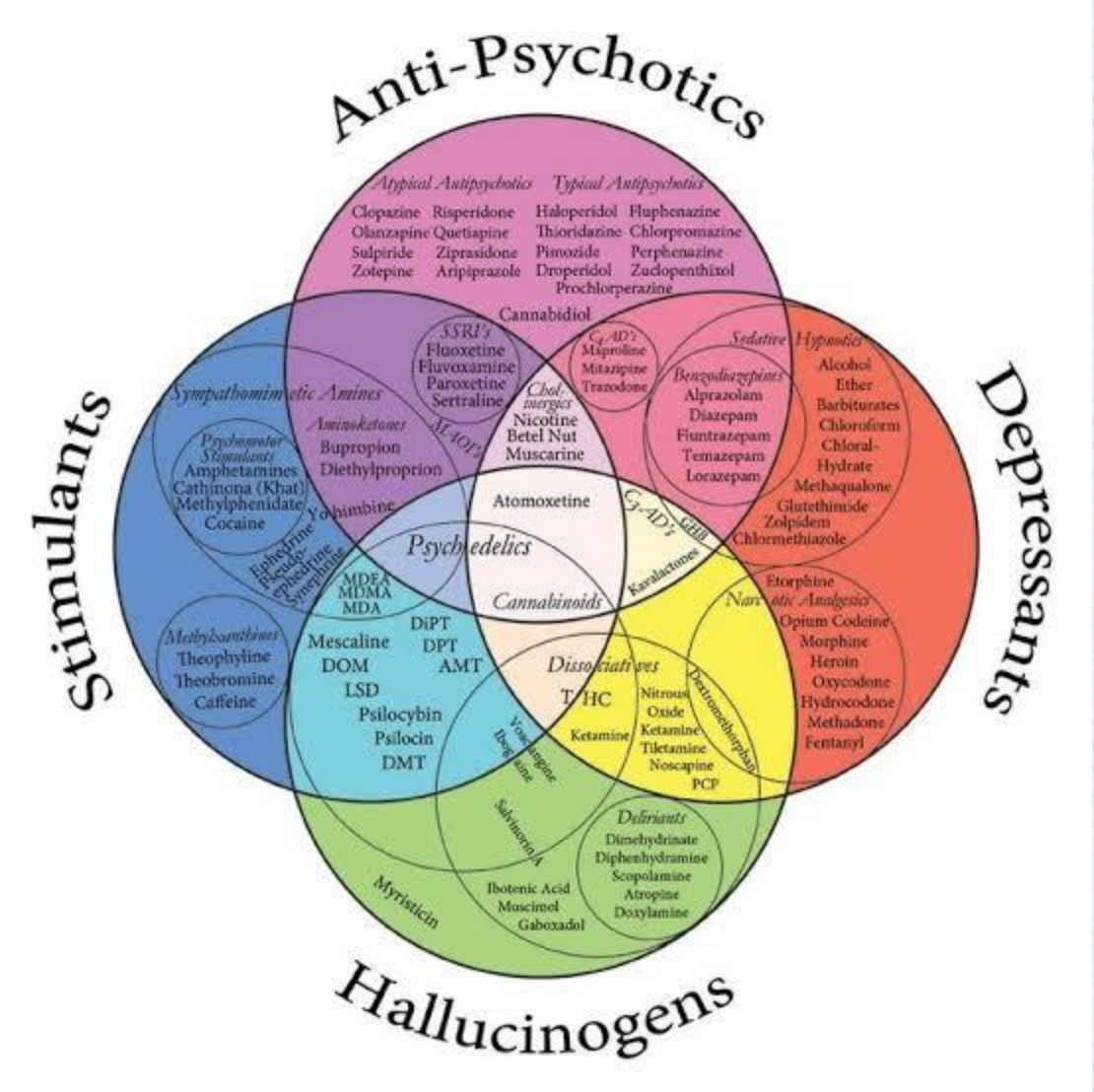
Marco Atzori

History and Solidification of the concept of SYNAPSE at the beginning of 1900

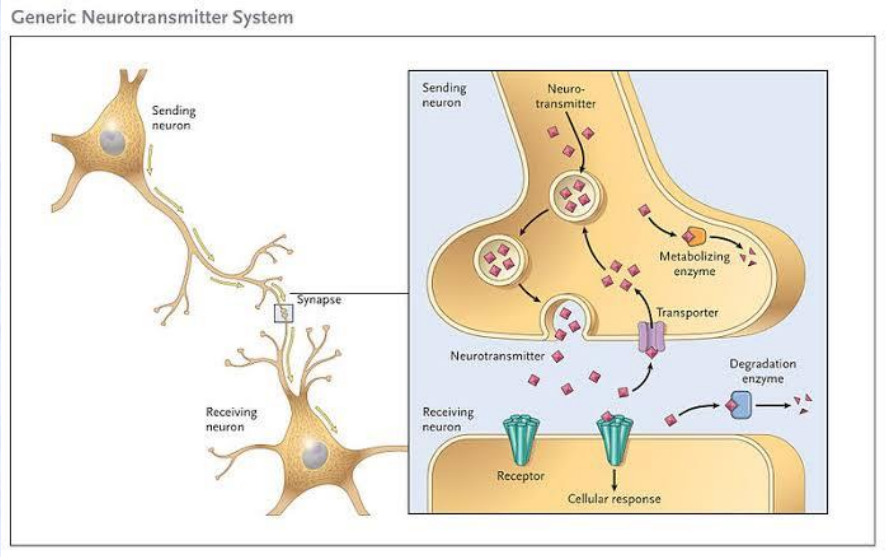
texts
1) history of the synapses (history of neuroscience)
(History of the Synapse, M. Bennett)
2) structure, function and physiology of CNS synapses
(Synapses, Cowan, Sudhof, Stevens)

