Synaptic transmission I

Neurobiology course, 2018/10

Chun XU

Menu

- The term ‘synapse”
- Scientific progress on synaptic transmission.
- The debate about Chemical synapse and Electrical synapse
- The cellular machineries for synaptic transmission
- The modern era of ‘synapse’
- Synapse and beyond

The frontiers of modern neuroscience

- The ultimate goal of neural science is to understand how the flow of electrical signals through neural circuits gives rise to mind—to how we perceive, act, think, learn, and remember.

- How does the brain develop?
- How do nerve cells in the brain communicate with one another?
- How do different patterns of interconnections give rise to different perceptions and motor acts?
- How is the communication between neurons modified by experience?
- How is that communication altered by disease?

《Principles of Neural Science, 5th edition》

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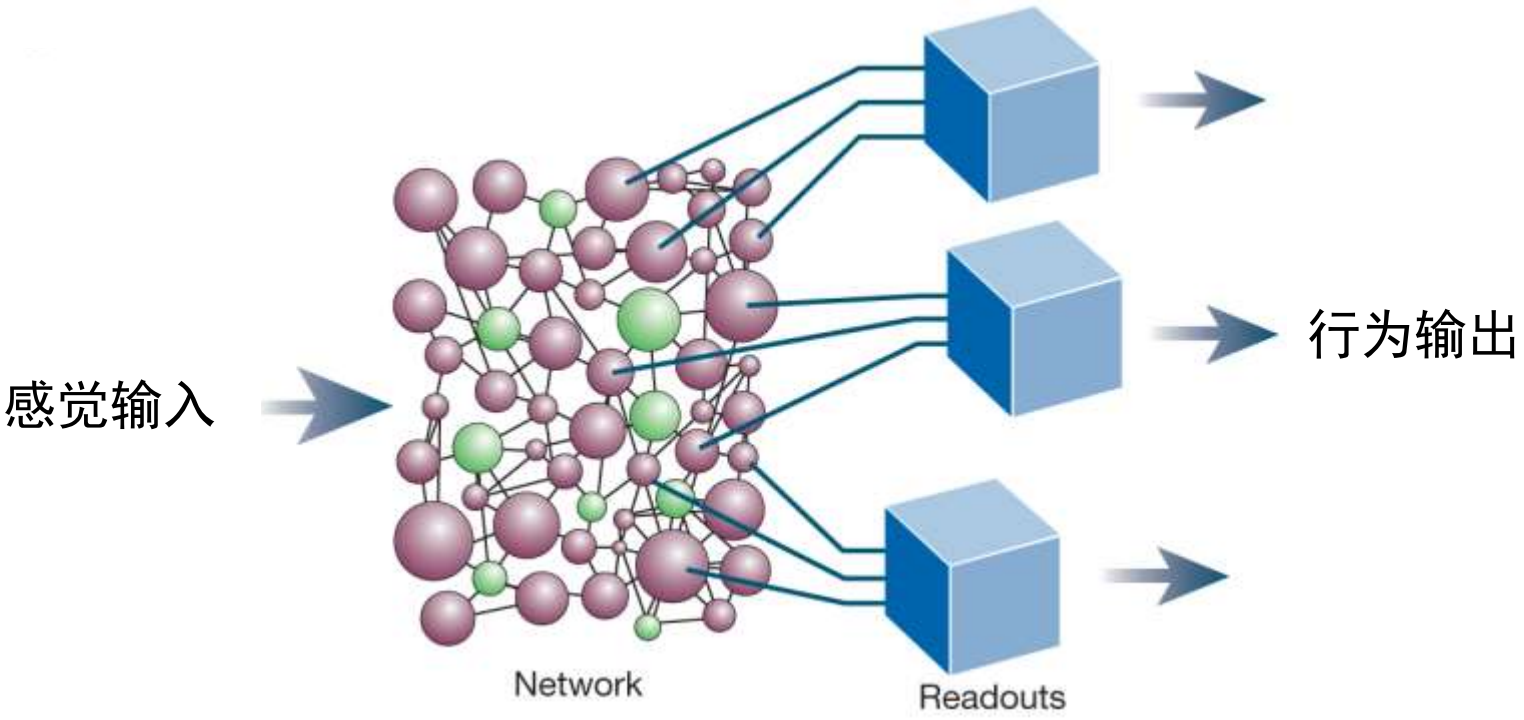
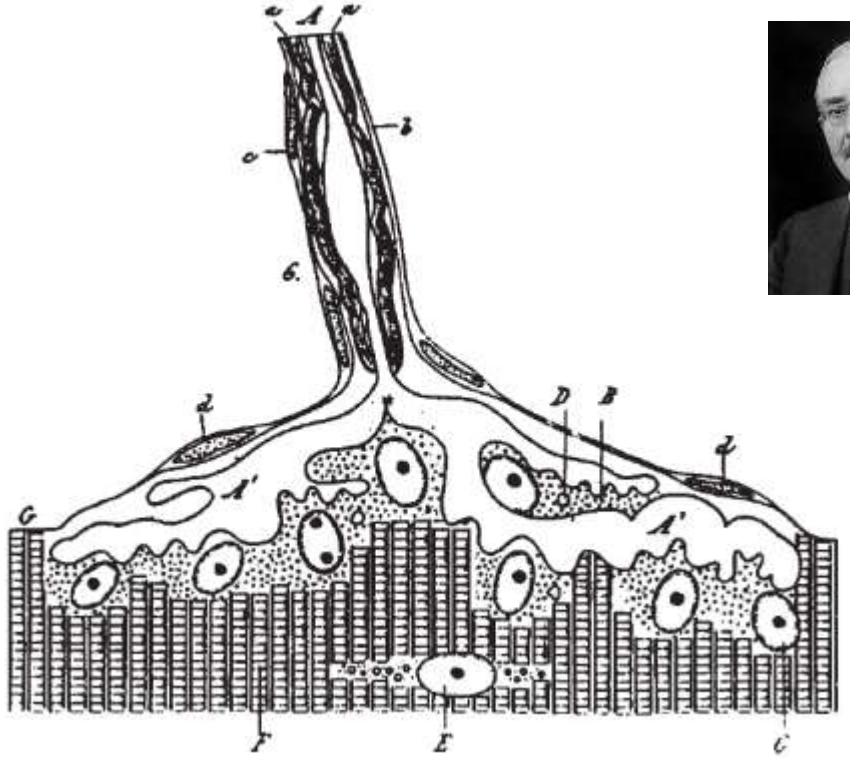
《Principles of Neural Science, 5th edition》

基因 – 分子 – 神经元 – 神经环路 – 行为



神经环路的关键部分：神经元内在特性，连接图谱，突触连接强度和可塑性

The term Synapse by Sherrington in 1897



Schematic summary view of the mammalian neuromuscular junction.

