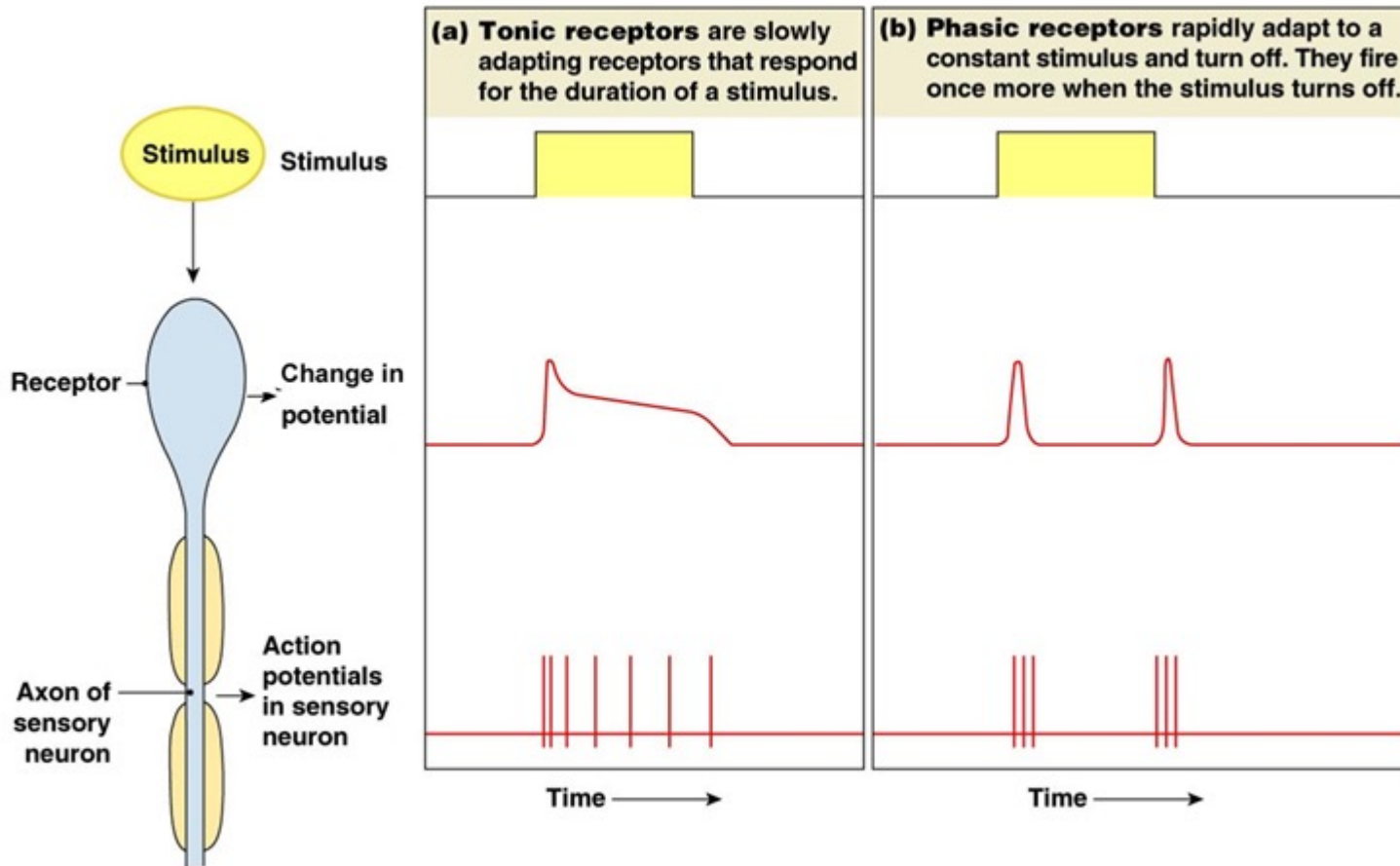
# Needle insertion site



# Receptors



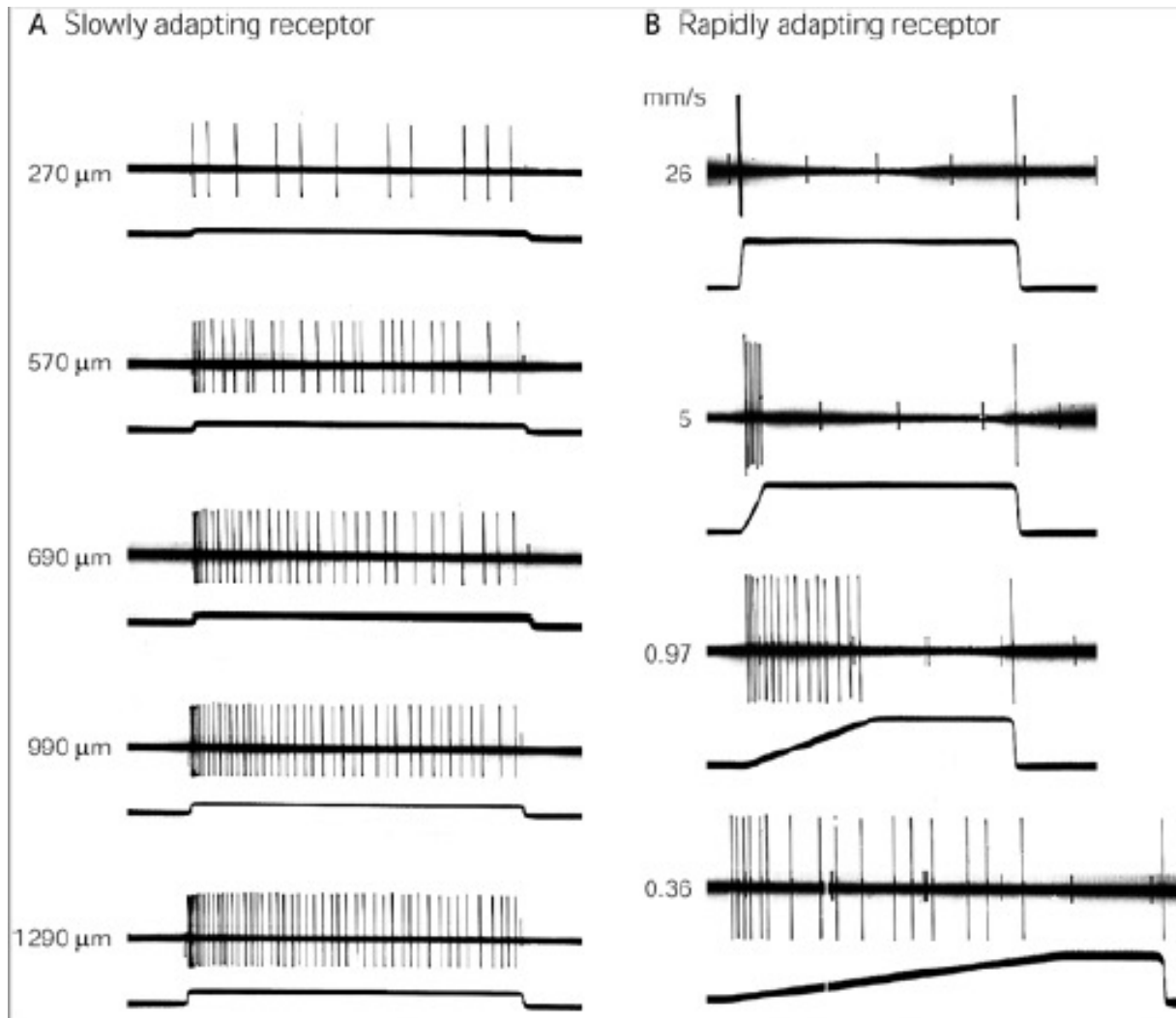
# Characteristic of receptors



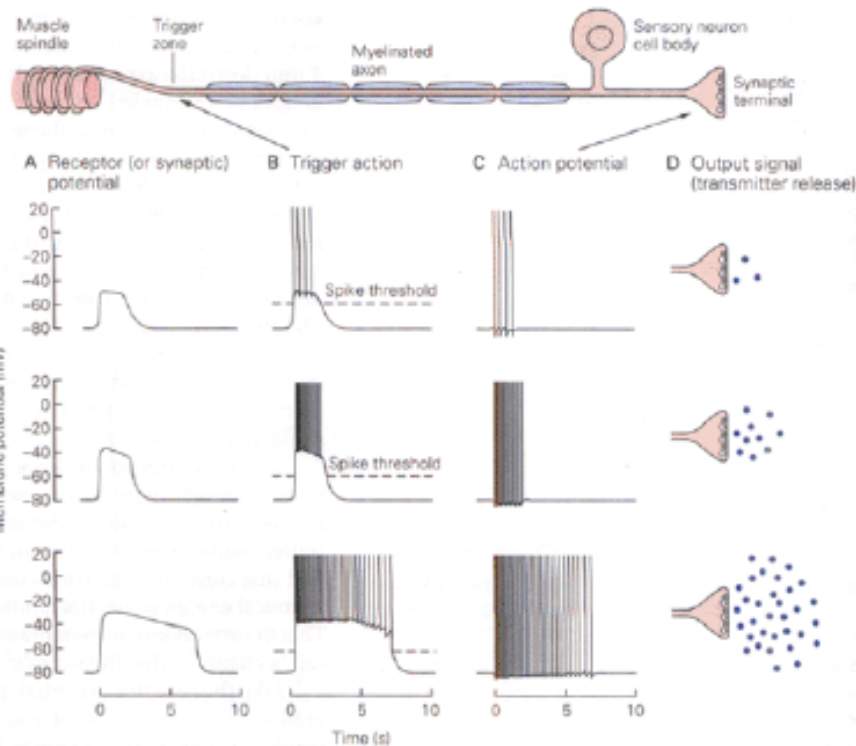
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Fig. 10-8

# Characteristic of receptors



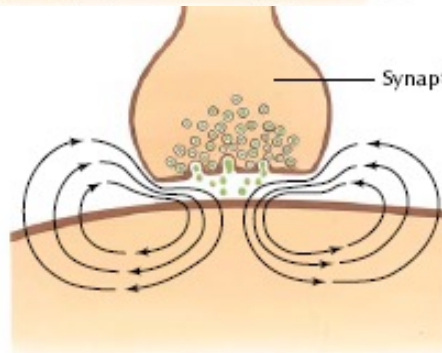
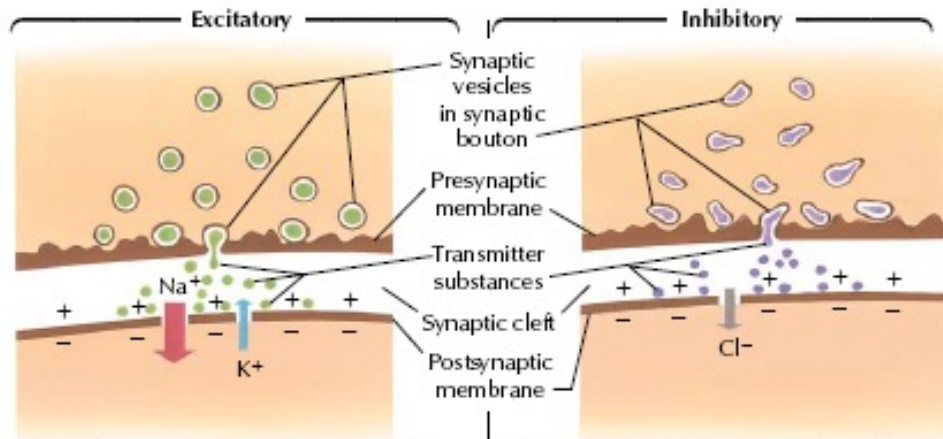
# Neuron Behavior



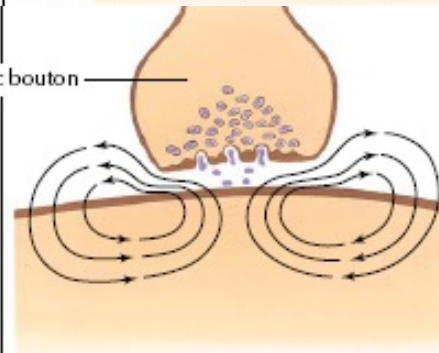
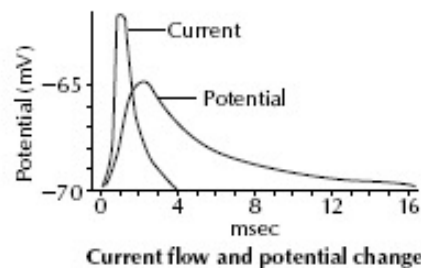
- The input signal (receptor or synaptic potential) varies in amplitude and duration
- The trigger zone integrates the input signals and decides if the action potential is generated

- Every action potential has the same waveform and travels over the axon. The info can be represented only by the time and frequency of spikes

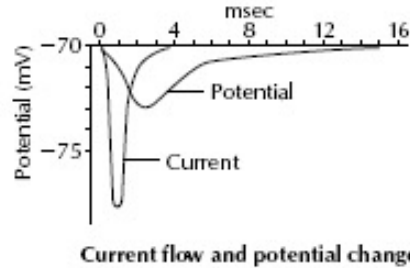
# Types of synaptic transmission



Resultant net ionic current flow is in a direction that tends to depolarize postsynaptic cell. If depolarization reaches firing threshold, an impulse is generated in postsynaptic cell

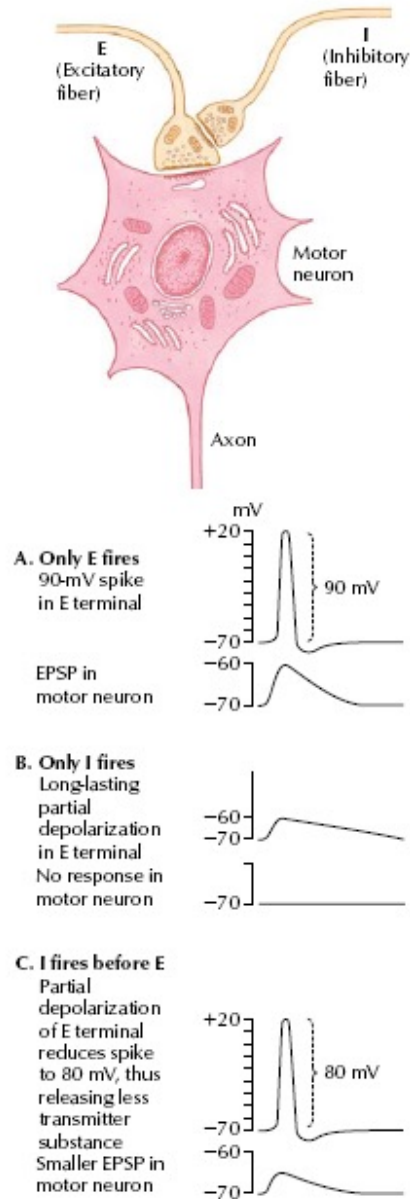


Resultant ionic current flow is in direction that tends to hyperpolarize postsynaptic cell. This makes depolarization by excitatory synapses more difficult—more depolarization is required to reach threshold