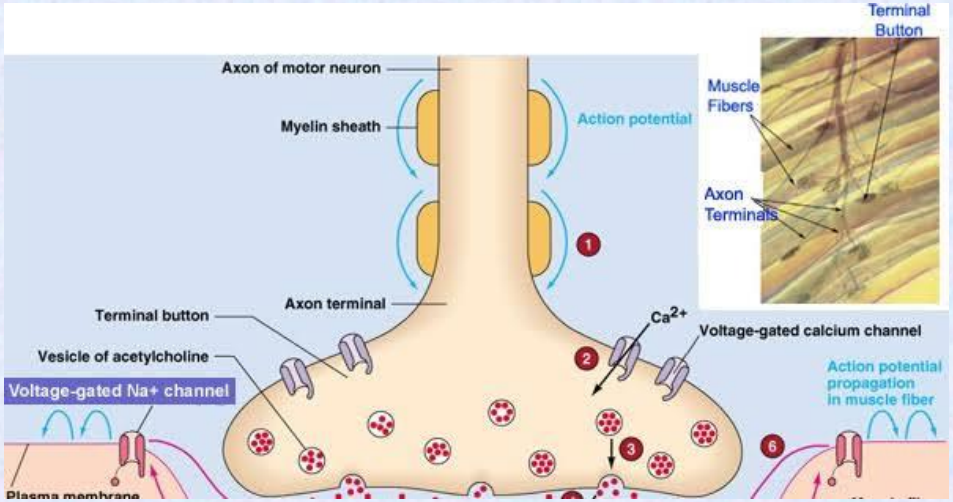

Anti-Psychotics
Depressants
Stimulants
Hallucinogens
Atypical Antipsychotics
Typical Antipsychotics
Clopazine
Risperidone
Olanzapine
Quetiapine
Sulpiride
Ziprasidone
Zotepine
Aripiprazole
Haloperidol
Fluphenazine
Thioridazine
Chlorpromazine
Pimozide
Perphenazine
Droperidol
Zuclopenthixol
Prochlorperazine
Cannabidiol
SSRI's
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
TCAD's
Maprotiline
Mitazipine
Trazodone
Sedative Hypnotics
Benzodiazepines
Alprazolam
Diazepam
Fluntrazepam
Temazepam
Lorazepam
Alcohol
Ether
Barbiturates
Chloroform
Chloral-Hydrate
Methaqualone
Glutethimide
Zolpidem
Chlormethiazole
Sympathomimetic Amines
Psychomotor Stimulants
Amphetamines
Cathinona (Khat)
Methylphenidate
Cocaine
Aminoketones
Bupropion
Diethylproprion
MAOI's
Cholinergics
Nicotine
Betel Nut
Muscarine
Yohimbine
Ephedrine
Pseudo-ephedrine
Synephrine
Atomoxetine
Psychedelics
Cannabinoids
TCAD's
GHB
Kavalactones
MDEA
MDMA
MDA
DiPT
DPT
AMT
Mescaline
DOM
LSD
Psilocybin
Psilocin
DMT
Methylxanthines
Theophyline
Theobromine
Caffeine
Dissociatives
THC
Nitrous Oxide
Ketamine
Ketamine
Tiletamine
Noscapine
PCP
Dextromethorphan
Etorphine
Narcotic Analgesics
Opium Codeine
Morphine
Heroin
Oxycodone
Hydrocodone
Methadone
Fentanyl
Vasicine
Ibogaine
Salvinorin A
Myristicin
Ibotenic Acid
Muscimol
Gaboxadol
Delirients
Dimehydrinate
Diphenhydramine
Scopolamine
Atropine
Doxylamine

Synapse

connection between two neurons

connection between a neuron and a muscle fiber



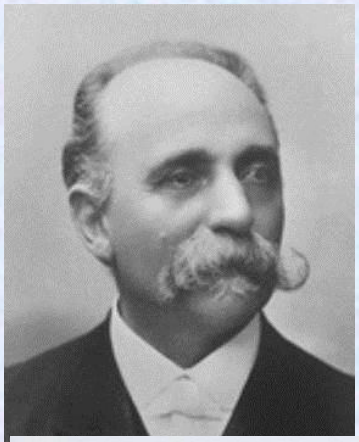


central or peripheral

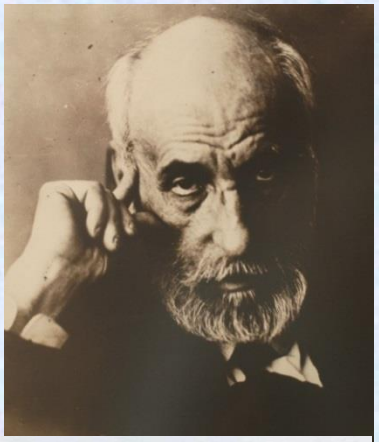
neuromuscular junction

Background: anatomy: the NEURON is the biological unit of the CNS

Early Problem: **is the Central Nervous System a continuum or is made up by discrete neurons?**

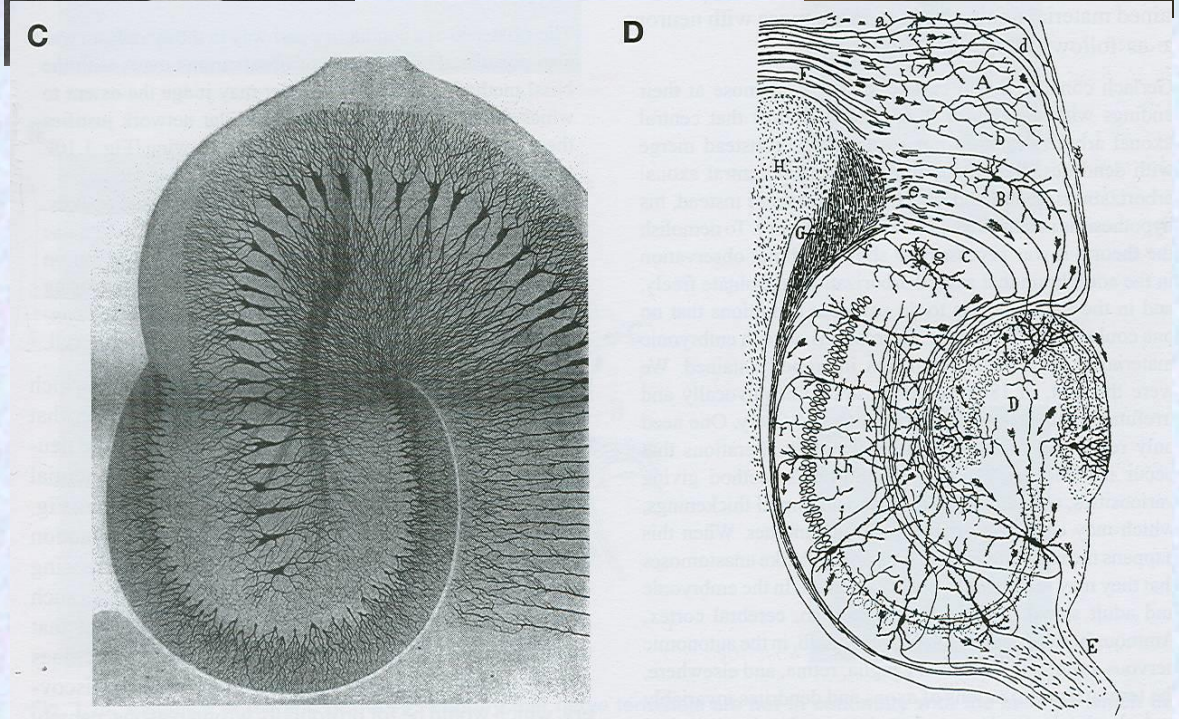


Lattice vs. Neurons



Contributions of the anatomy:
Ramon y Cajal vs. Golgi and the Controversy on the neuronal vs. lattice theory