'So far as our present knowledge goes, we are led to think that the tip of a twig of the arborescence is not continuous with but merely in contact with the substance of the dendrite or cell body on which it impinges. Such a special connection of one nerve cell with another might be called a synapse.'

Sherrington, C.S. (1897) in Textbook of Physiology (Foster, M., ed.), p. 60

While Ramóny Cajal was laying the anatomical basis for modern neuroscience, Sherrington's work was laying the basis for the physiological principles

The scientific history for chemical synaptic transmission

Emil DuBois-Reymond, 1877

Thomas Elliott

1904

Impulses by adrenaline

Walter Dixon

1907

Muscarine-like substance

Henry Dale

1914

Adrenaline and acetylcholine

Otto Loewi

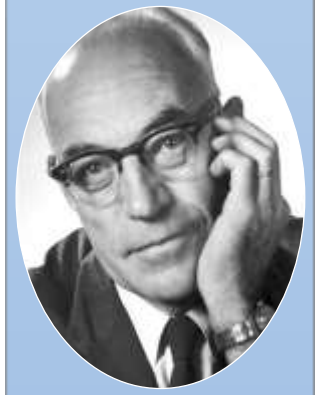
1921

Chemical transmission

Te-Pei Feng

1940

End-plate potential



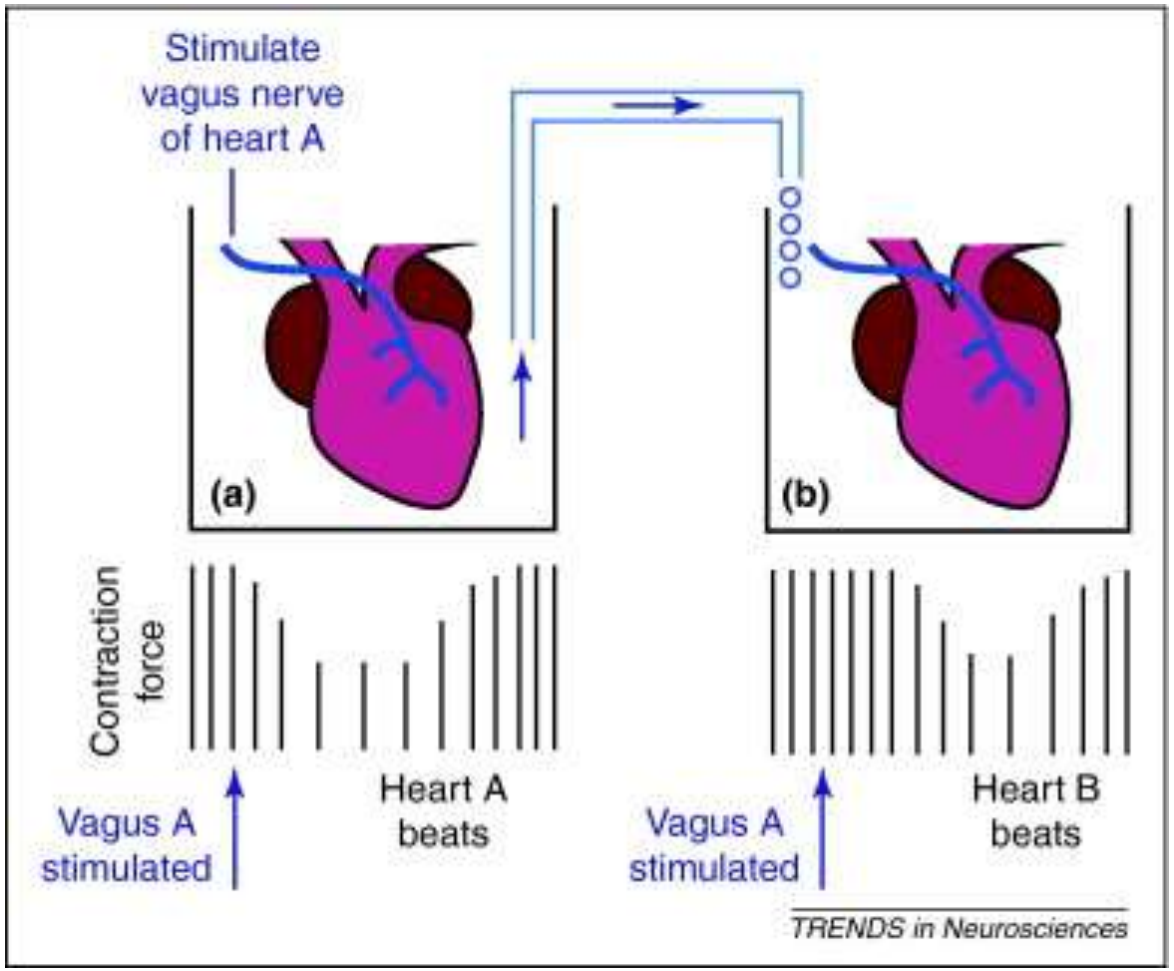
Bernard Katz

1940s

End-plate potential

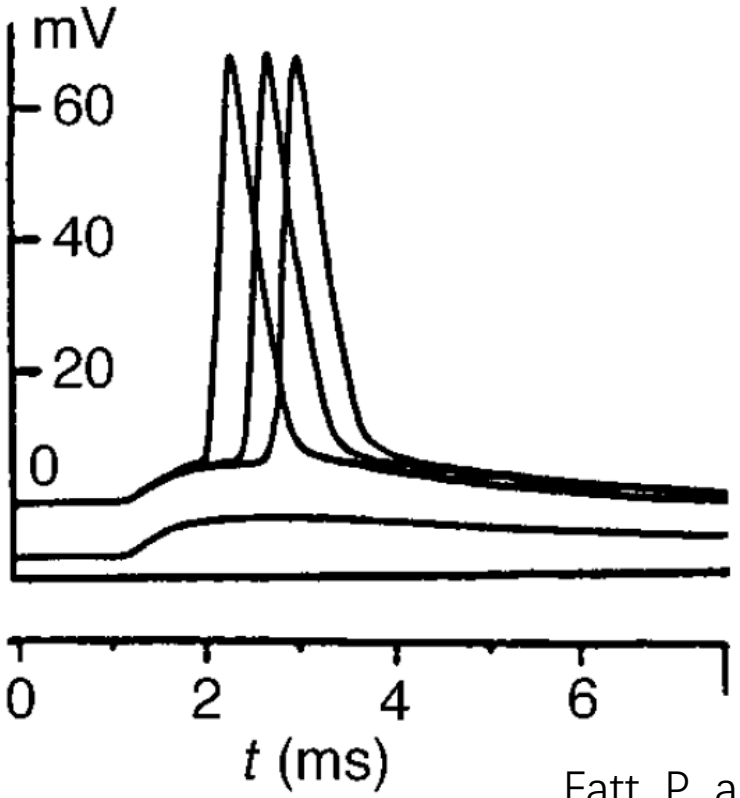
"Either there exists at the boundary of the contractile substance a stimulatory secretion . . . or the phenomenon is electrical in nature." (Reymond, 1877)