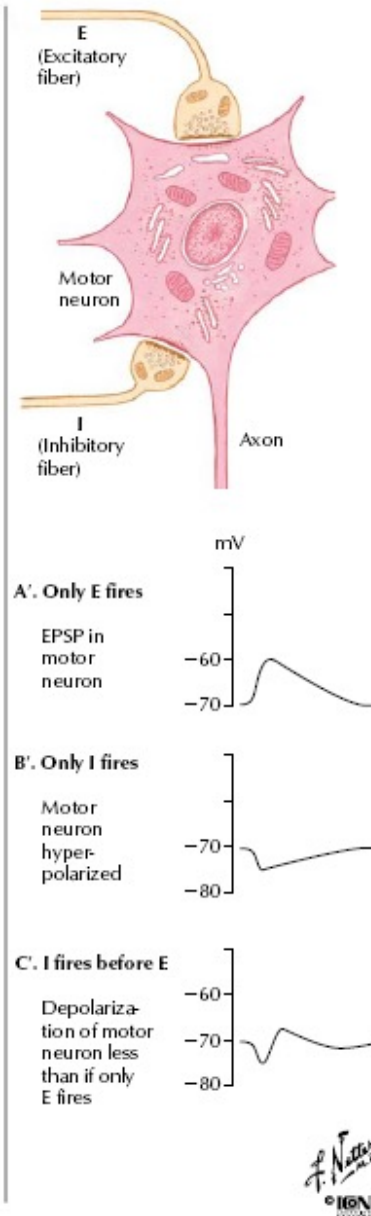


# Inhibitory mechanisms

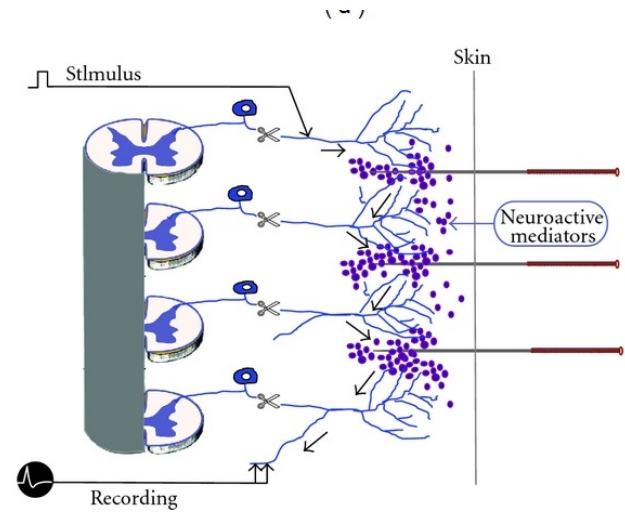
## Pre-synaptic Inhibition



## Post-synaptic Inhibition



# Needle insertion site



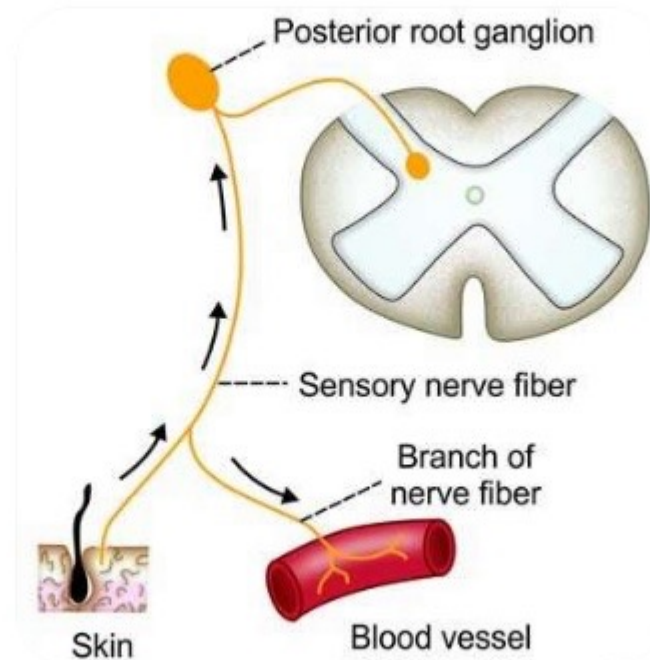
(b)



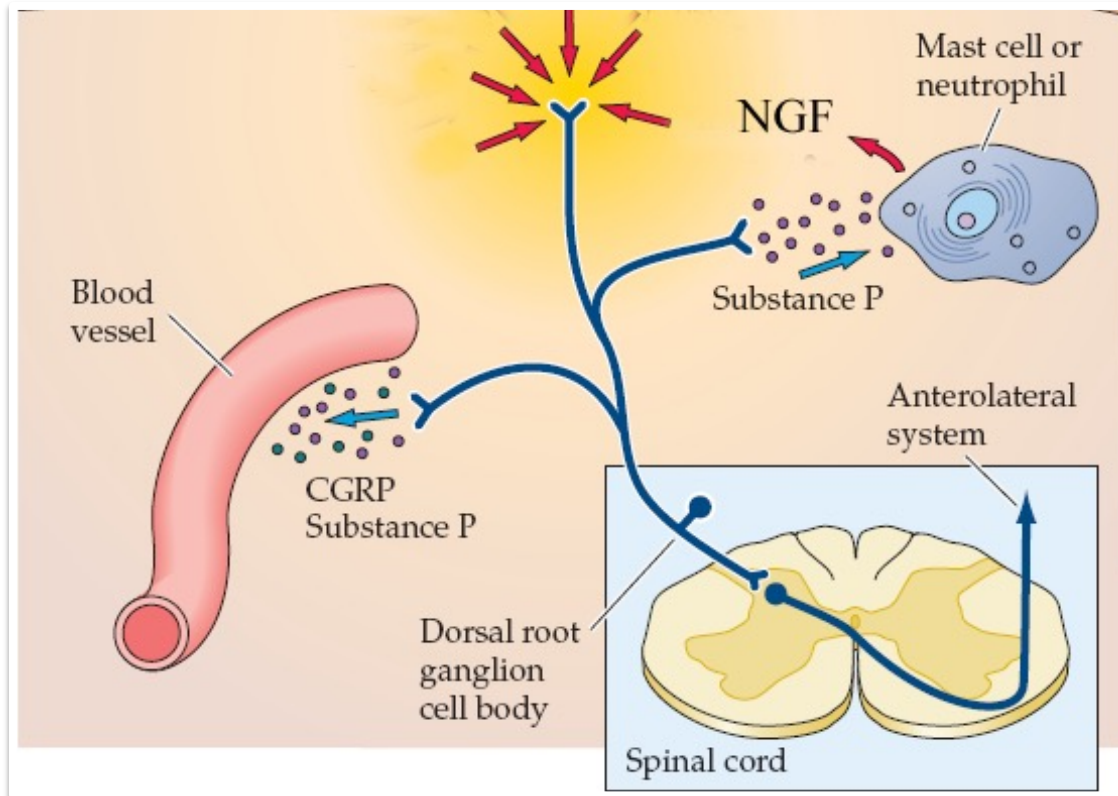
# Needle insertion site

## Axon Reflex

A response in which impulses initiated in sensory nerves are relayed antidromically down other branches of the sensory nerve fibers



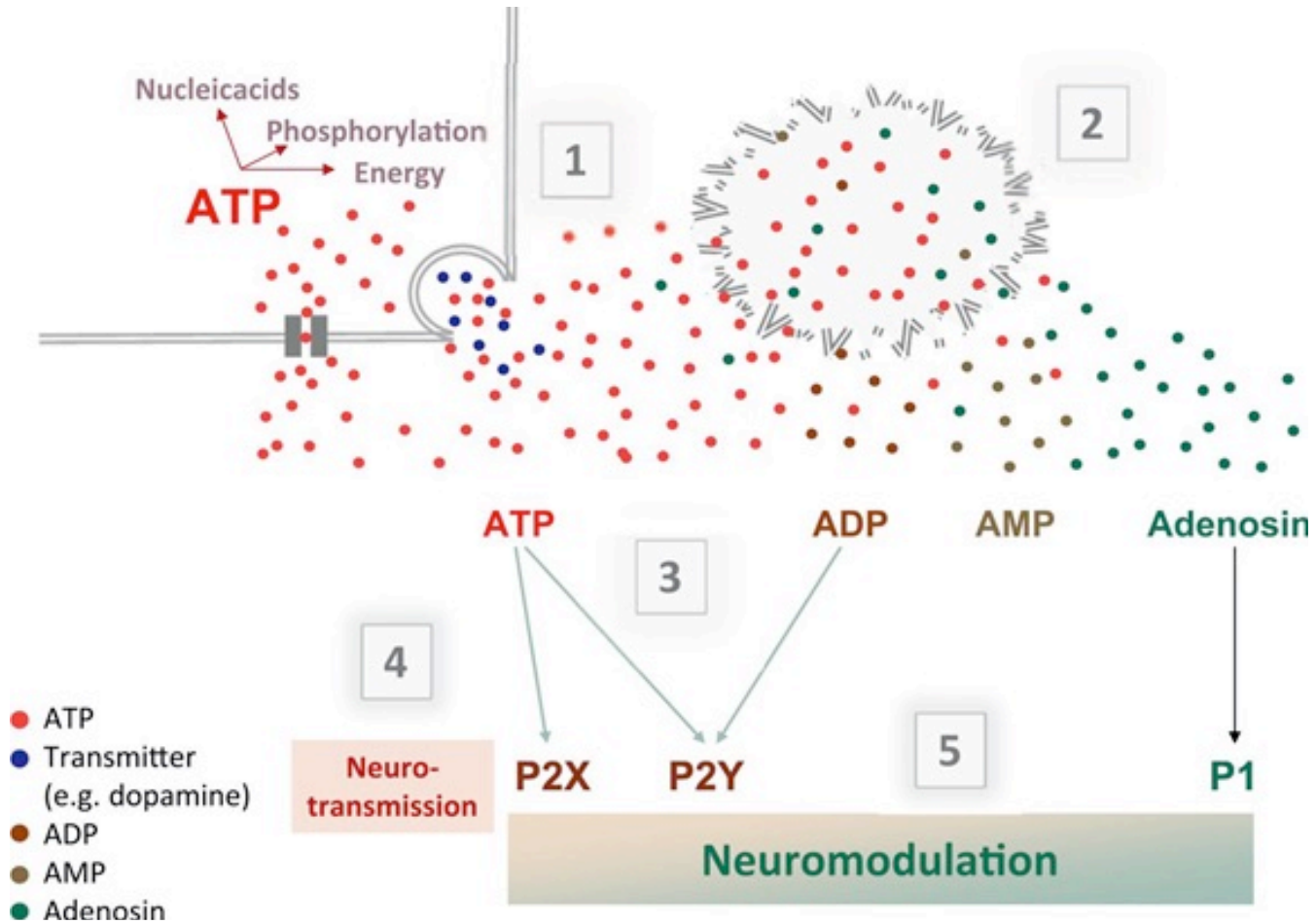
# Needle insertion site



Axon and dorsal root reflexes → local vasodilatation by release of neurotransmitters (CGRP, SP, VIP and NGF) → increased nutritional blood flow