Ramon y Cajal uses extensively Golgi's silver stain based method



1906: Sherrington makes up the word SYNAPSE

Sherrington gives a name (synapse) to the connection between two neurons. His analysis of the spinal synapse is lucid but far from definitive. Open questions:

What is the nature of synaptic transmission: (chemical or electric?

What is qualitative difference between synaptic excitation and inhibition?

Sherrington had concluded: "…in relation to inhibition at the synapse that might be mediated by an agent, moreover, one whose existence lies outside the intrinsic properties of pure nerve-fiber and with a, so to say, more chemical mode of origin and function than the nerve impulse per se." (1925)

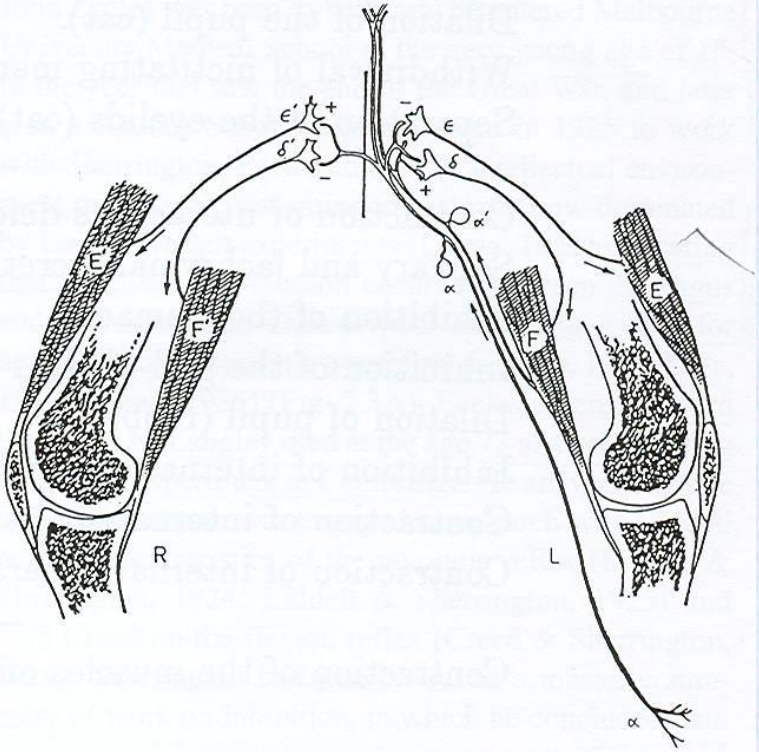


Fig. 2.1. Sherrington's 1906 diagram 'indicating connections and actions of two afferent spinal root-cells (dorsal root ganglia), α and α'' in regard to their reflex influence on the extensor and flexor muscles of the two knees.
Flexor and extensor muscles of the knee joint on the right (R) and left (L) sides are shown together with the inputs to the spinal cord by a cutaneous afferent (α) and a muscle spindle afferent (α′). The reflex pathways postulated show flexor (F) excitation (+) and extensor (E) inhibition (–) ipsilaterally and flexor (F) inhibition (–) and extensor (E) excitation (+) contralaterally. In Sherrington's 1906 words, 'the sign + indicates that at the synapse which it marks the afferent fibre (α (and (α′) excites the motor neurone to discharge activity, whereas the sign – indicates that at the synapse which it marks the afferent fibre α (and α′) inhibits the discharging activity of the motor neurones. The effect of strychnine and of tetanus toxin is to convert the minus sign into a plus sign'.

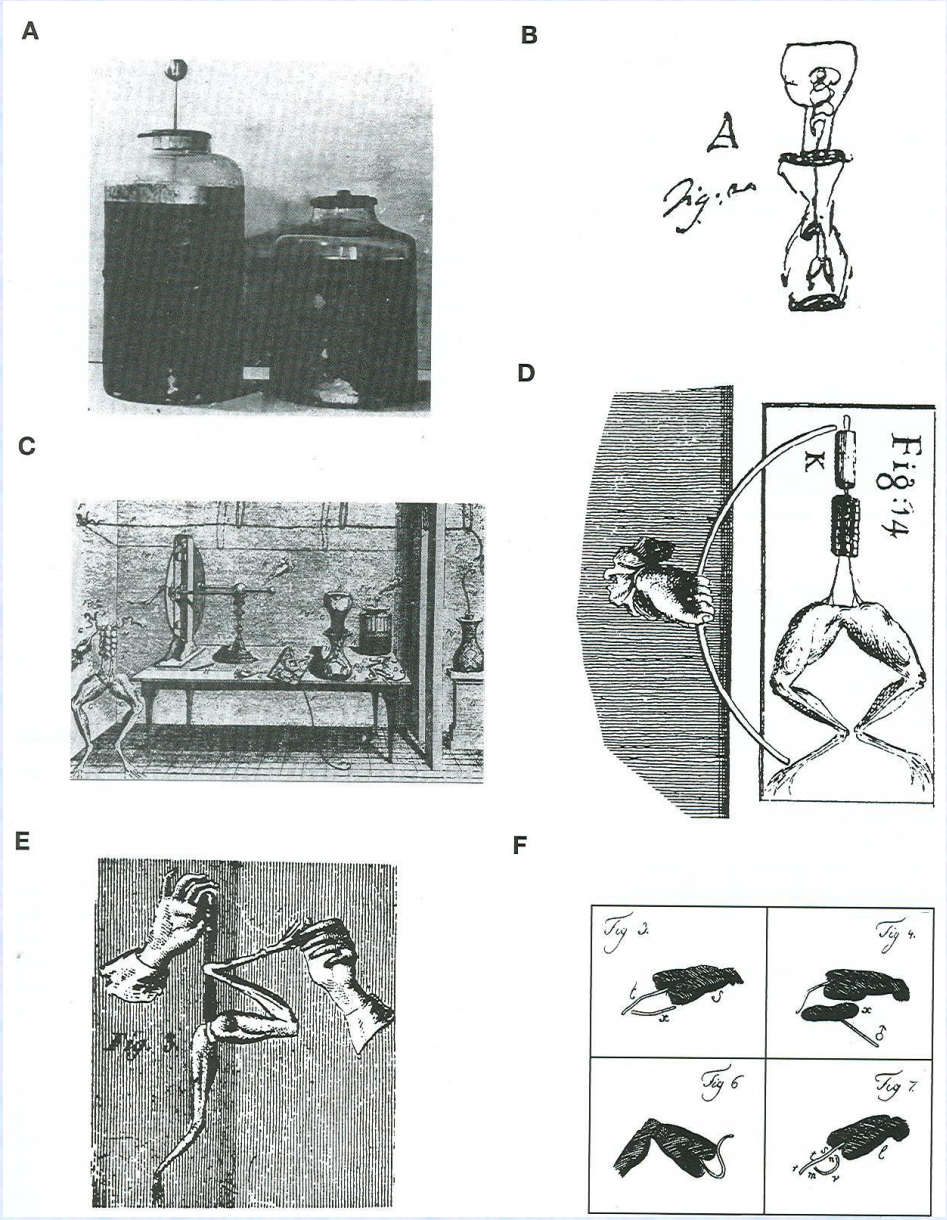
Background: physiology nerve conduction is ELECTRICAL