One of the key evidences for chemical ‘synaptic’ transmission

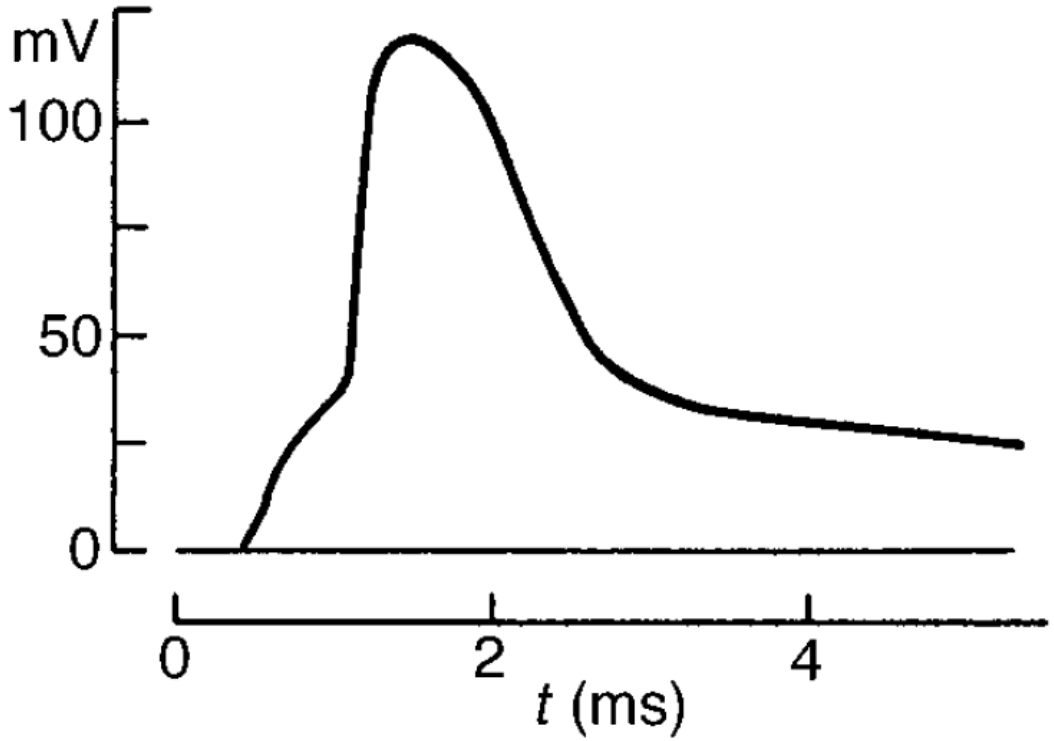


One of the key evidences for chemical synaptic transmission

Presyanptic impulse potential



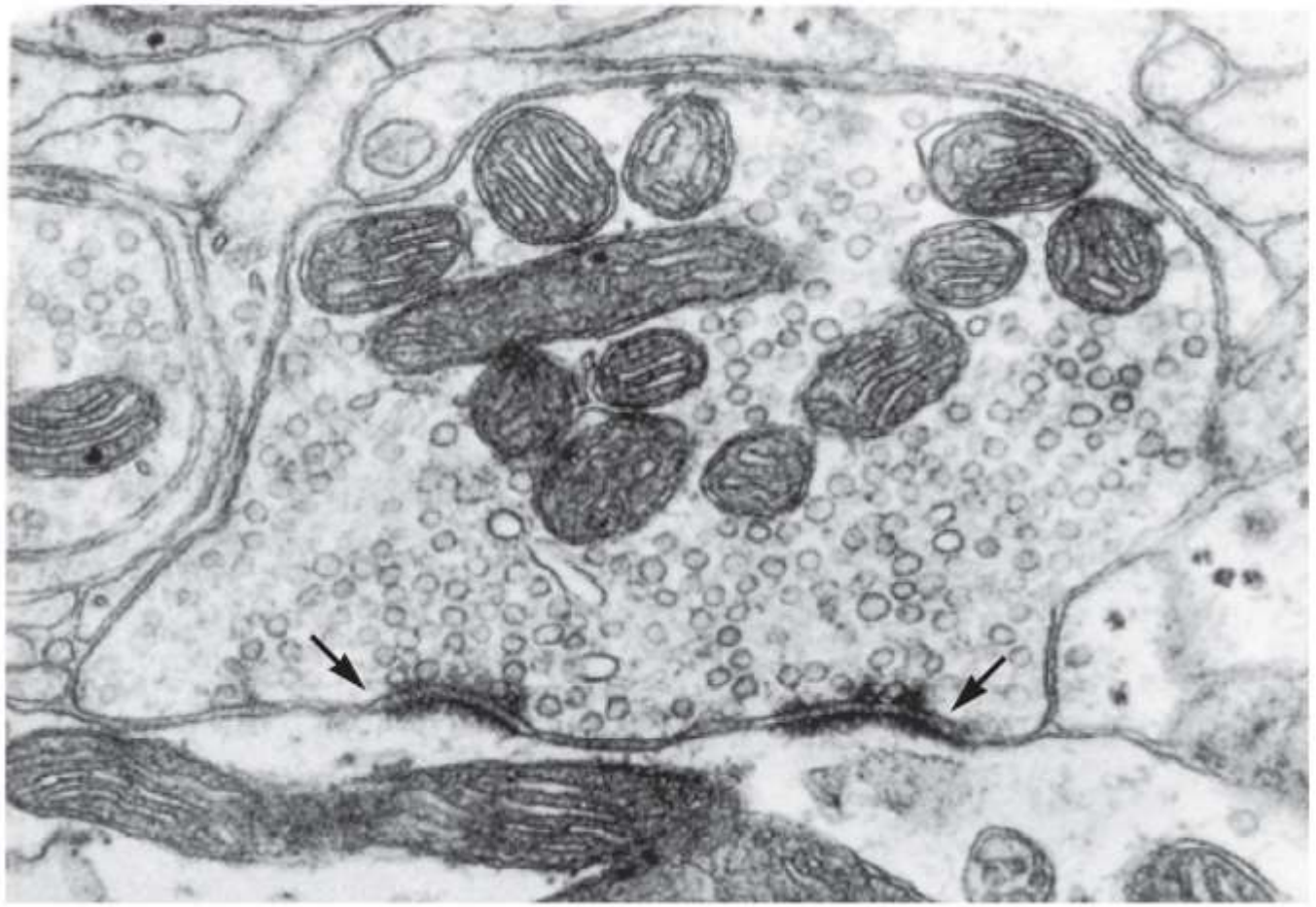