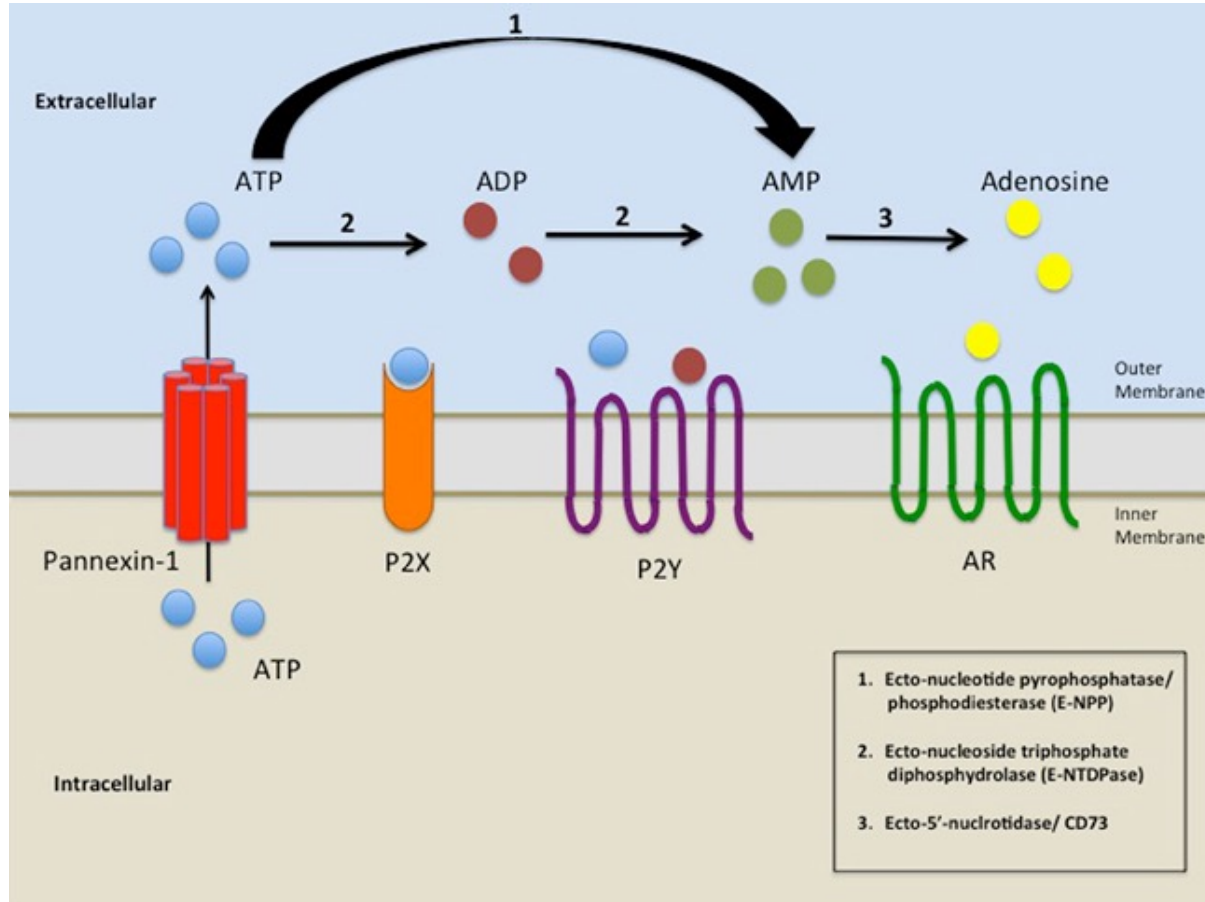
# Needle insertion site

## The neuronal purinergic system

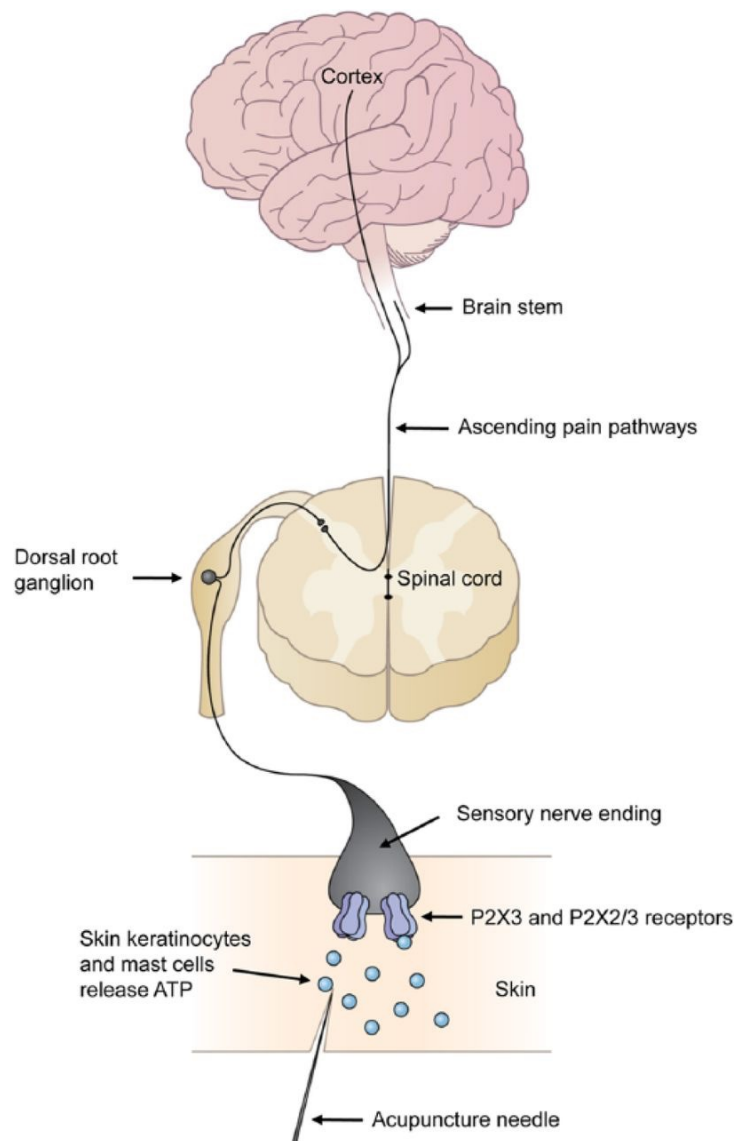


# Needle insertion site

## The neuronal purinergic system



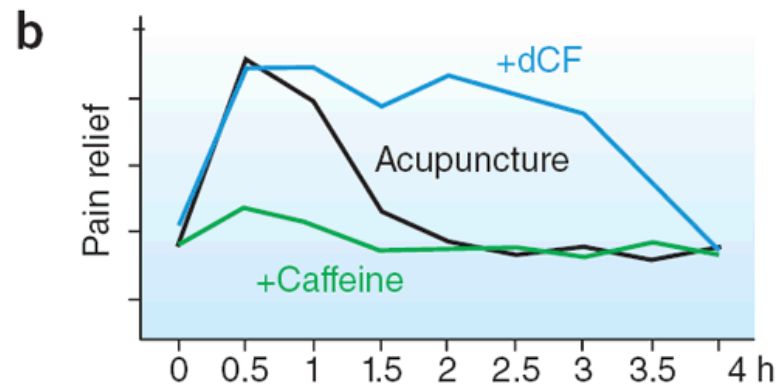
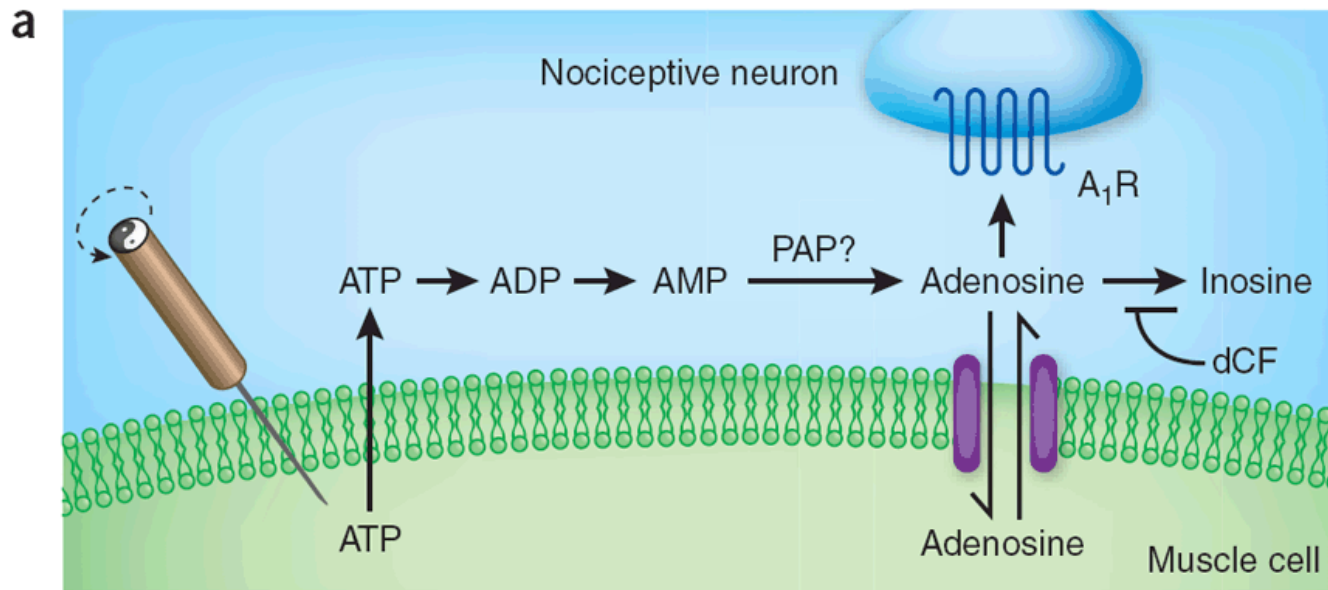
# Needle insertion site



Insertion and twisting of the acupuncture needles releases **ATP** by mechanical stimulation of **keratinocytes**, the major cell type of the skin and from subcutaneous **mast cells**, without a direct damage to the respective cell membranes.

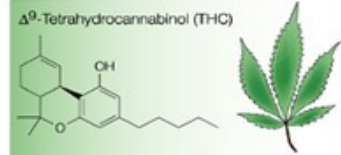
Yong Tang et al. Neuroscientist 2016;22:563-578

# Needle insertion site

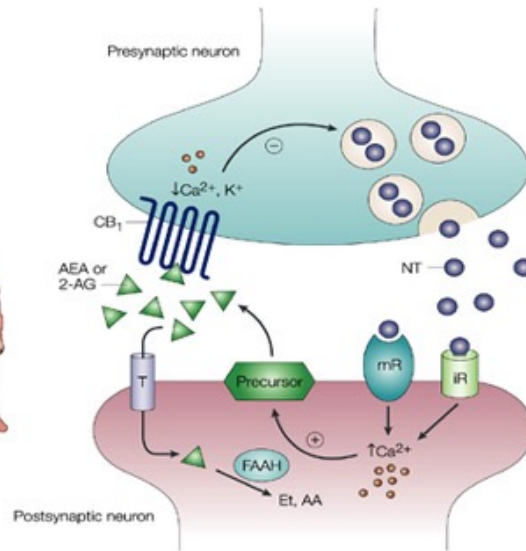
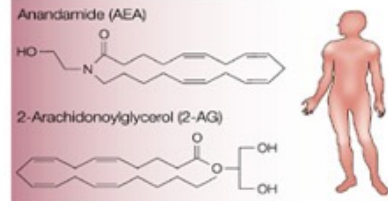


# Ricerca scientifica sull'agopuntura

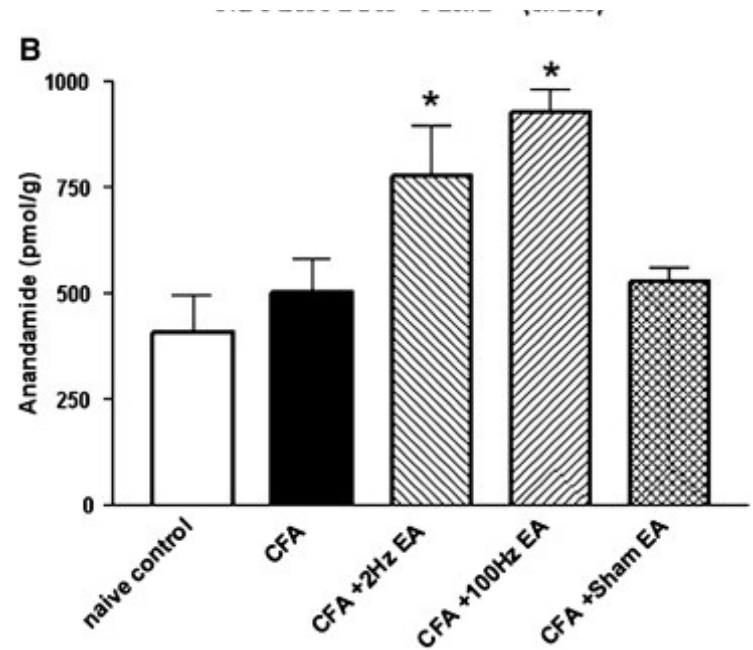
## Plant-derived cannabinoid



## Endogenous cannabinoids

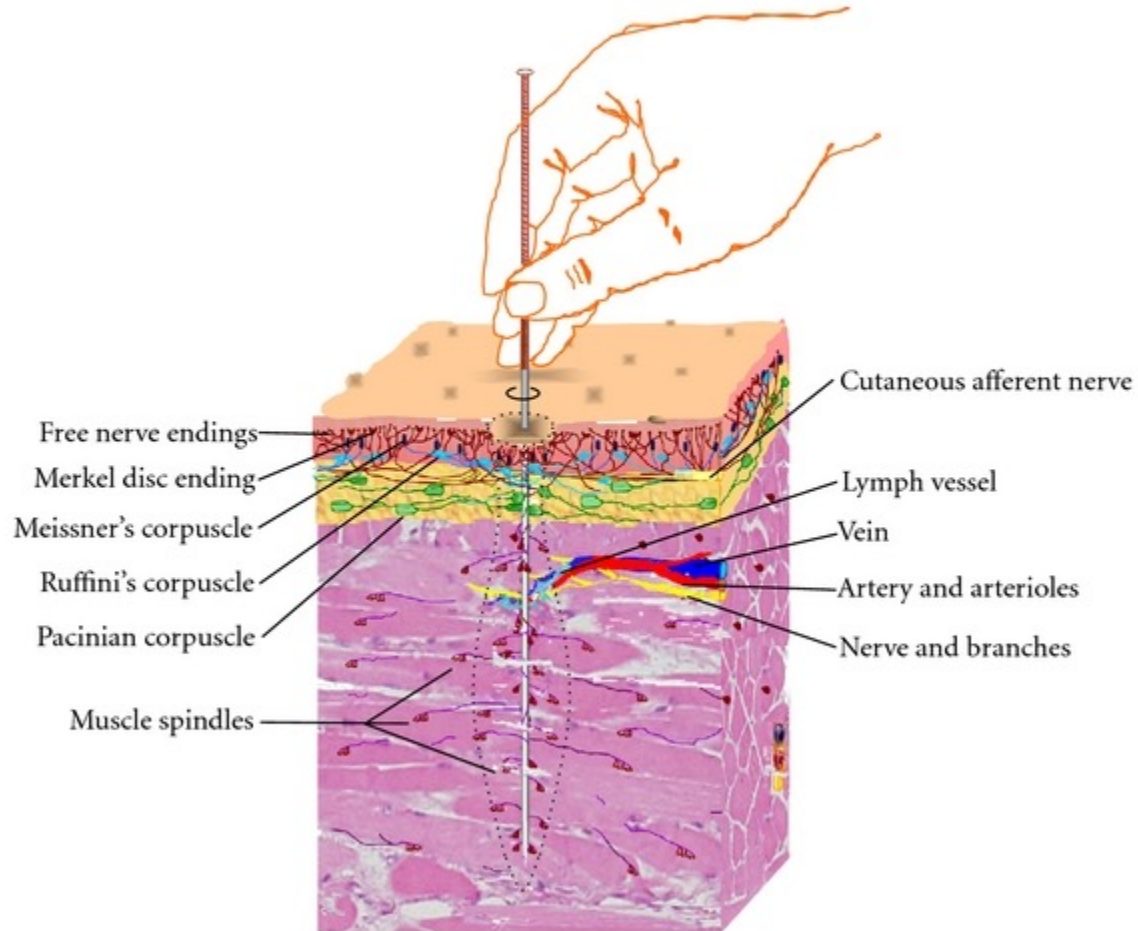


Nature Reviews | Cancer



# Somatosensory system: Detection of stimuli

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# Sensory stimulation by acupuncture

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- Dequi “sensations” are close to deep muscle pain.
- Sign of activation of A-delta and C fibers.
- Such fibers innervate low and high threshold mechanoreceptors (ergoreceptors) normally activated by strong muscle contraction as well as polymodal receptors.
- Therapeutic effect of acupuncture can also be noted during muscle exercise.

# Somatosensory system: Detection of stimuli

TABLE 2: Classification of NAUs based on a predominance of somatosensory receptors.