Galvani (second half of 1700) becomes expert in a frog exposed spinal cord-leg preparation.

By chance his assistant provokes an electric discharge in a Leiden bottle (two metal surfaces where electric charge has been accumulated) by touching it with the frog spinal cord, and the frog's muscle's contracted.

This discovery is fundamental not only in determining that **the nature of the nerve impulse is electric**,

but also in the **discovery of the battery by Volta** in the following years (the interface between different metal surfaces generates a different of V inducing muscle twitching).



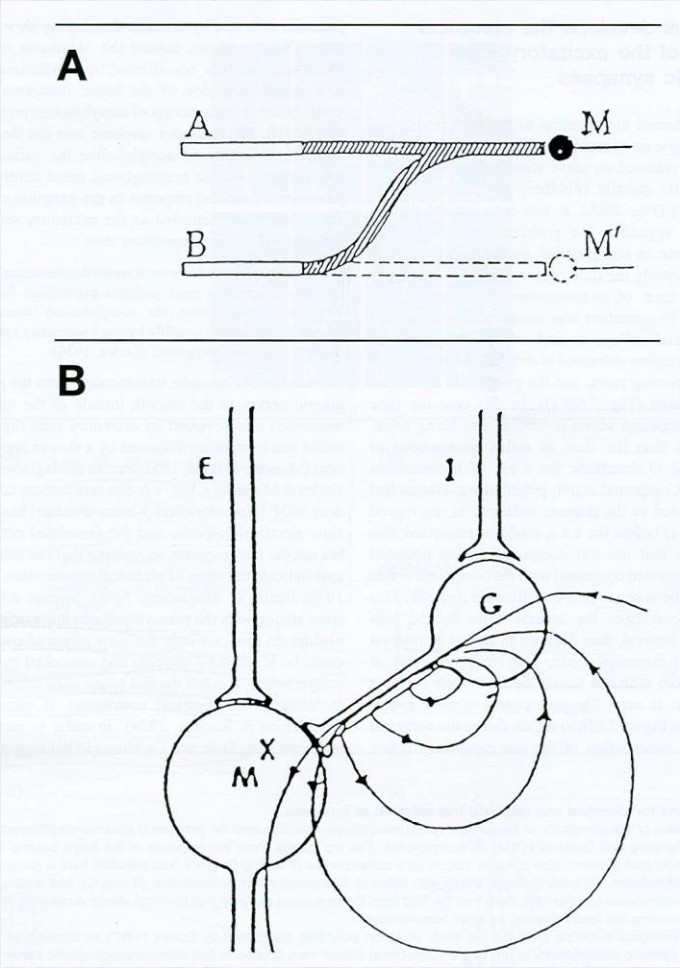
Lucas and Adrian formulate (but do not demonstrate empirically) the electric theory of the synapse.

Lucas had just argued that “central **inhibition might be brought about by the interference of high-frequency discharges in the nerves as they approached their synaptic connections on neurons”** **(Lucas, 1917).**

In this way the refractory state of an axon following the impulse could operate to induce inhibition.

He followed Adrian criticism that:".. If an inhibiting substance is produced, its production must be almost instantaneous and it must disappear very rapidly; what the present theory assumes is that the "substance" is to be identified with the refractory states and not to a steady production of an inhibiting substance (1924).

Sherrington and Adrian share the Nobel price for Medicine and Physiology in 1932



Electrical model of excitation and inhibition

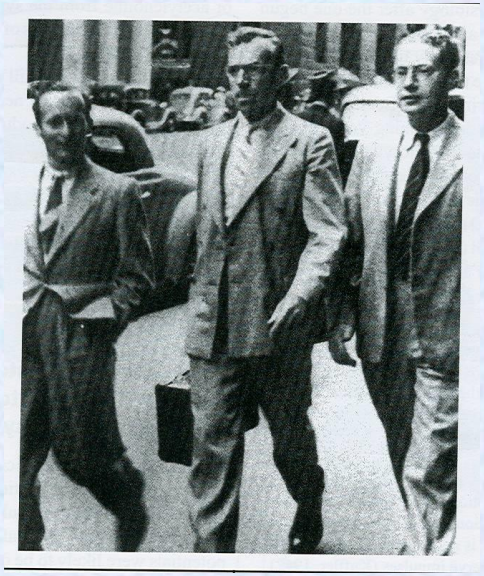
More players get involved in the search for the mechanisms of synaptic transmission