End-plate potential



Fatt, P. and Katz, B. (1950) J. Physiol. 111, 46P–47P

Impulse potential is much smaller than **End-plate potential**

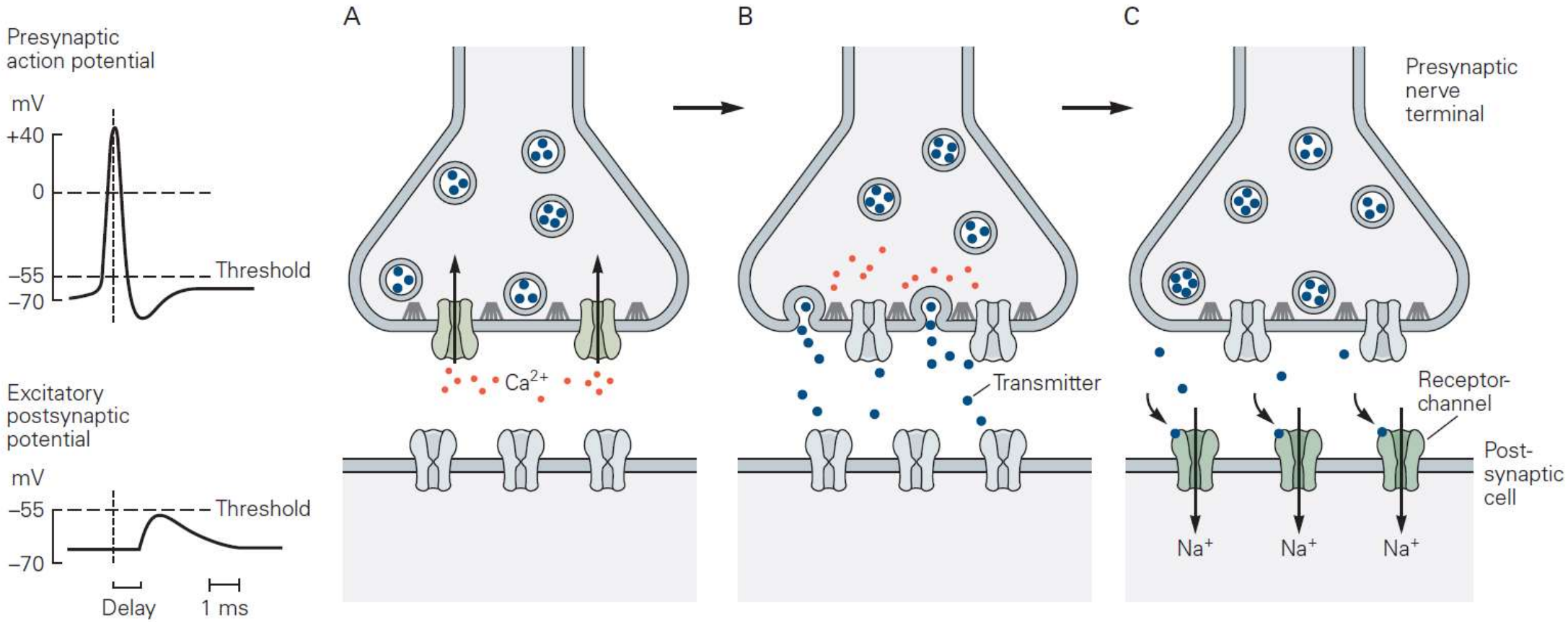
The fine structure of a presynaptic terminal of Chemical Synapse.