Type	Definition and characteristics	Related acupoints
Muscle-spindle-rich NAUs	When an acupuncture needle is inserted, a large portion of the inserted needle body is surrounded by muscle fibers. Muscle spindles are the major neural components in this type of NAUs. There are about 210–2,860 muscle spindles/cm <sup>3</sup> in muscle tissues in the back of the Bladder-Meridian [225].	Nearly 60% acupoints located on thick muscle areas contain this type of NAUs, for example, Zu-San-Li (ST36), He-Gu (LI4), and Huan-Tiao (GB30). Most acupoints can be performed with large-scale manual techniques.
Cutaneous-receptor-rich NAUs	Relatively dense and concentrated cutaneous receptors dominate in NAUs. About 100–240 encapsulated cutaneous receptors/mm <sup>2</sup> and 300 free nerve endings/mm <sup>2</sup> are distributed in the cutaneous tissues of the finger pads [226].	Most acupoints containing this type of NAUs are located on the finger pads, palms, plantar areas, and the surrounding of the lips, for example, Shao-Shang (LU11), Lao-Gong (PC12), and Ren-Zhong (GV26). Only prick and shallow needling can generally be performed on these acupoints.
Tendon-organ-rich NAUs	Tendon organs, Ruffini and Pacinian corpuscles dominate in NAUs.	Most acupoints containing this type of NAUs are located around the elbow, wrist, knee, and ankle joints, for example, Chi-Ze (LU5), Da-Ling (PC7), Du-Bi (ST35), and Jie-Xi (ST41).

# Somatosensory system: Detection of stimuli

The Major Classes of Somatic Sensory Receptors

<i>Receptor type</i>	<i>Anatomical characteristics</i>	<i>Associated axons<sup>a</sup> (and diameters)</i>	<i>Axonal conduction velocities</i>	<i>Location</i>	<i>Function</i>	<i>Rate of adaptation</i>	<i>Threshold of activation</i>
Free nerve endings	Minimally specialized nerve endings	C, A $\delta$	2–20 m/s	All skin	Pain, temperature, crude touch	Slow	High
Meissner's corpuscles	Encapsulated; between dermal papillae	A $\beta$ 6–12 $\mu$ m		Principally glabrous skin	Touch, pressure (dynamic)	Rapid	Low
Pacinian corpuscles	Encapsulated; onionlike covering	A $\beta$ 6–12 $\mu$ m		Subcutaneous tissue, interosseous membranes, viscera	Deep pressure, vibration (dynamic)	Rapid	Low
Merkel's disks	Encapsulated; associated with peptide-releasing cells	A $\beta$		All skin, hair follicles	Touch, pressure (static)	Slow	Low
Ruffini's corpuscles	Encapsulated; oriented along stretch lines	A $\beta$ 6–12 $\mu$ m		All skin	Stretching of skin	Slow	Low
Muscle spindles	Highly specialized (see Figure 8.5 and Chapter 15)	Ia and II		Muscles	Muscle length	Both slow and rapid	Low
Golgi tendon organs	Highly specialized (see Chapter 15)	Ib		Tendons	Muscle tension	Slow	Low
Joint receptors	Minimally specialized	—		Joints	Joint position	Rapid	Low

# The polymodal receptor hypothesis

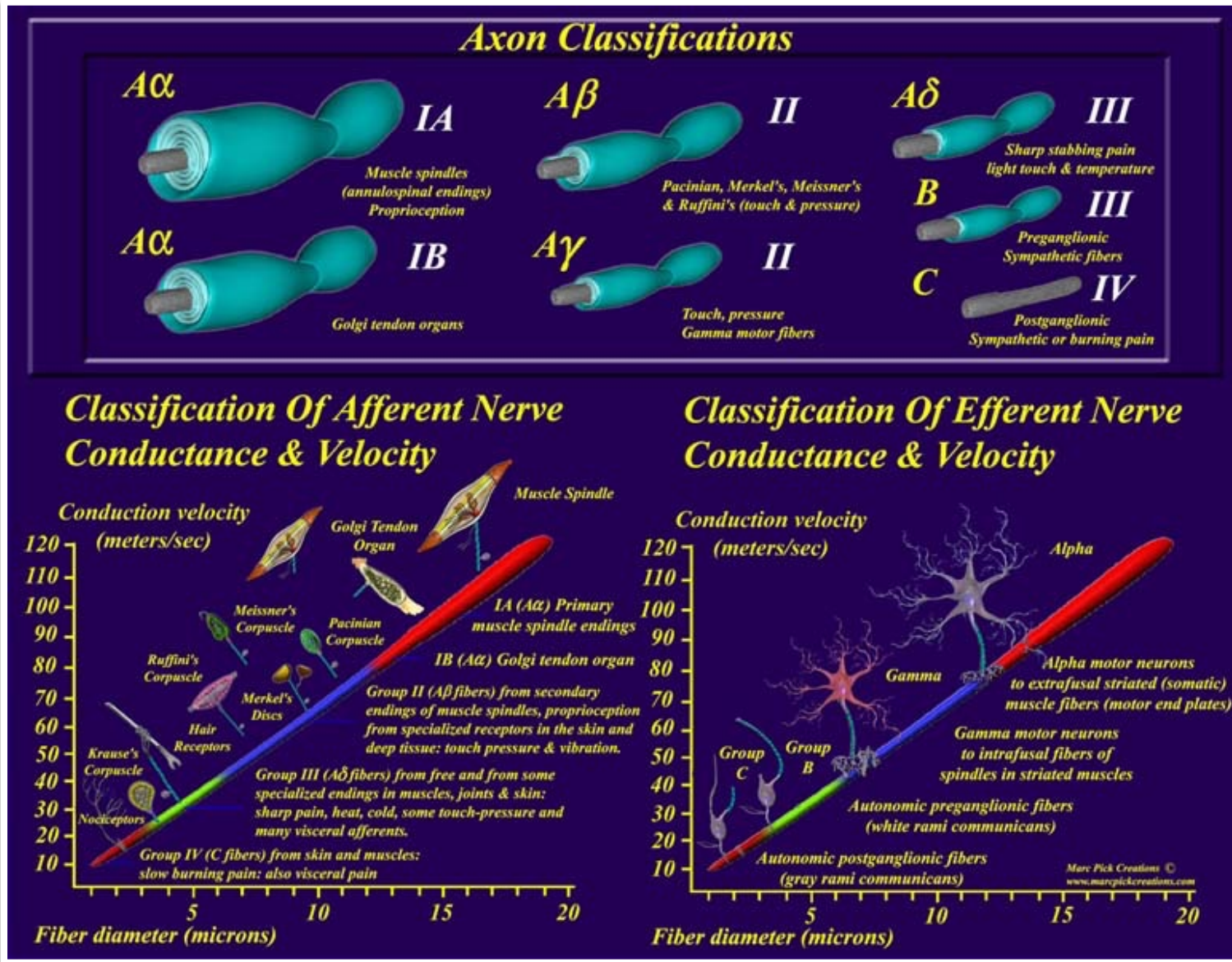
Table I

Characteristics of the polymodal-type receptors and their relations to the nature of acupuncture and moxibustion, and features of the acupuncture/trigger points

Polymodal-type receptors	Acupuncture and moxibustion	Acupuncture/trigger points
A kind of nociceptor (wide dynamic range)	basically noxious stimuli (not always painful)	
Responsive to mechanical, thermal and chemical stimuli	acupuncture (mechanical+chemical) moxibustion (thermal+chemical)	
Effector functions (neurogenic inflammation)	produce local inflammatory responses (flare and wheal)	reaction points (low impedance, palpable band)
Sensitized by various mediators (decreased pain threshold)	applied to tender region (ah-shi-points) (ah-shi-points)	close relations between the points (localized tenderness)
Deep dull pain evoked (fascia is a sensitive tissue)	acupuncture sensation (de-qi) and local twitch response are produced	easy to produce “de-qi” sensation and local twitch response
Free nerve endings (distribute to various tissues) (distribute to entire body)	stimulate various tissues (skin, fascia, muscle etc.) stimulate entire body	no specific structures (nerve bundles and vessels) (distribute to entire body)

*Int Congr Series, 1238:63; 2002*

# Stimulus propagation



# Sensory stimulation by acupuncture

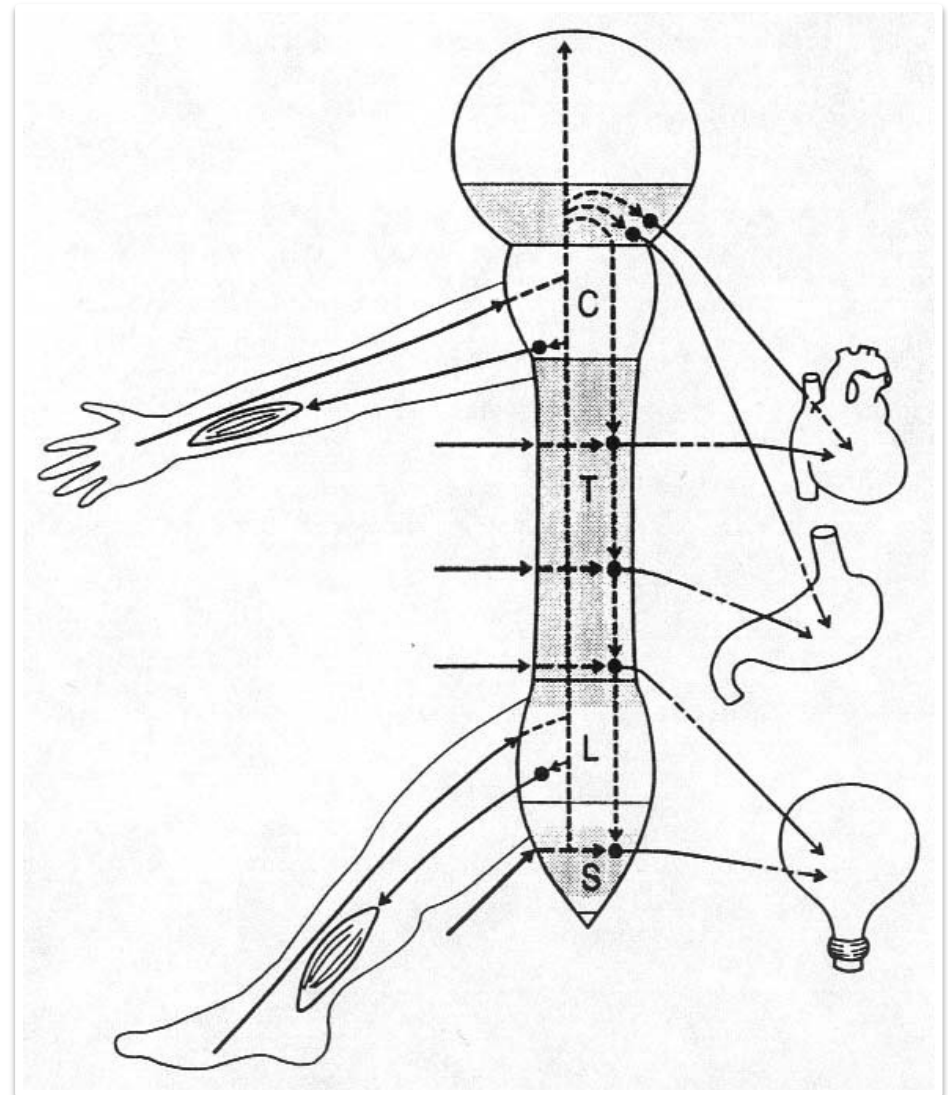
**Table 3.1 Correlation between fibre type, physiological function, and role in acupuncture analgesia and needle sensation (after J. Thompson, personal communication)**

<i>Nerve type</i>	<i>Function</i>	<i>Evidence for role in acupuncture analgesia</i>	<i>Needle sensation experienced (Wang et al., 1985)</i>
A alpha	muscle spindle	Lu, 1983	
A beta	touch, vibration	Lu, 1983; Toda and Ichioka, 1978	
A gamma	flower spray, muscle spindle		numbness
A delta	pinprick, cold; pressure; muscle ergoreceptor	Chung <i>et al.</i> , 1984; Baldry, 1993; Bowsher, 1987; Andersson and Lundberg, 1995	distension, heaviness
C	deep pain, itch	Liu <i>et al.</i> , 1986	soreness

# Spinal/segmental effects

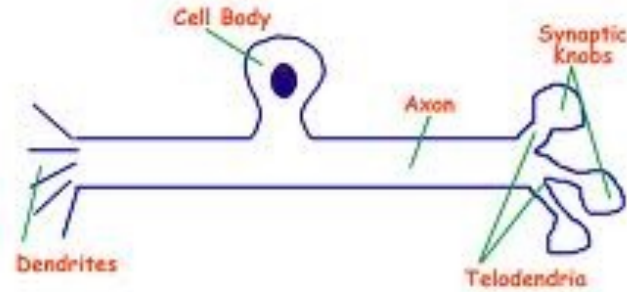
Pain Modulation

Somato-Visceral reflexes

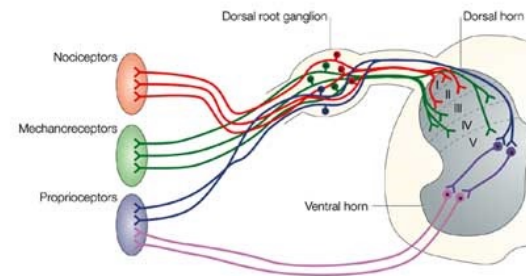
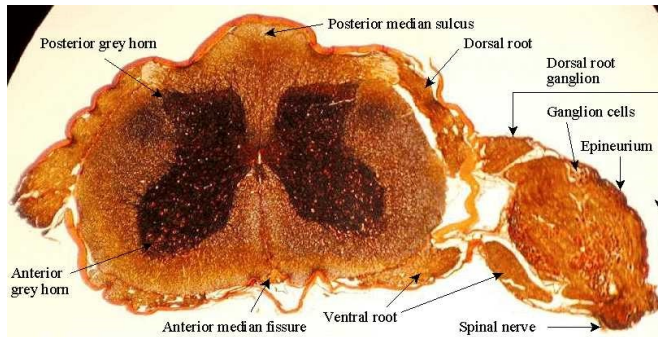