Langley **Lucas and Adrian** **Loewi (Germany)**

Sherrington **Gaskell Von Euler** **Dale** **Elliott** **Dixon**

Eccles **(then in Australia)** **Del Castillo** **Fatt** **Katz** **Kuffler**

Dodge and Rahamimoff **Miledi**

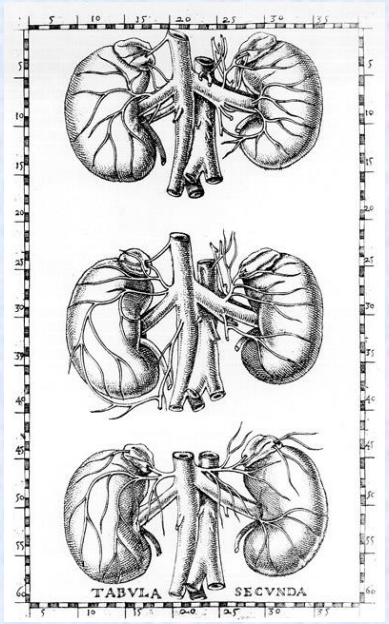


Kuffler, Eccles, and Katz

Dale

Langley discovers the effect of adrenaline on the sympathetic system

1901



A

Table 1

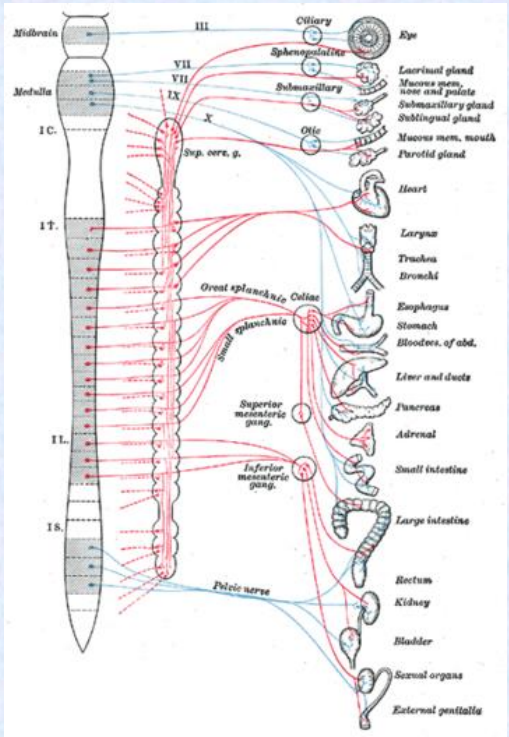
Rise of blood-pressure.

Inhibition of the sphincter of the stomach and of the intestine (rabbit).
Inhibition of the bladder.
Dilation of the pupil (cat).
Withdrawal of nictitating membrane (cat) } slightly less readily
Separation of the eyelids (cat) } than the foregoing.

Contraction of uterus, vas deferens, seminal vesicles, etc. (rabbit).
Salivary and lachrymal secretion.
Inhibition of the stomach.
Inhibition of the gall-bladder and increased bile secretion.
Dilation of pupil (rabbit).
Inhibition of internal anal sphincter (rabbit).
Contraction of internal anal sphincter (cat) } effects relatively
Contraction of internal generative organs (cat) } slight.

Contraction of the muscles of the hairs.

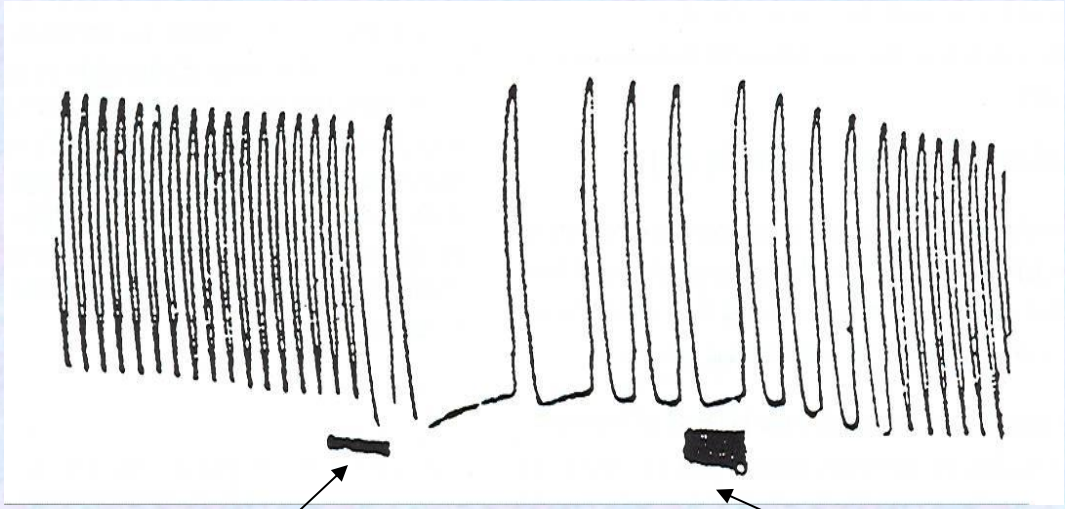
Contraction of tunica dartos of scrotum } no certain effect.
Secretion of sweat }



"...it is noteworthy that the effect of the suprarenal extract are almost all such as are produced by stimulation of some one or the other sympathetic nerve…it is hardly impossible to avoid the conclusion that in these cases the extract acts directly on the unstriated muscle, and, if it is so, it is probable that in all cases the effect is direct."

Dixon, unpublished experiment, 1906

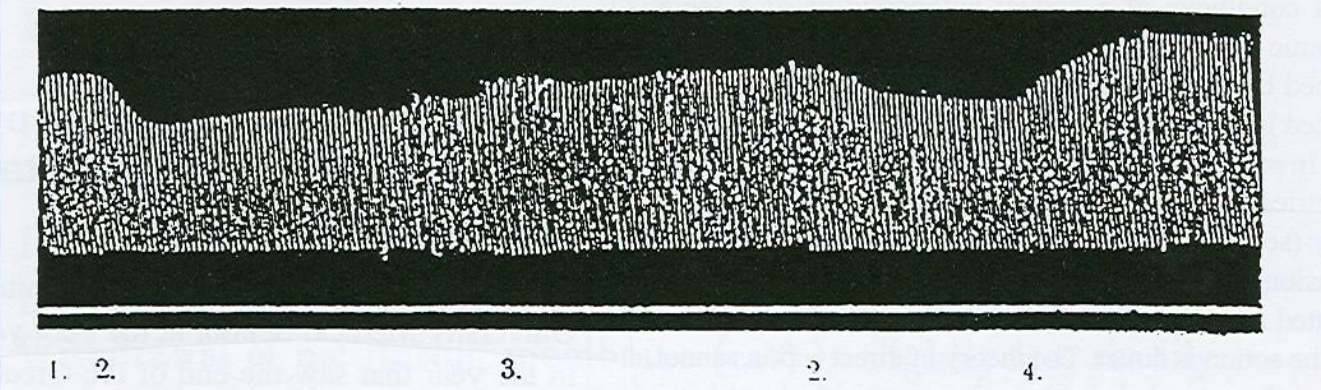
Dixon, even before Loewi, saw that whatever substance was released by stimulation of the vagus nerve (we now know it to be acetylcholine), it dicreases heart beat, and atropine reverses it.