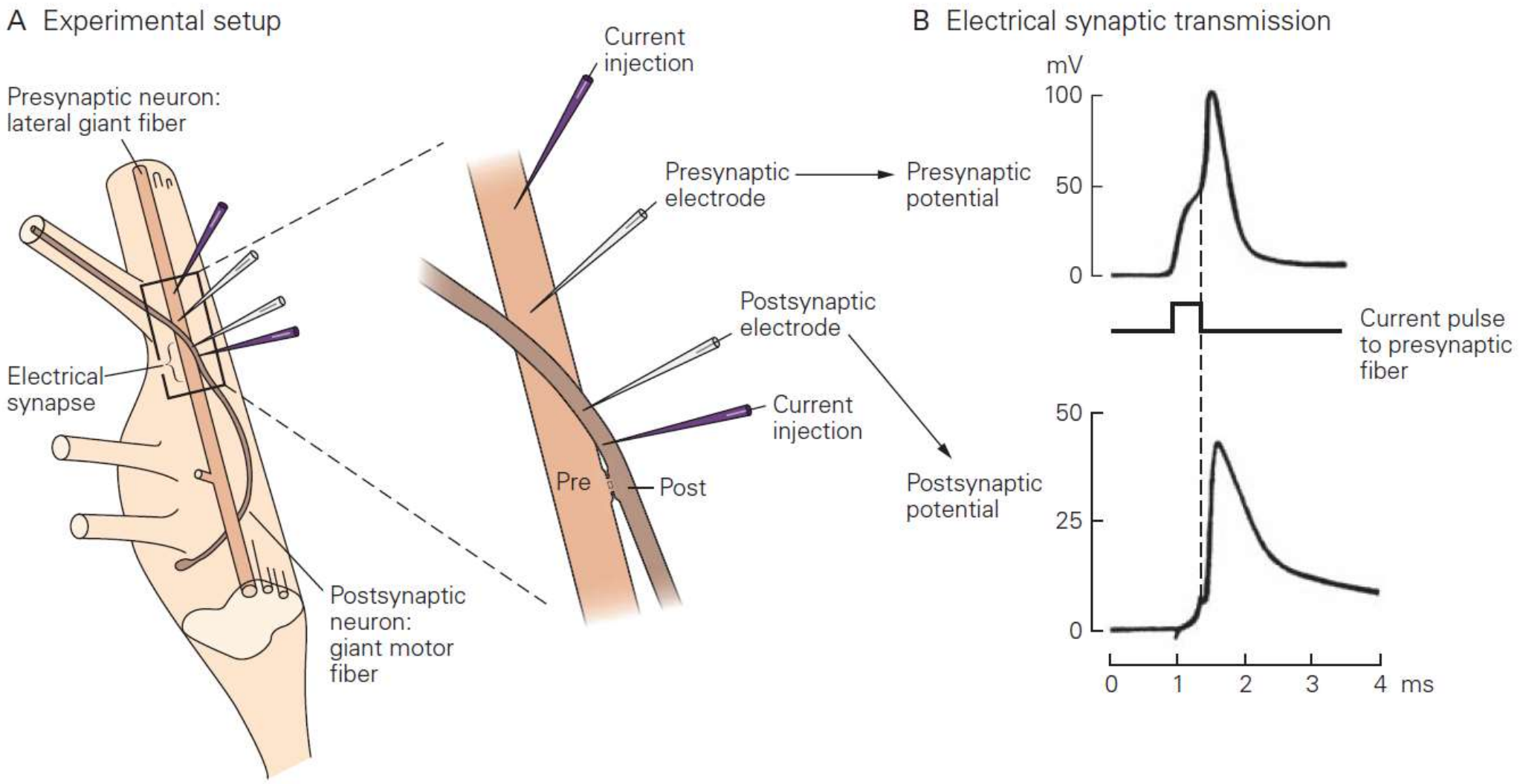
early 1950s

Another key evidences for chemical synaptic transmission by EM technique

Synaptic transmission at chemical synapses

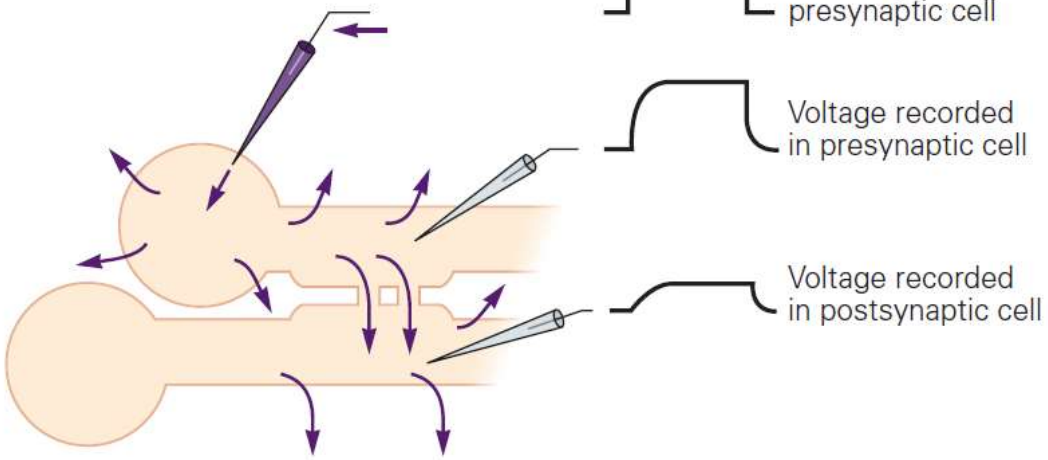


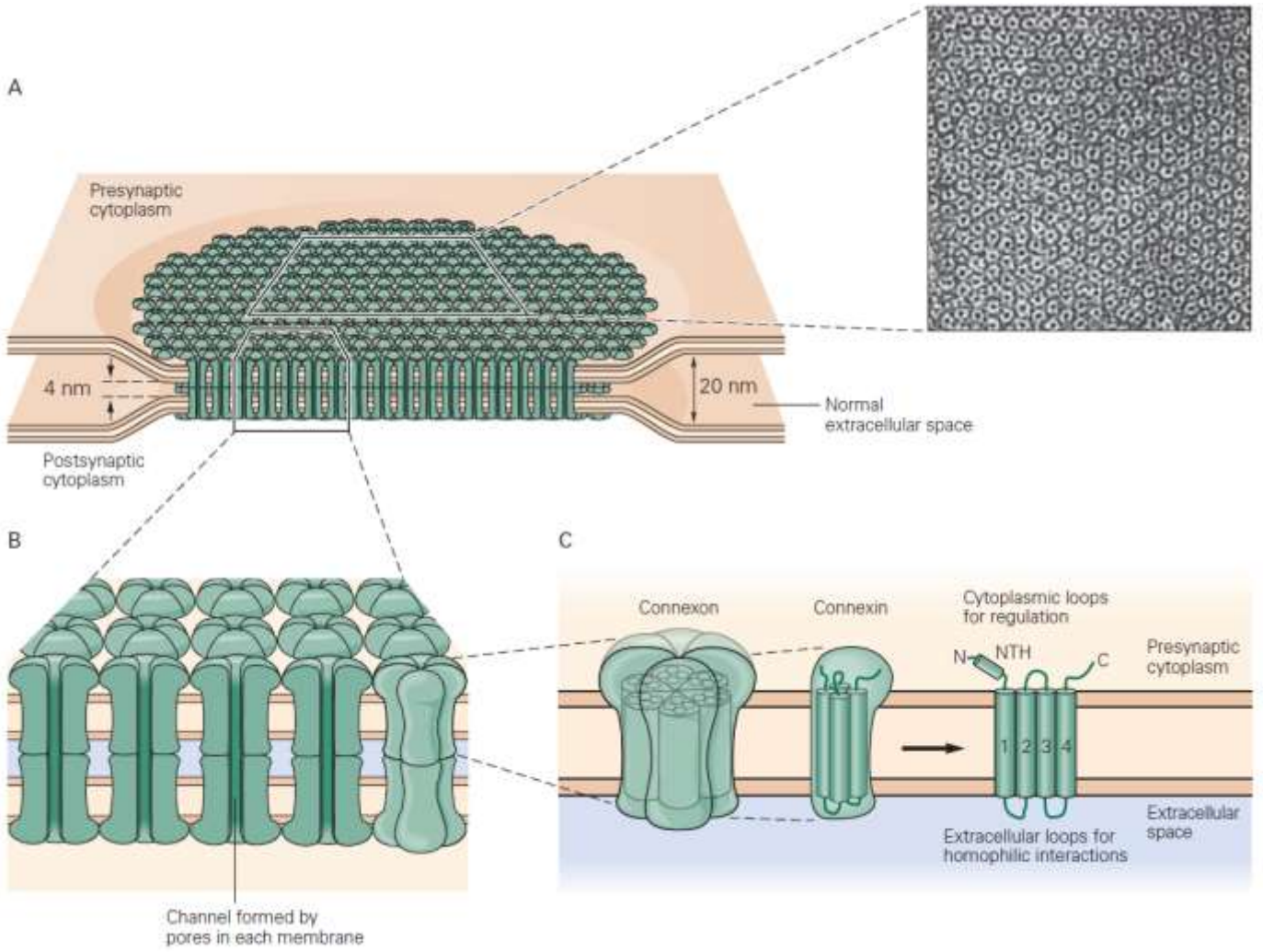
Electrical synaptic transmission



Furshpan and Potter 1957 and 1959

Electrical synaptic transmission

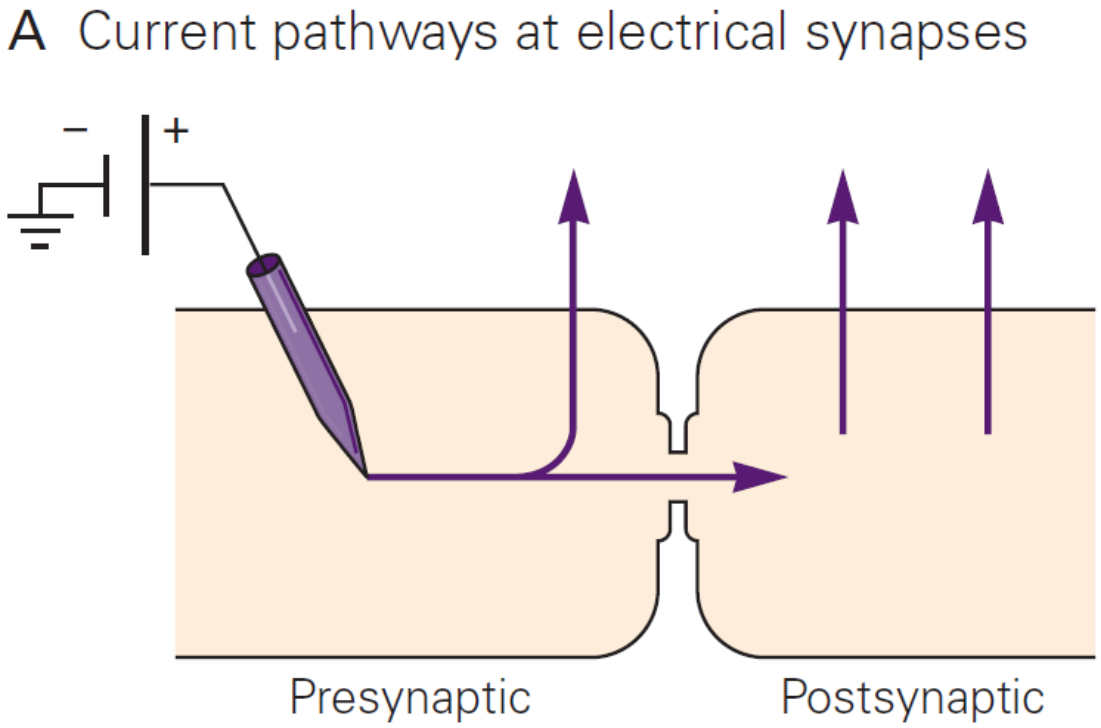




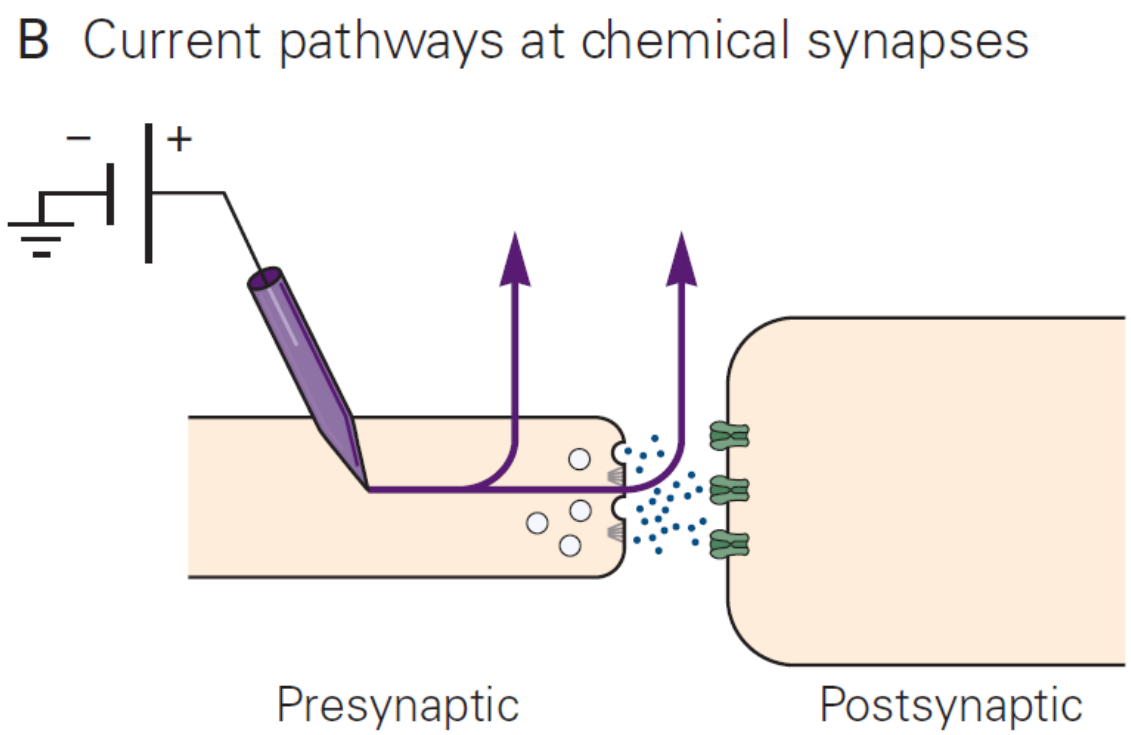
Makowski et al. 1977

Unwin and Zampighi 1980

Neurons communicate through Synapses



John Eccles



Dale and others

Compare electric and chemical synapse

	Electric synapse	Chemical synapse
speed		

Compare electric and chemical synapse

	Electric synapse	Chemical synapse
Speed	Sub-millisecond	1 – 5 ms. Some 0.3 ms
Distance (between Pre & Post)	Very close	20 nm
Amplitude (signal)	Attenuating	Could be amplified
Plasticity	Limited	Bi-directional, wide-range
Signal direction	same	Same or converted
Receptor	channel	Iono- & meta-tropic receptor
Beyond synapse		Neuromodulation