# Somatosensory system: Detection of stimuli

## Pseudounipolar Neuron



## Functions to carry somatic sensory information

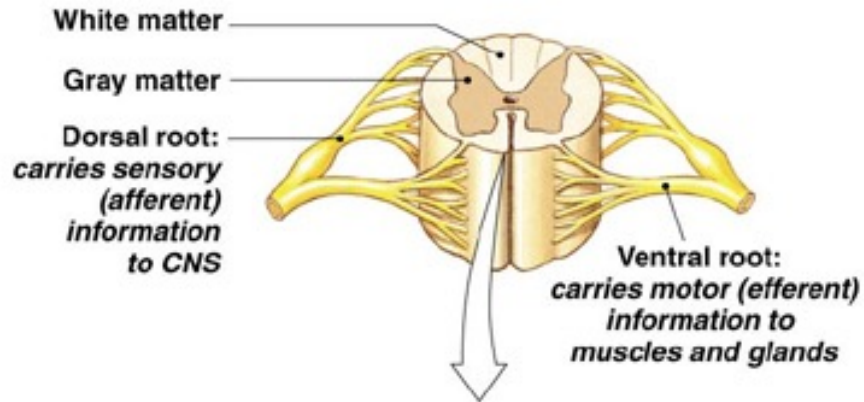


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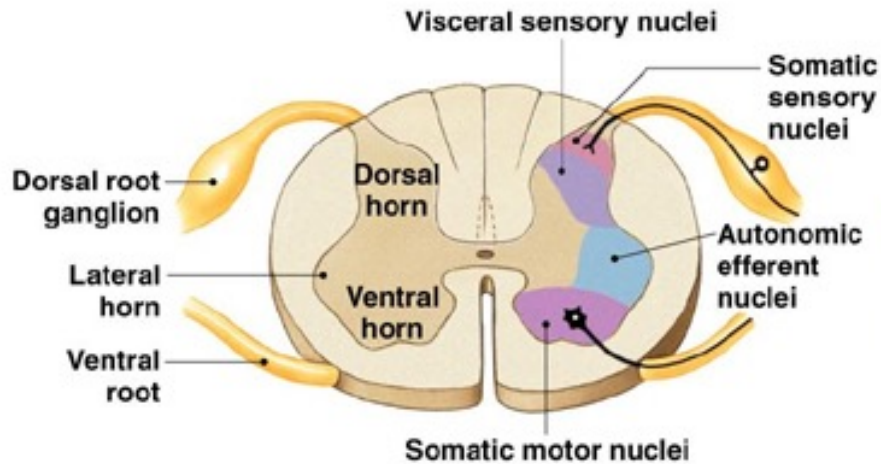


# Spinal cord

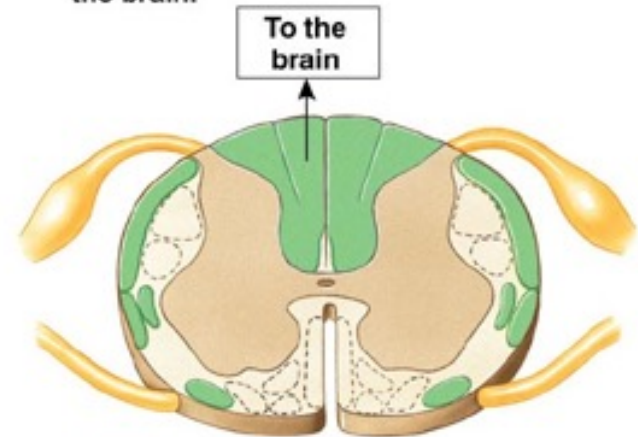
(a) One segment of spinal cord, ventral view, showing its pair of nerves



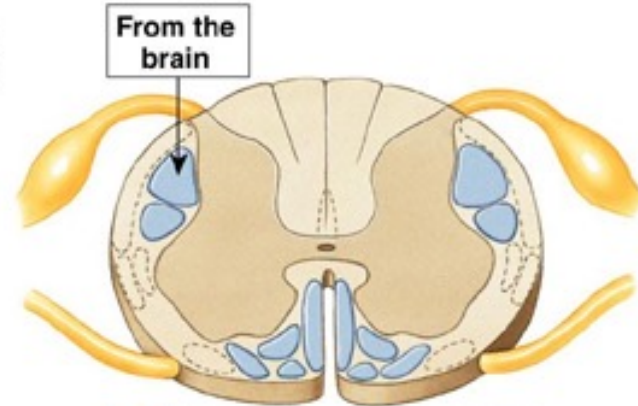
(b) Gray matter consists of sensory and motor nuclei



(c) White matter in the spinal cord consists of axons carrying information to and from the brain.

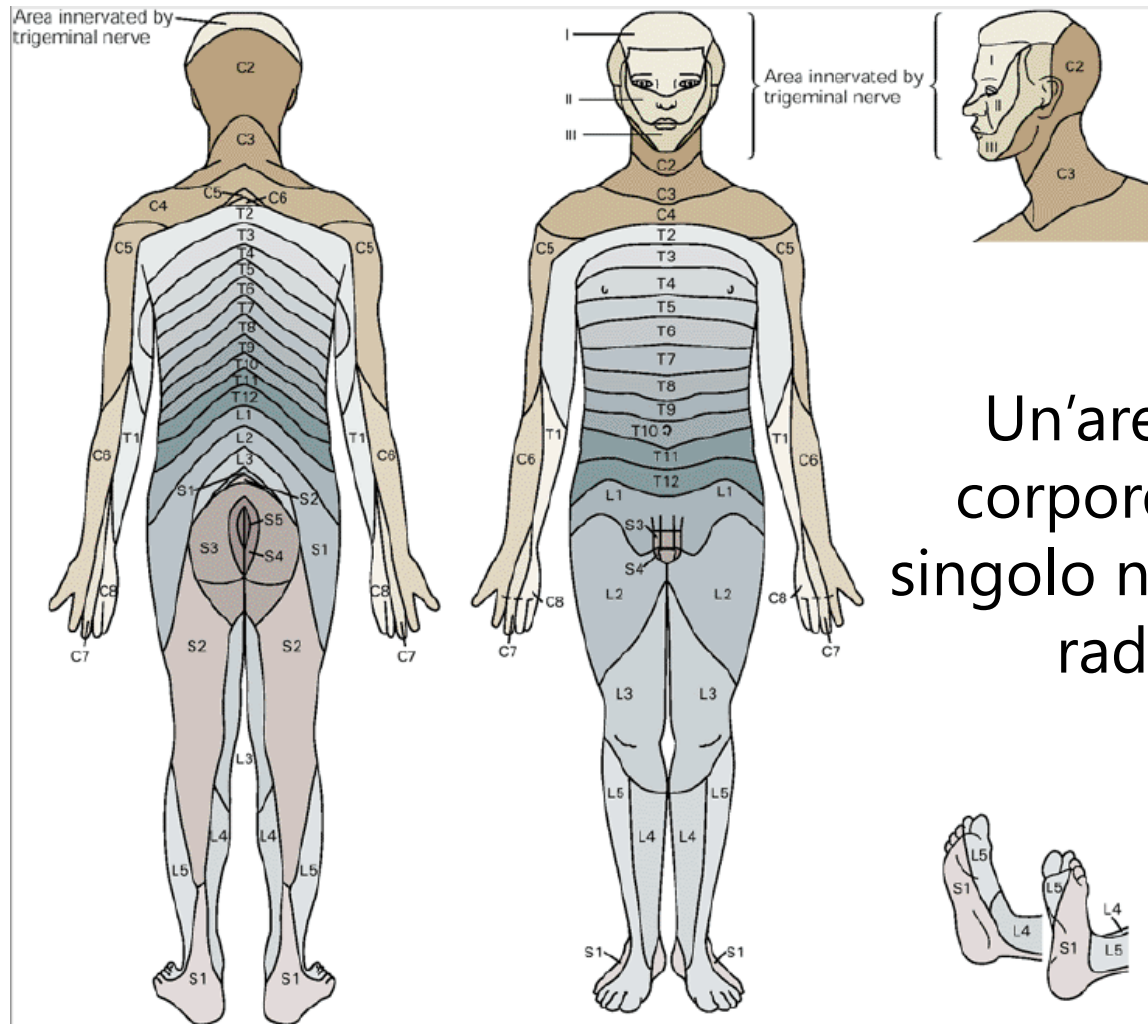


Ascending tracts carry sensory information to the brain.



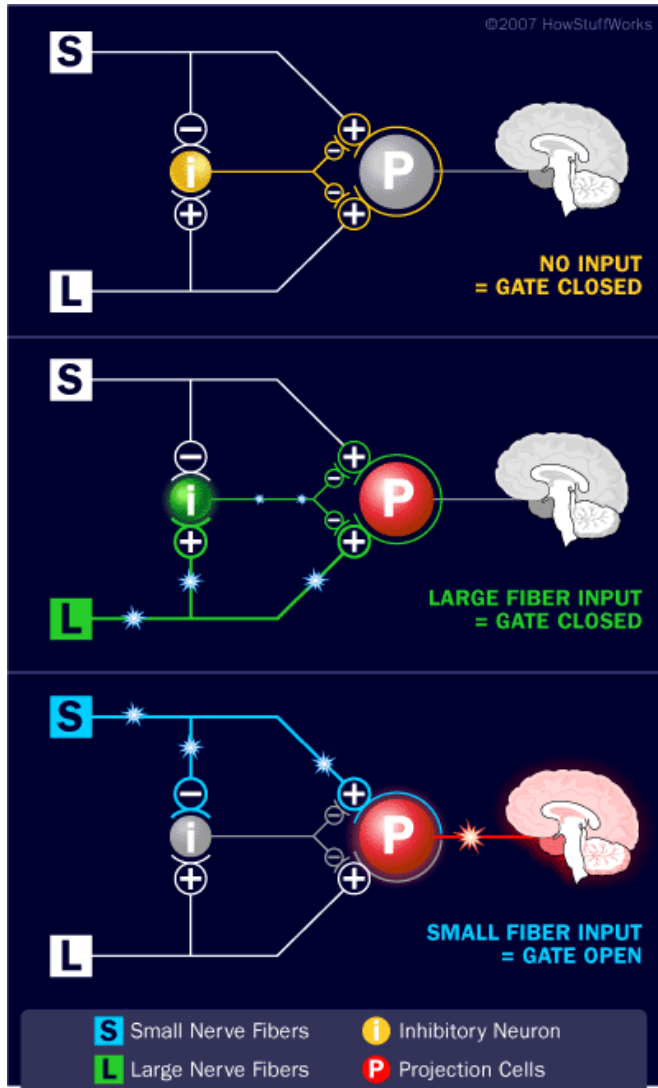
Descending tracts carry commands to motor neurons.

# Sensory Dermatomes



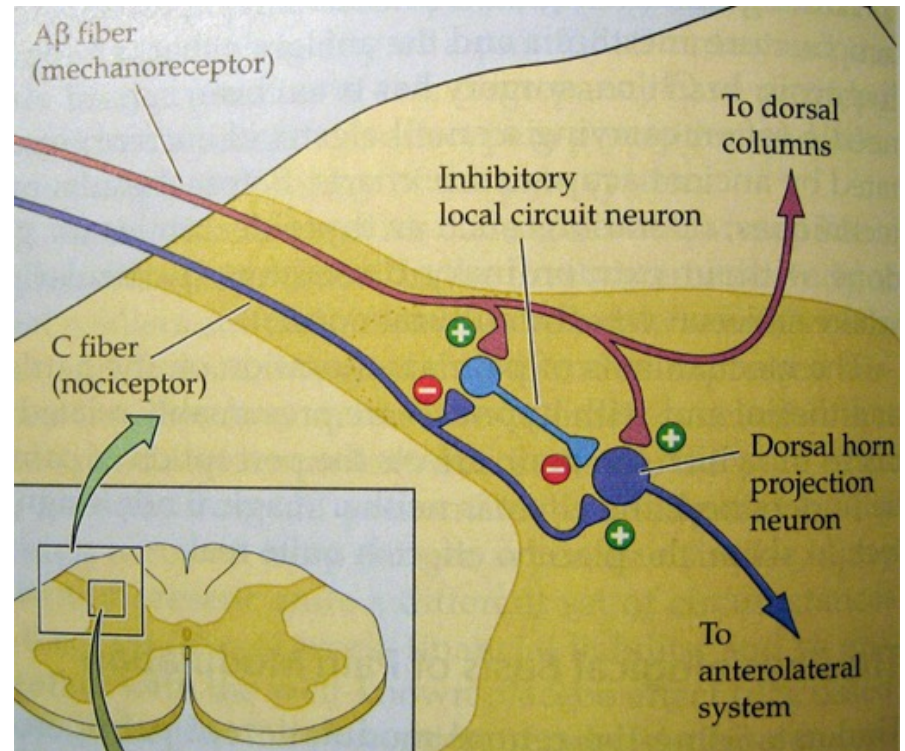
Un'area della superficie corporea innervata da un singolo nervo spinale (singola radice posteriore).