Extract from dog's vagal stimulated heart

atropine

Otto Loewi
experiment on frog's, heartbeat (before 1921, year of the publication)



1 Control
2 contact with vagustoff (15 min stimulation in another heart)
3 contact with vagus unstimulated solution
2 again contact with vagustoff
5 atropine (which as we now know is a cholinergic muscarinic blocker)

Dale and acetylcholine, 1914

Dale came across acetylcholine accidentaly, as a constituent of a sample of ergot, a rye disease produced by a fungus

Dale was aware of Dixon's and Loewi's results on the heart, and observed:

"… I was led to make a detailed study of its (acetylcholine's) action. This, I think, gave the first interest for physiology. Then I was struck by the remarkable fidelity with which I compared to that with which adrenaline reproducs the effects of the other, true sympathetic, division of the autonomic system."

Eccles, australian, age 15 (1918), won a fellowship for going to the university of Oxford with Sherrington. Loewi had just discovered the effect of the "vagustoff" (acetylcholine) similar to Dixon's experiments.

He entered Oxford the year that Langley died at age 73 right after performing a 6 hour-long experiment in Cambridge.

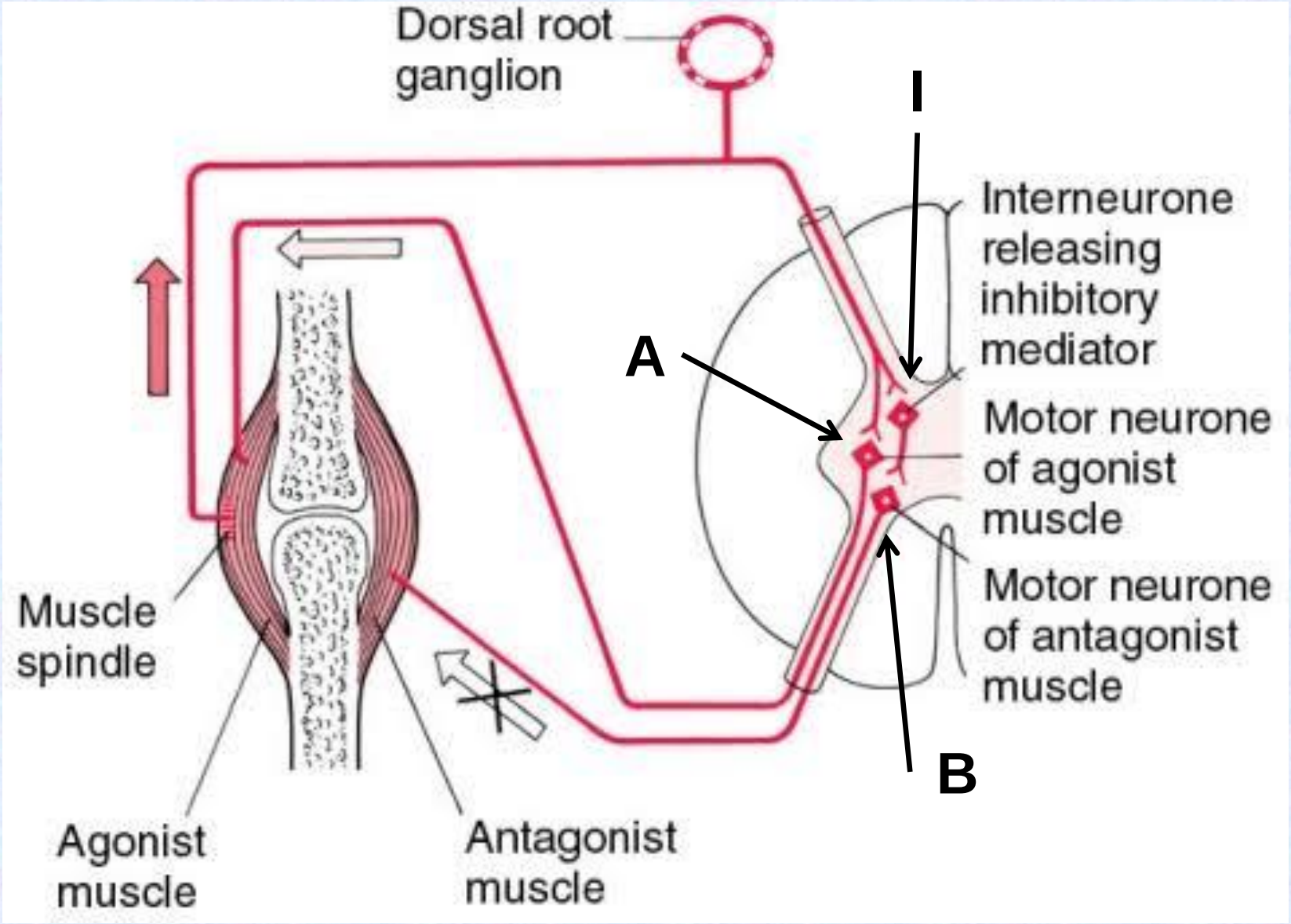
Dale's work had just shown that acetylcholine could be the "vagustoff"

From this observations it would look like we were very close to identify as chemical the mode of inhibitory transmission….It would not be so.