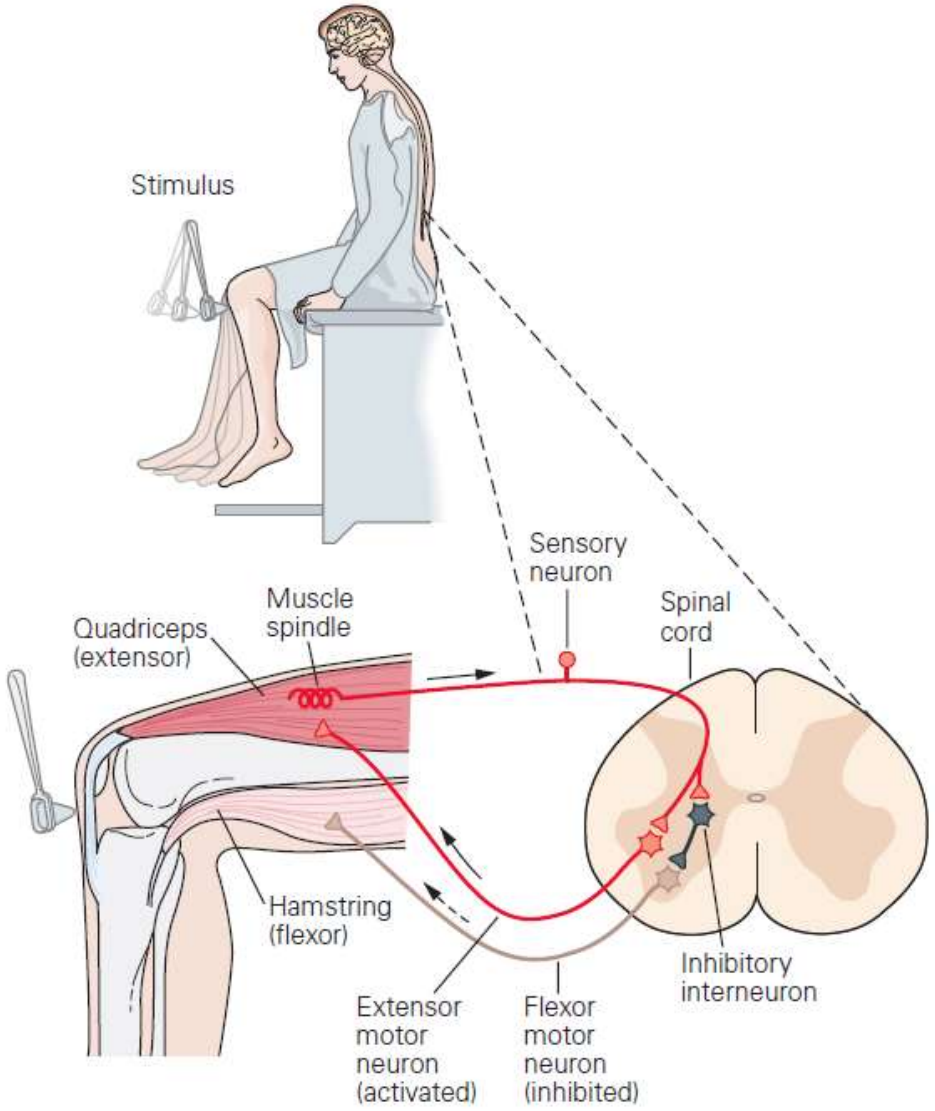
The debate for synaptic transmission in CNS

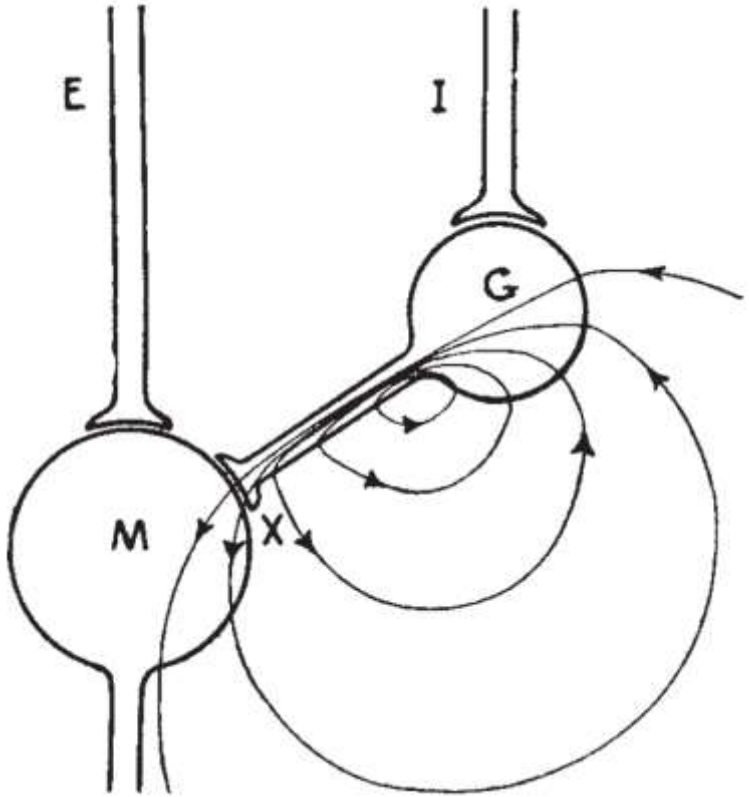
One of the most important experiments in neurophysiology in the twentieth century took place in the physiology laboratories at the University of Otago, New Zealand, in August 1951.

In the Nobel lecture Dale speculated on the possibility of neurochemical transmission in the CNS. He cited the known reservoirs of acetylcholine in the basal ganglia and other brain structures. He tentatively proposed "I take the view however that we need a much larger array of well authenticated facts before we can theorise."

Photograph taken at University of Otago, 1952, just before John Eccles left for Oxford to deliver the Waynflete lectures. Front row, Rosalind Eccles, Jack Coombs, Wilfred Rall, John Eccles, Lawrence Brock, Bronwen Broomfield