# Modulation of pain transmission

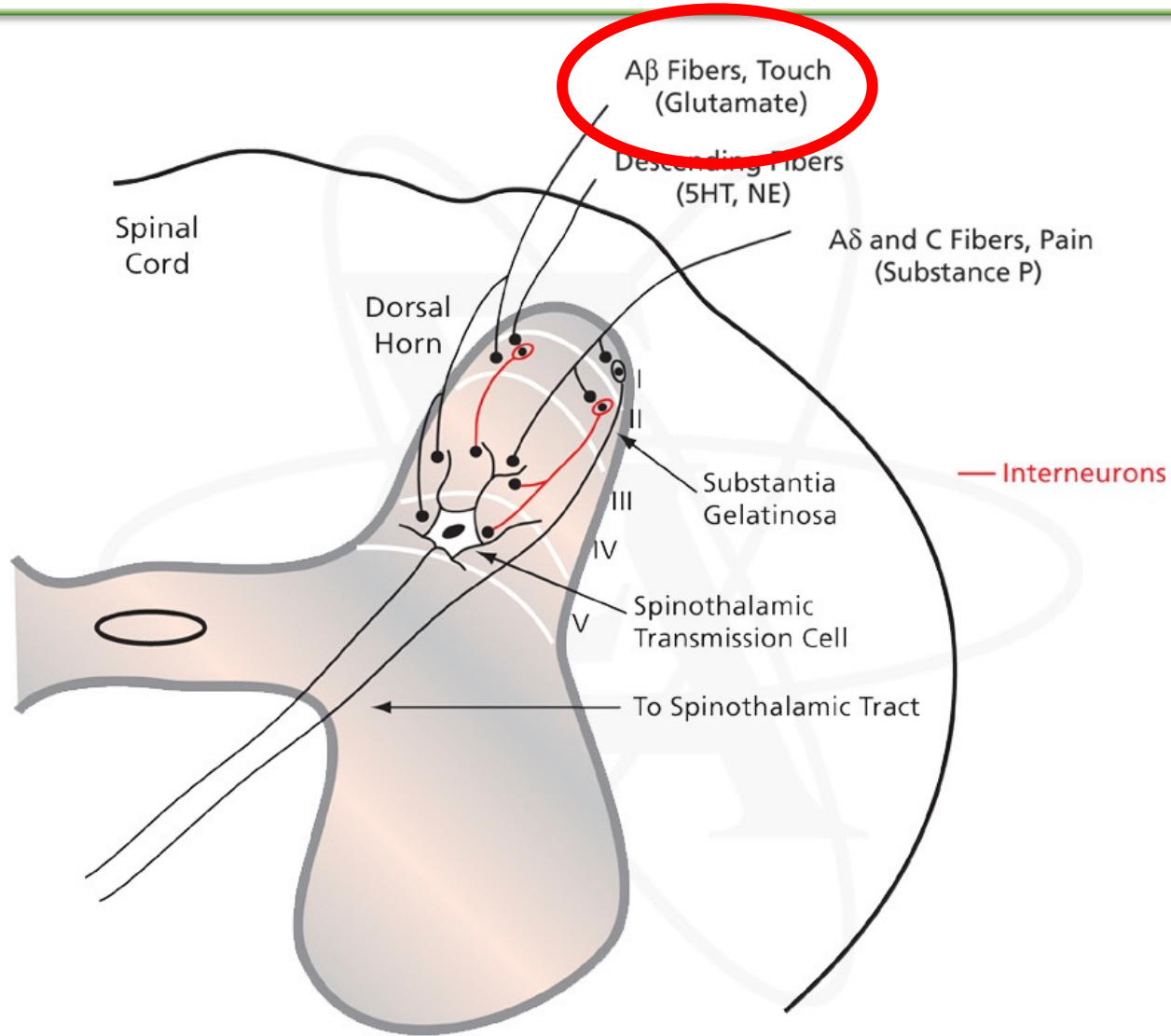


## Gate Control Theory

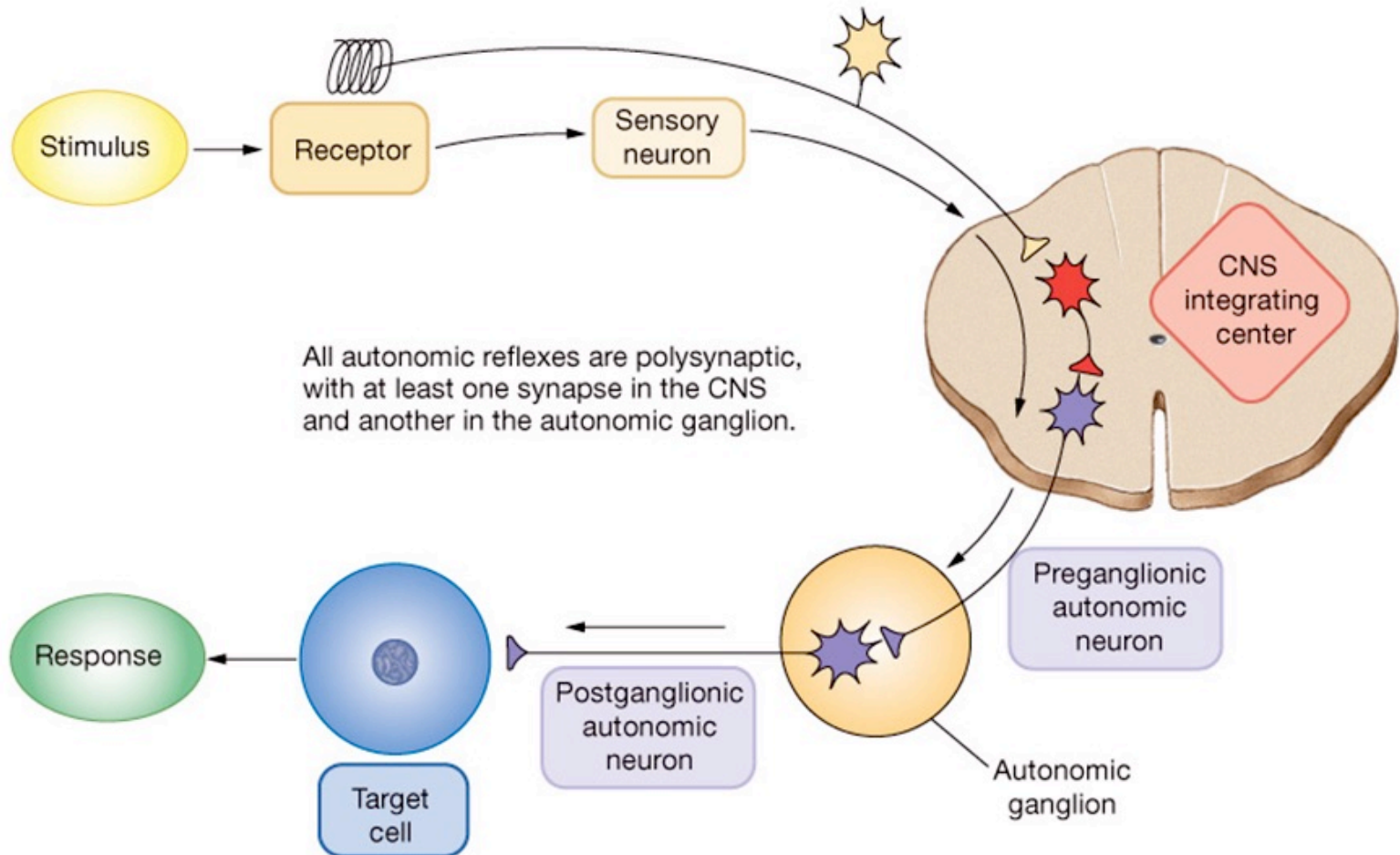
- Proposed in 1965 by Melzack & Wall
- Segmental inhibition of pain transmission
- Component of TENS analgesia



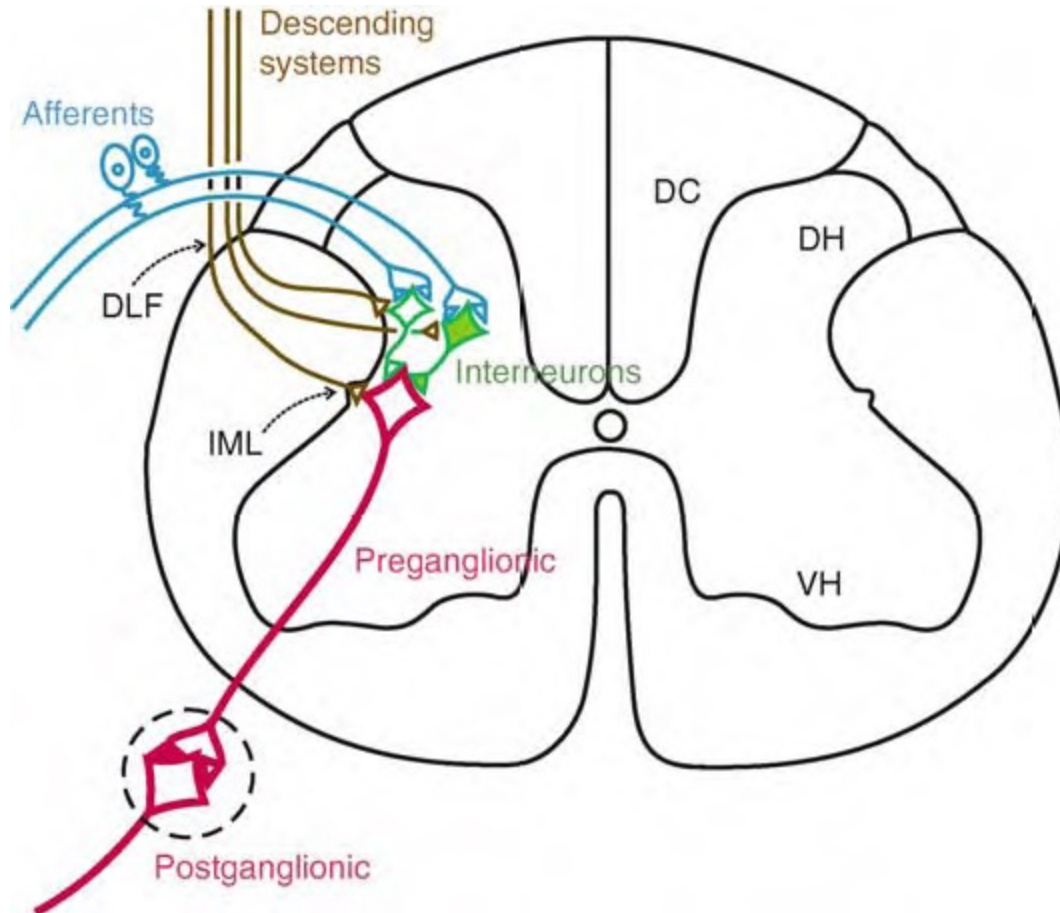
# Modulation of pain transmission



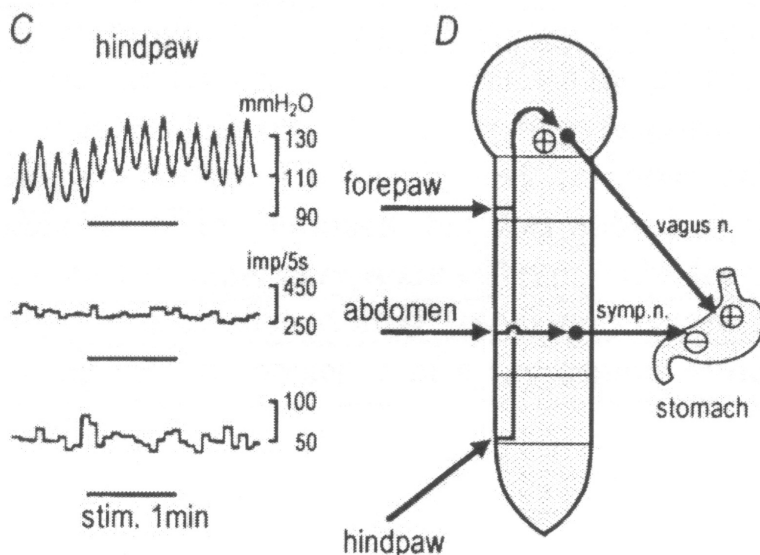
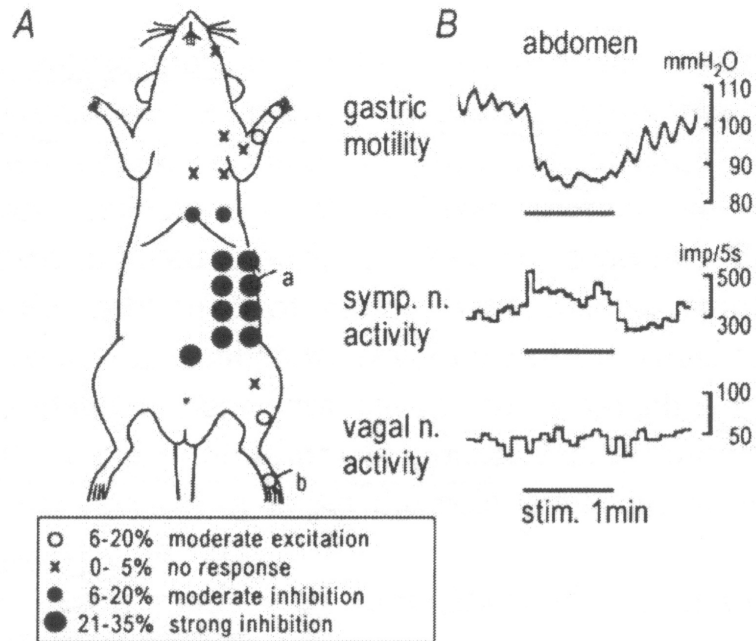
# Spinal/segmental effects