In spite of starting as Sherrington pupil, Eccles was strongly influenced by **Lucas and Adrian**, who were supporters of the electric transmission

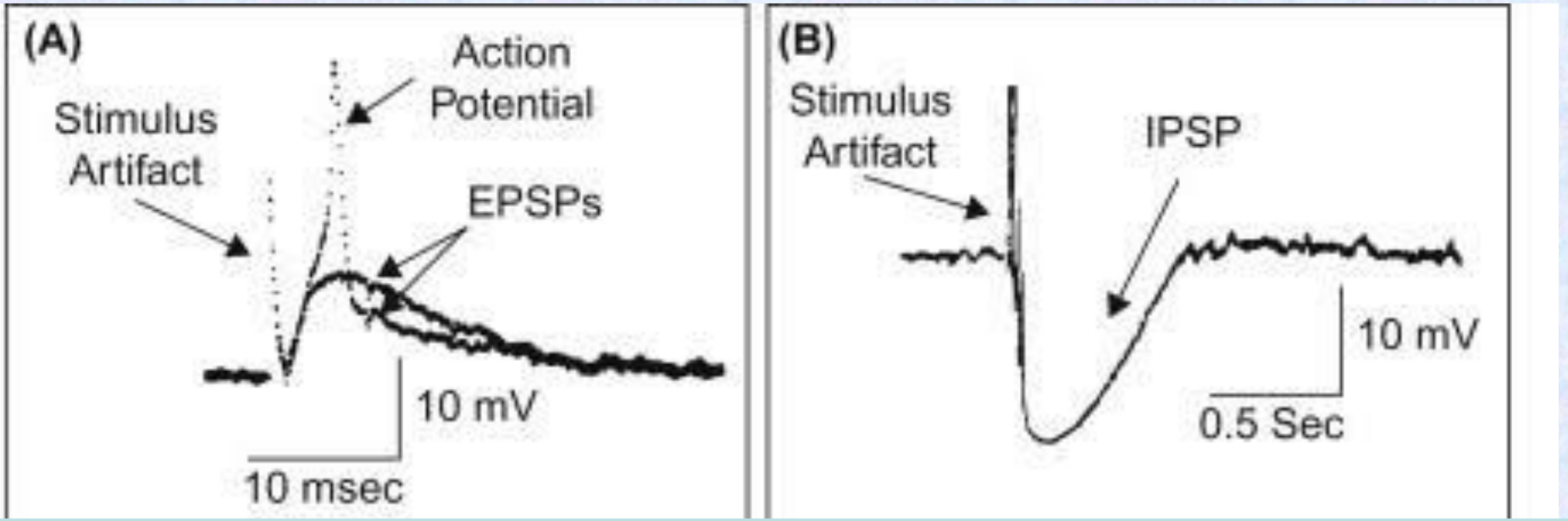
The (erroneous) concept of inhibition as interference of excitation will accompany Eccles for a long part of his career, as he will became on e of the strongest supporters of the (mostly incorrect) hypothesis of electric synaptic transmission.

Spinal network controlling agonist-antagonist muscle contraction



Eccles intracellular recordings from network neurons

agonist **antagonist**



Electrophysiological recordings show that the voltage in the antagonist muscle is turned persistently NEGATIVE during agonist muscle activation.

The shape of the membrane potential in the antagonist muscle during agonist activation does NOT resemble the shape expected by the “interference” theory of Lucas and Adrian of inhibition.

On the contrary, its characteristics and duration suggest that an intracellular ionic current brings anions inside the neuron, substantially overlasting any possible transient residual from one or more action potentials inducing the activation of the agonist muscle.

Death blow to the electric theory

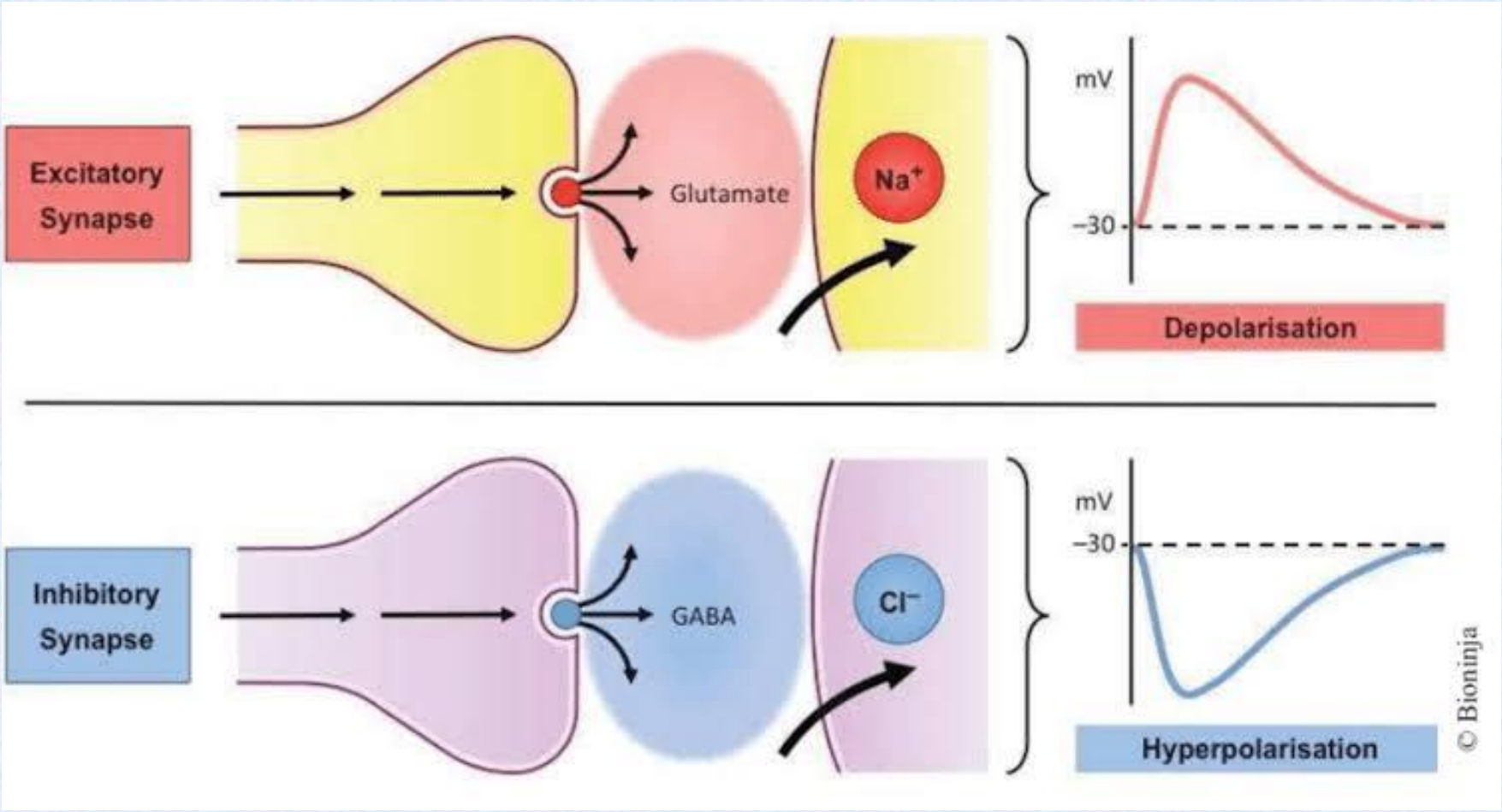
Intracellular recordings of inhibition show that the electrical potential change within the effector neuron is OPPOSITE to the sign expected in the framework of Adrian and Lucas interference of electric fields explanation of inhibition. In the words of Eccles himself:

"..the potential change observed (in inhibition) is directly opposite to that predicted by the (…Lucas and Adrian) hypothesis, which is thereby falsified… It may therefore be concluded that inhibitory synaptic action is mediated by a specific transmitter substance that is liberated from the inhibitory synaptic knobs and causes an increase in polarization (hyperpolarization) of the subjacent membrane of the neuron…"

In other words, if inhibition is caused by the same action potential, we cannot see it as a NEGATIVE response. Experiments demonstrate that this is the case, falsifying Adrian and Lucas ideas.

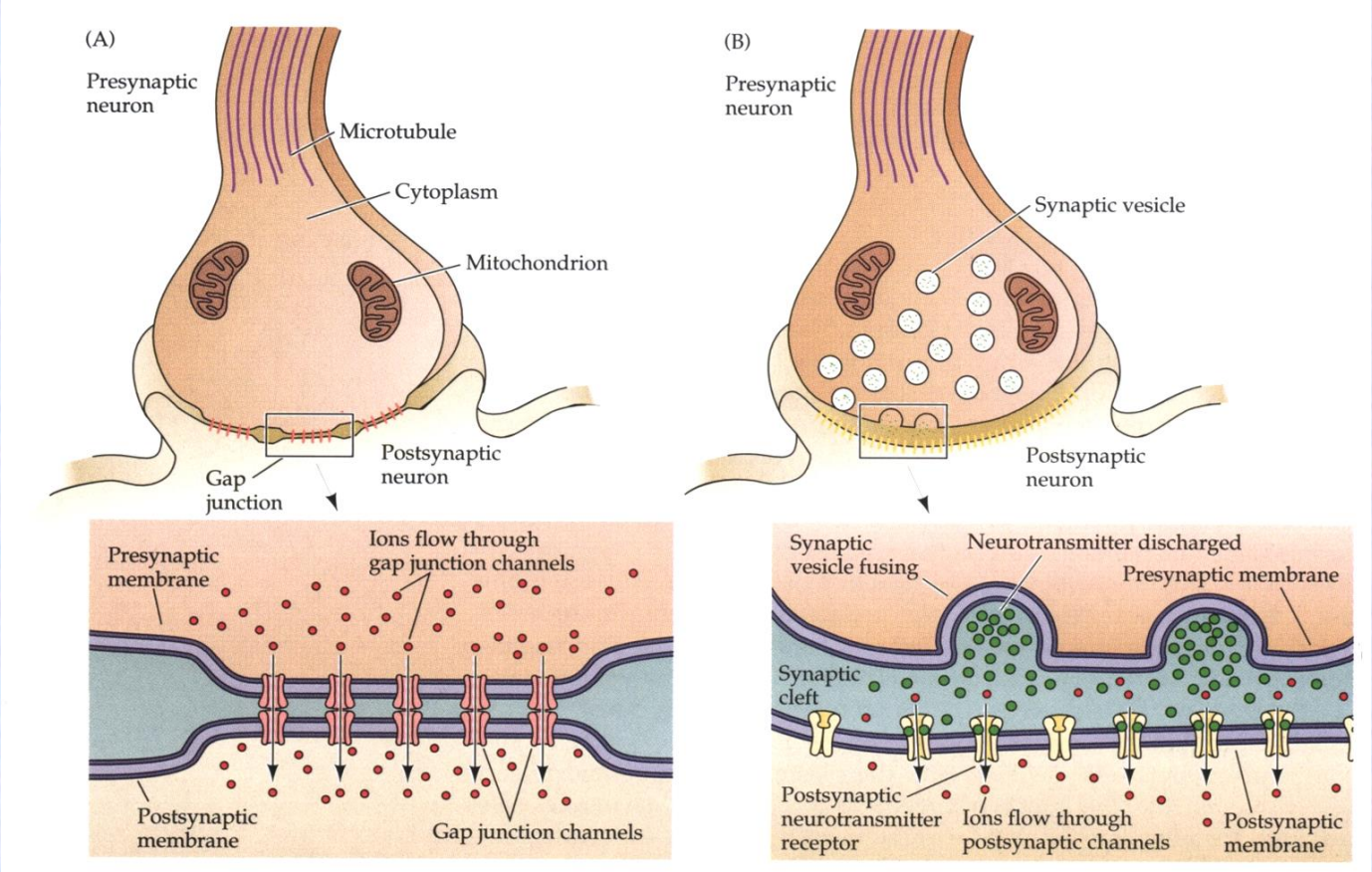
With this simple experiment but sophisticated argument the electric theory of synaptic conduction was definitively discarded. You can recognize a language (falsification) inherited from Karl Popper, the famous epistemologist with whom Eccles was good friend.

Current view of excitatory and inhibitory synapses



Electrical synapses

A relatively small (but still critical for some function) number of ELECTRICAL synapses do exist, particularly in the developing CNS and in specialized areas (retina, reticular nucleus of the thalamus, and a few other CNS areas)



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Conclusions (1):

- Synaptic inhibition is mediated by a chemical mediator
- A substance is released from the presynaptic neuron (I)
- This opens postsynaptic conductances (in B) that, in turn
- Produce a membrane hyperpolarization (in B)
- B remains hyperpolarized (=inhibited) during A activation
- Such hyperpolarization is the core of synaptic inhibition

Conclusions (2):

The concept of chemical synaptic transmission is easily extended to excitatory (vs. inhibitory) transmission

synaptic transmission theory

Eccles support the ELECTRICAL

Dale support the CHEMICAL

Is synaptic transmission Chemical or Electrical ?