# Autonomic reflex



# Autonomic reflex



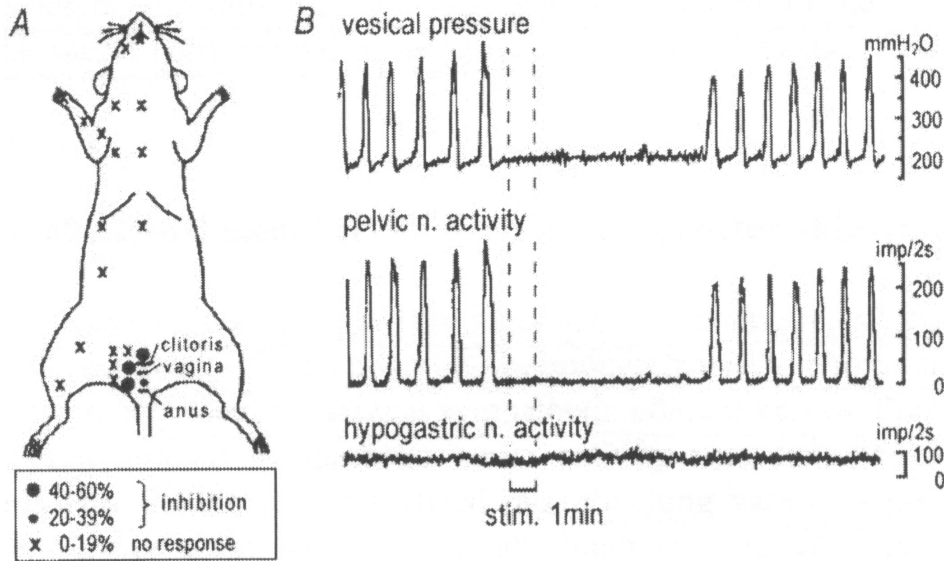
## Gastric motility

Segmental: inhibition,  
↑ sympathetic activity

Extra-segmental: increase,  
↑ parasympathetic activity

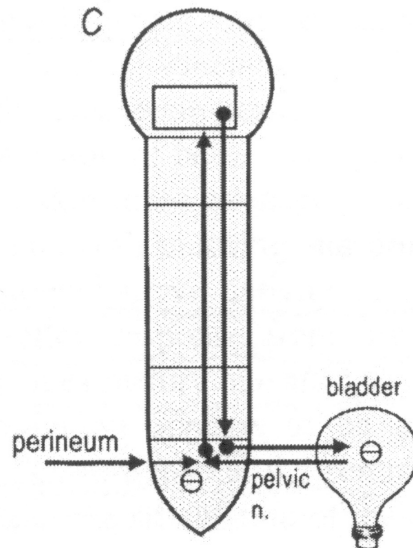
Neurosci Res 18:53;1993

# Autonomic reflex



**Bladder contraction  
(micturition)**

**Segmental: inhibition,  
↓ parasympathetic activity**



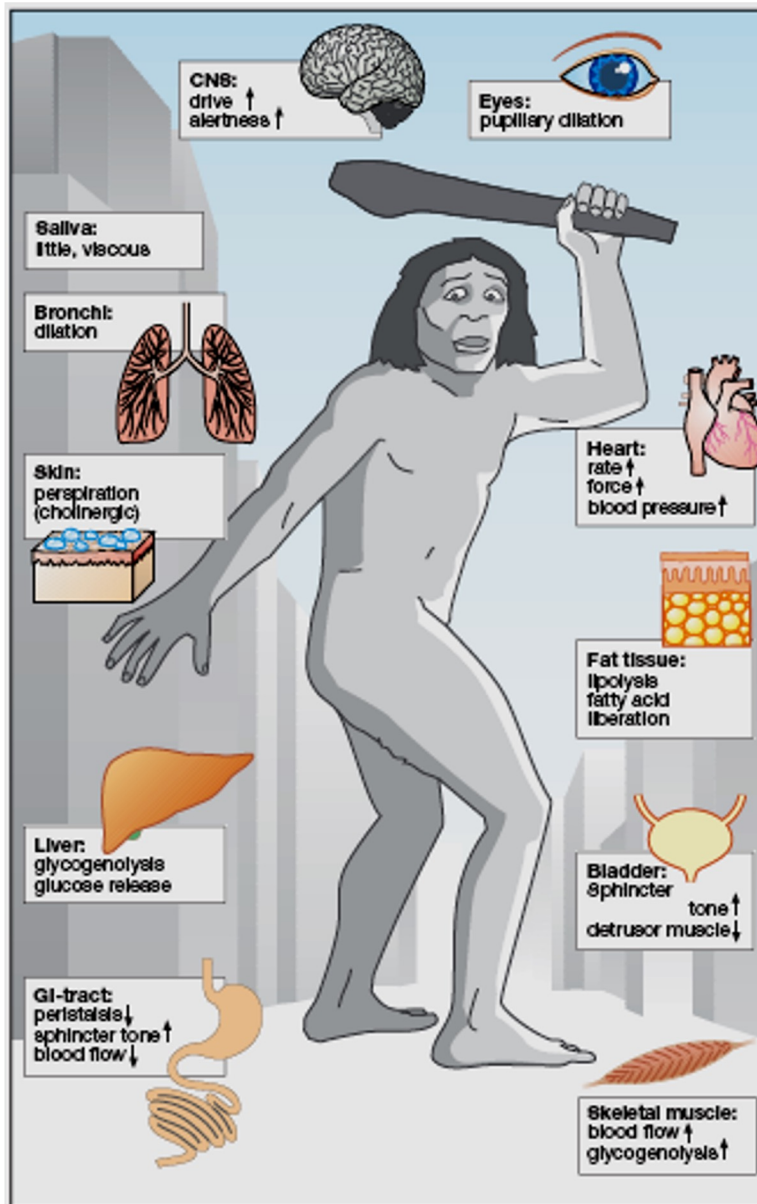
**Neurosci Res 15:189;1992**



## 1. Rapid excitation of sympathetic system:

- increase of heart rate
- regional vasoconstriction
- increase blood pressure
- more effective perfusion of the muscle
- Decrease blood flow to visceral organs
- Optimal adaptation to heavy load of the muscle

# Autonomic functions



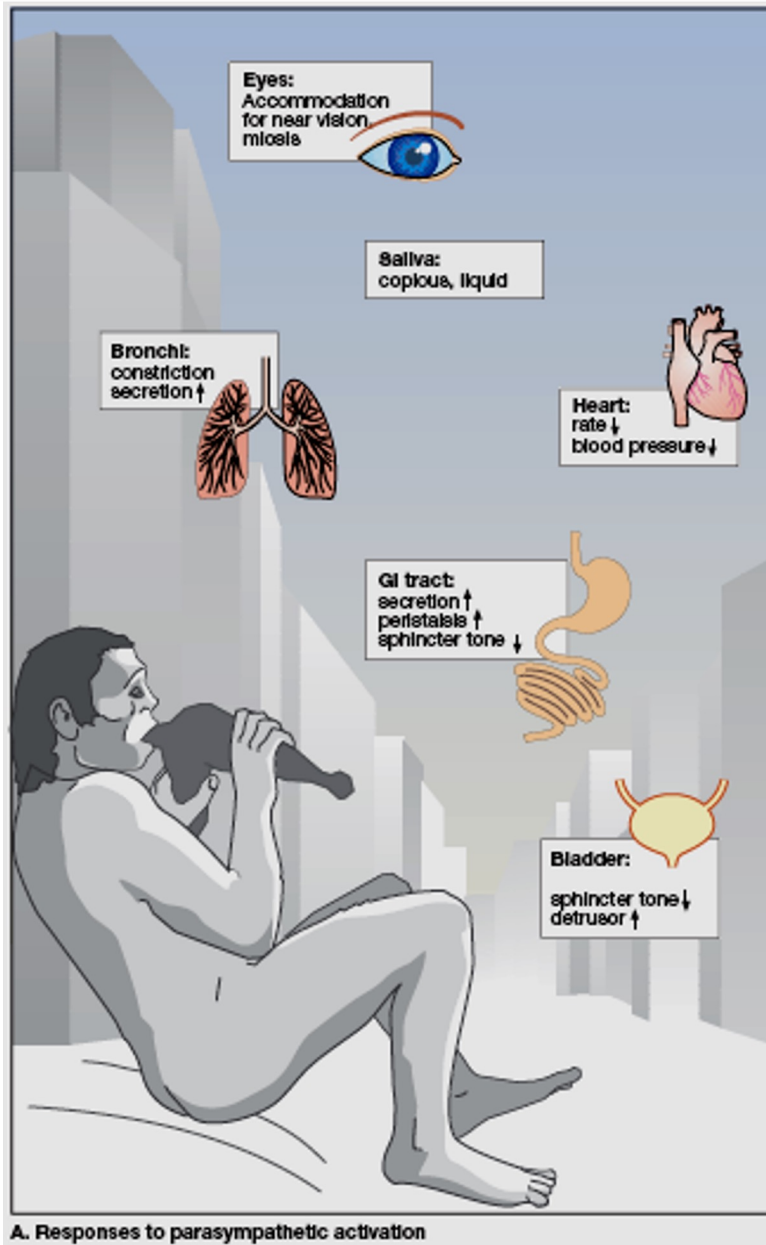
A. Responses to sympathetic activation

**Fight or Flight**

## 2. Opioid-mediated central inhibition of the sympathetic outflow:

- Evident after the end of EA or exercise
- Long-lasting
- Decrease of blood pressure
- Decrease of heart rate

# Autonomic functions



Rest &  
Digest

# Central effects of acupuncture

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## Modulation of control systems; opioids etc.

Descending pain inhibiting systems

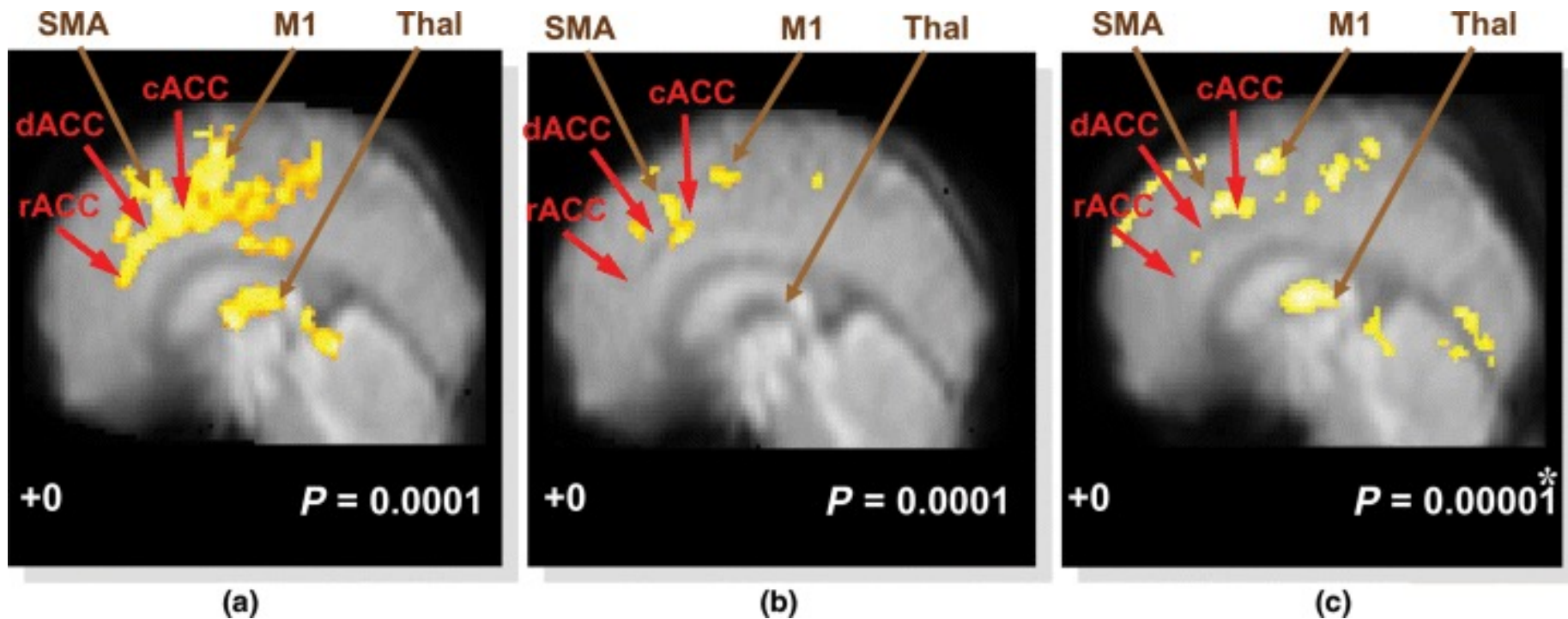
Central autonomic activity

Neuroendocrine effects (HPA, mood etc.)

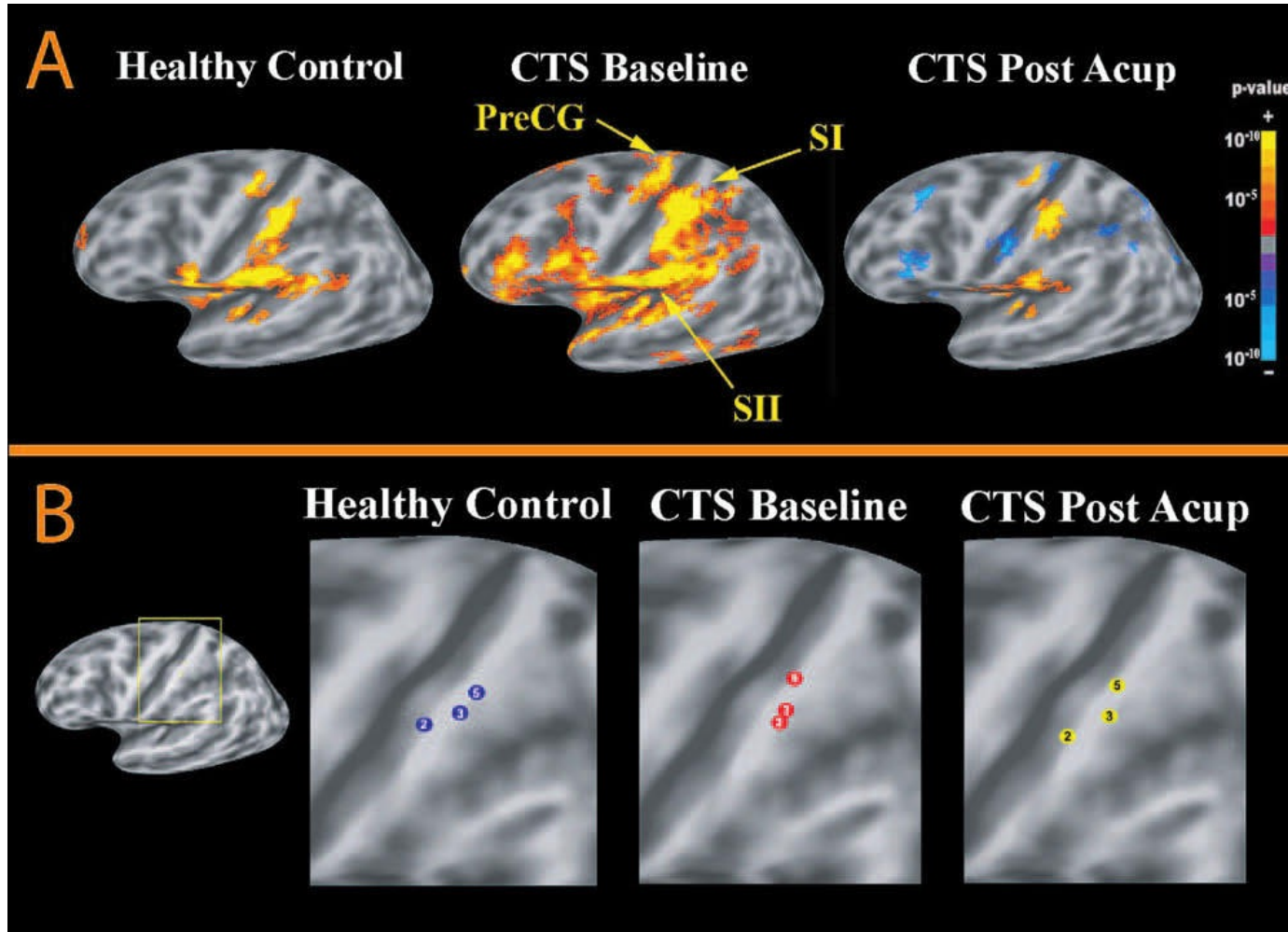
Neuroplasticity, stem cells, NGF, BDNF.

# Modulation of Pain

## Central modulation of pain processing



# Somatosensory cortex



# Acupoints specificity

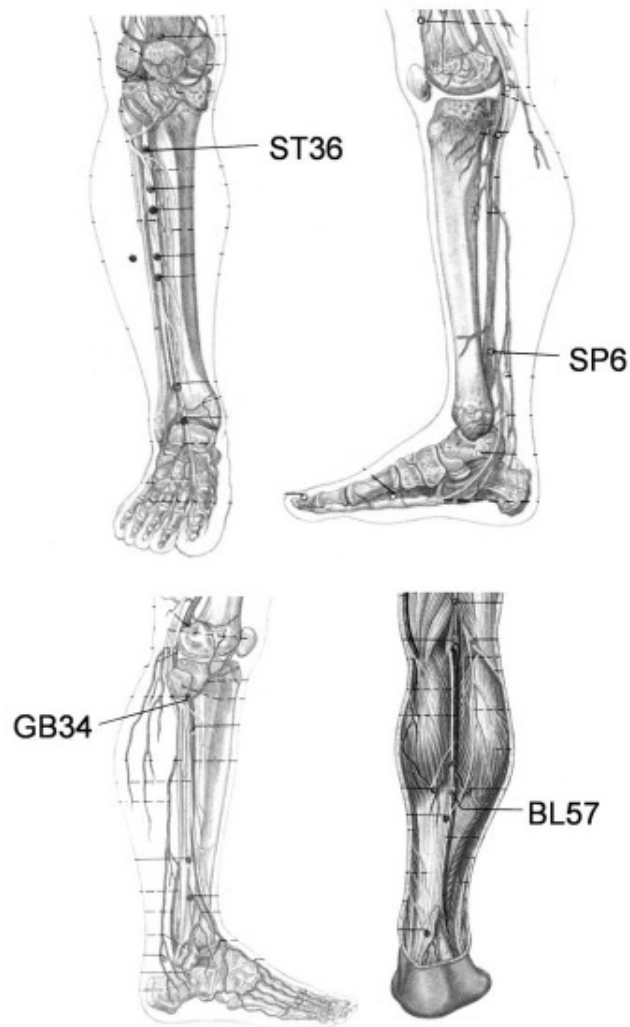


Table 1

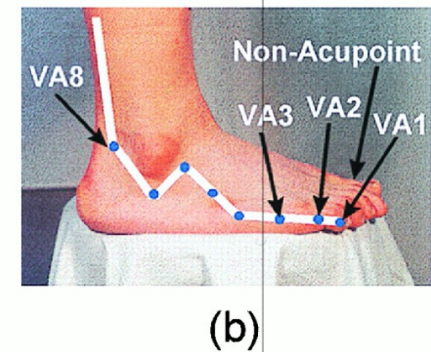
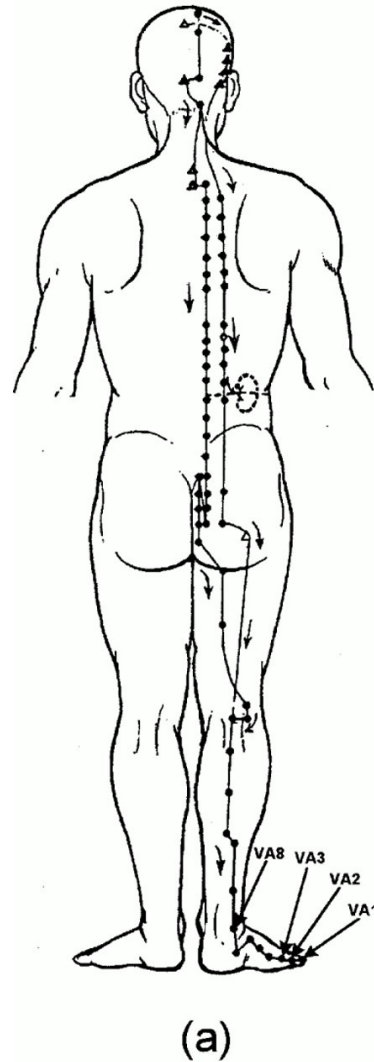
Brain areas activated by EA at different acupoints

Brain areas	ST36/SP6	GB34/BL57
R-SI	+	+
L-SI	+	
B-MI/PMC		-
B-SII/Insula	+	+
B-Parietal BA40	+	+
L-Parietal BA7	-	
Thalamus		
B-Ventral anterior	+	
B-Ventral posterior		+
R-Dorsal		+
B-Orbital Frontal	+	
B-Temporal	+	+
B-Cerebellum	+	+
R-Putamen	+	+
B-Amygdala	-	-
B-Hippocampus	-	
B-Pons		+



# Acupoints specificity

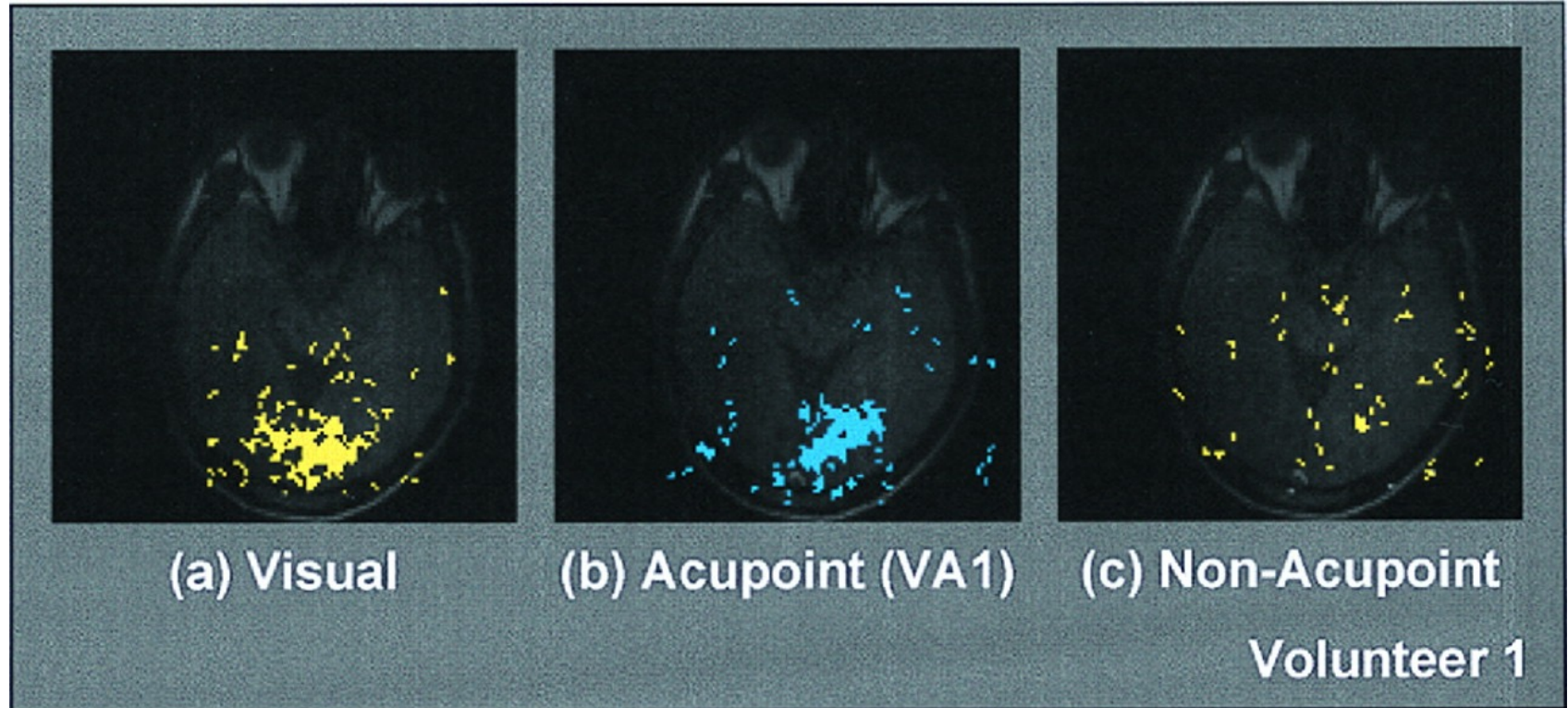
- EA at GB meridian acupoints specific for visual diseases, differentially modulates visual cortex activity in different subjects.



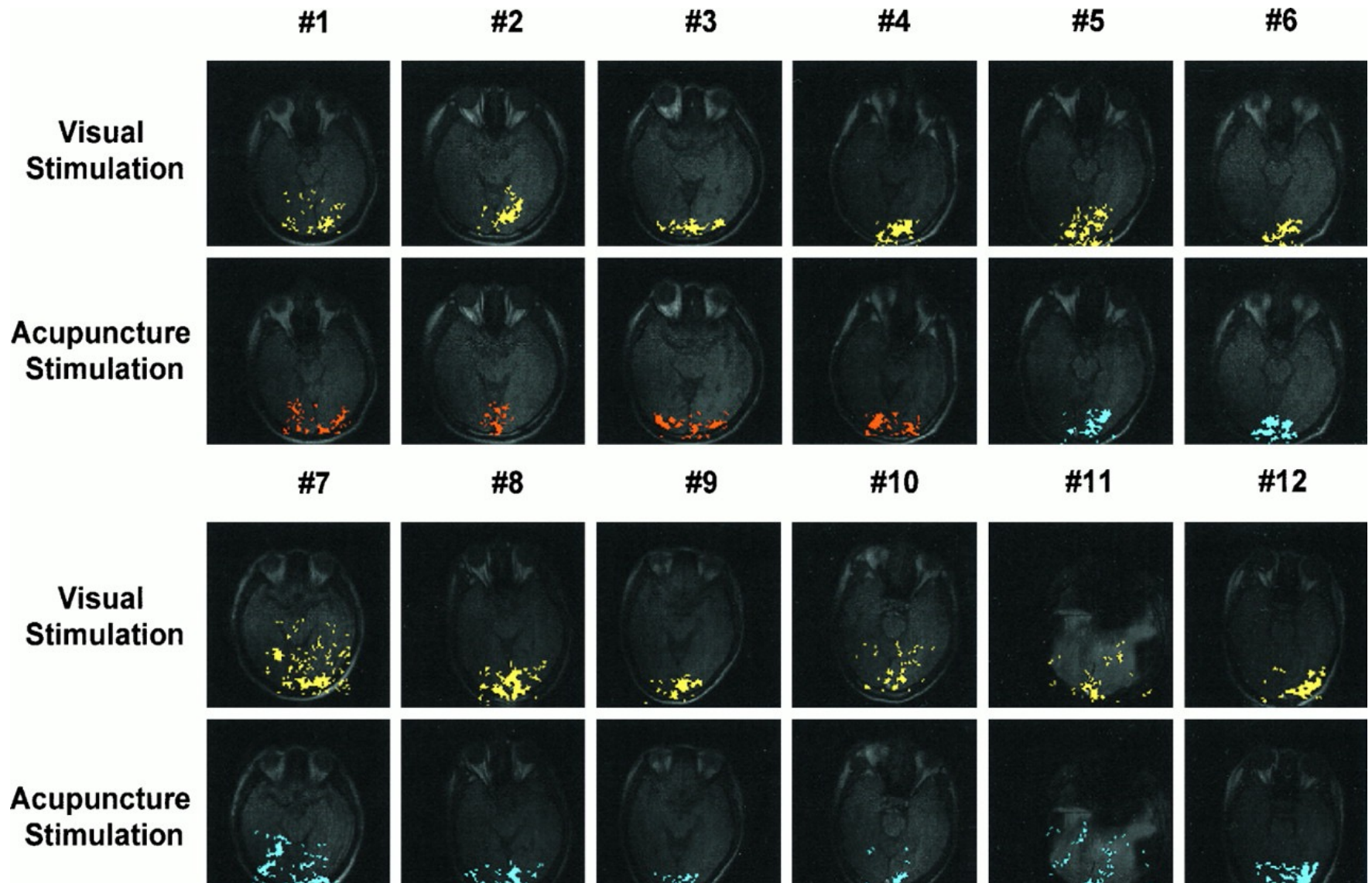
Proc Natl Acad Sci U S A. 1998 March 3; 95(5): 2670–2673.

# Acupoints specificity

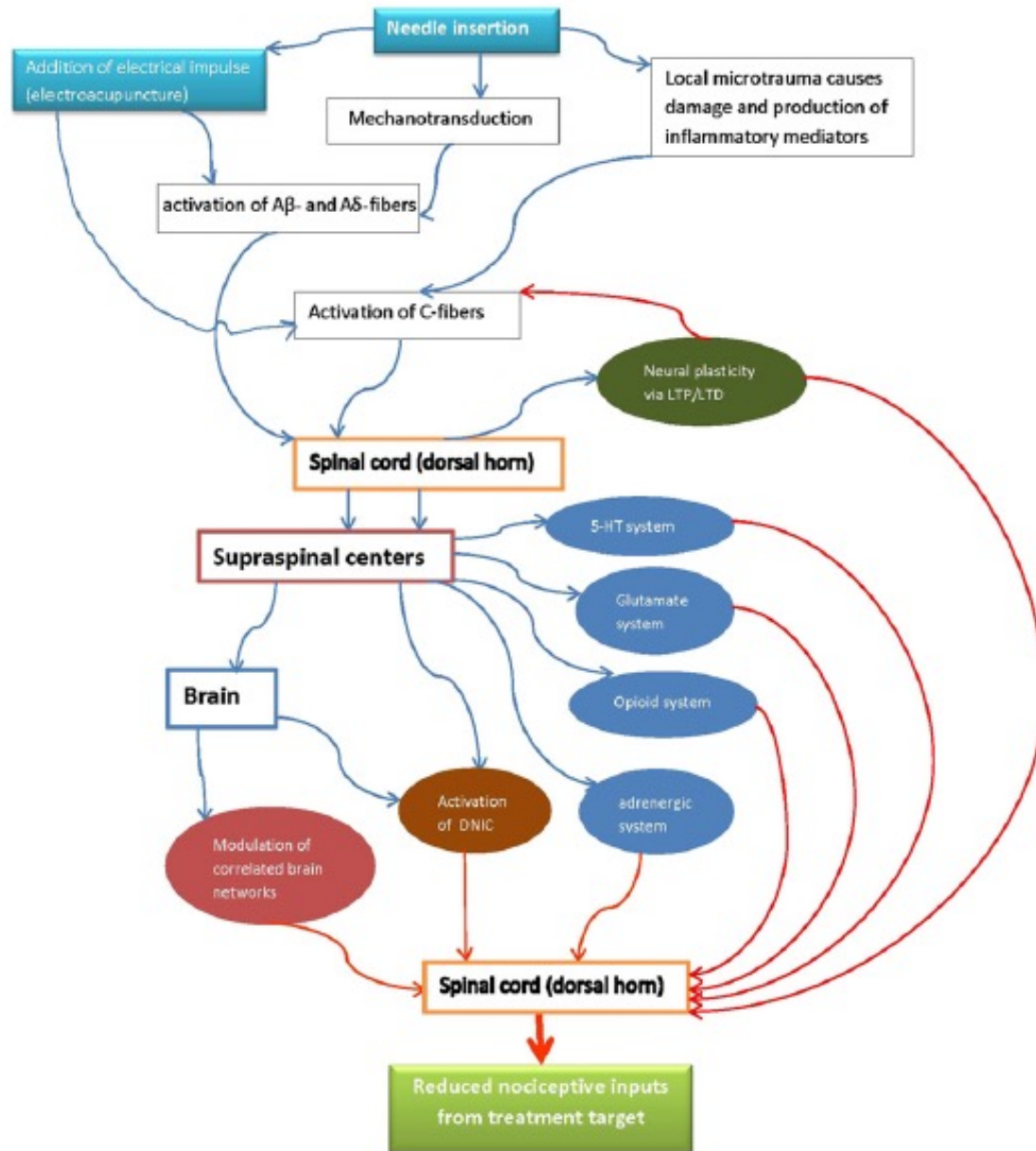
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# Acupoints specificity



# Summary



# A Yin-Yang matter?