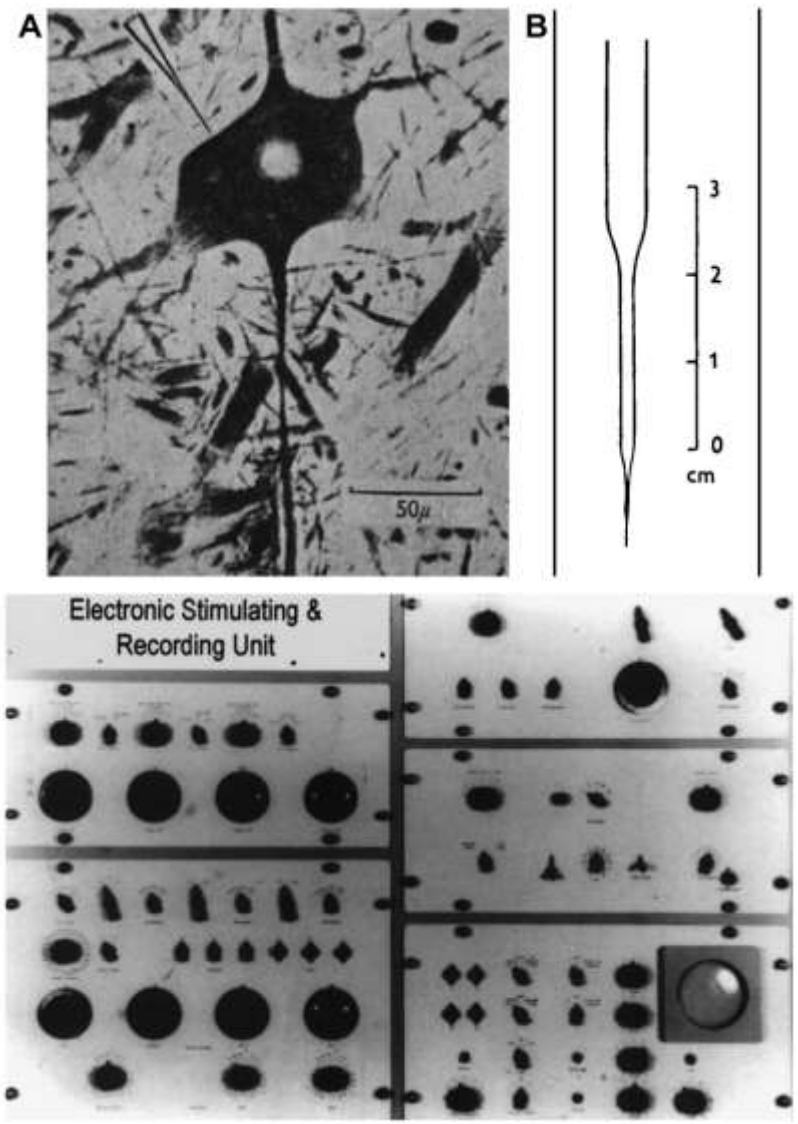
Golgi-cell hypothesis

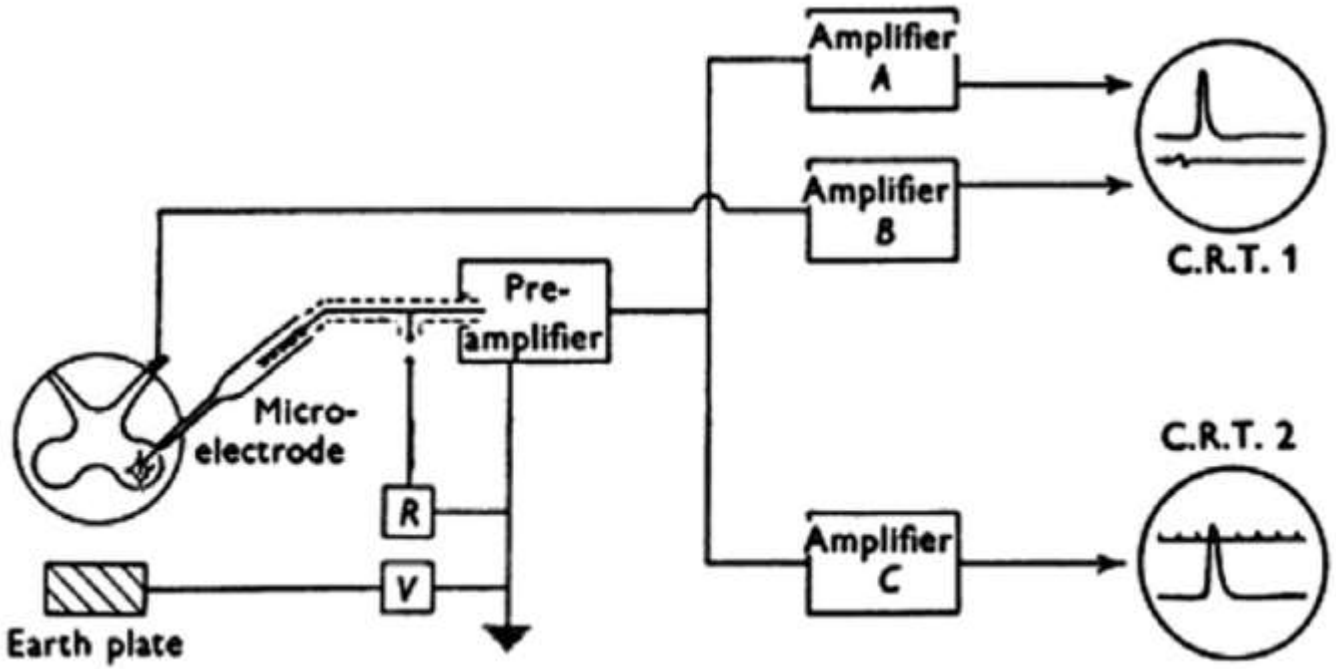




Golgi-cell hypothesis (Brooks & Eccles, 1947)

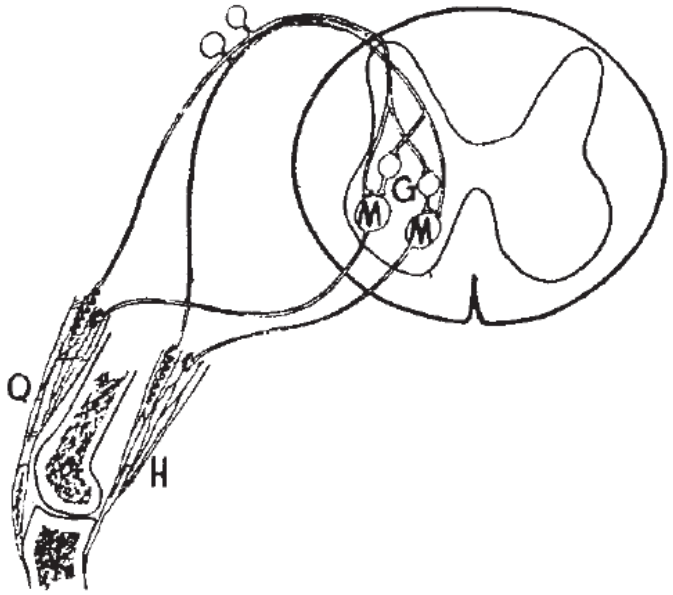
The crucial experiments by the team of Eccles

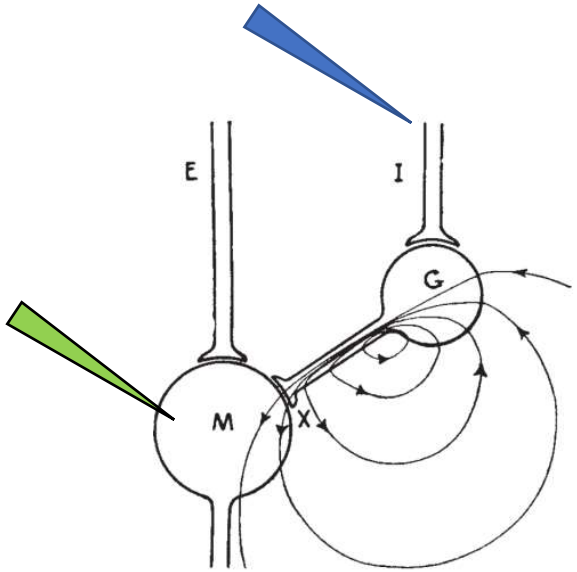


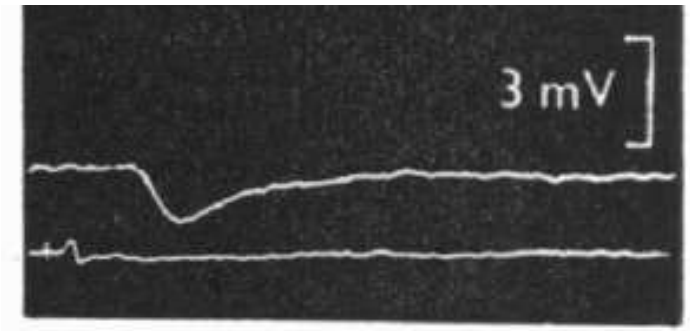


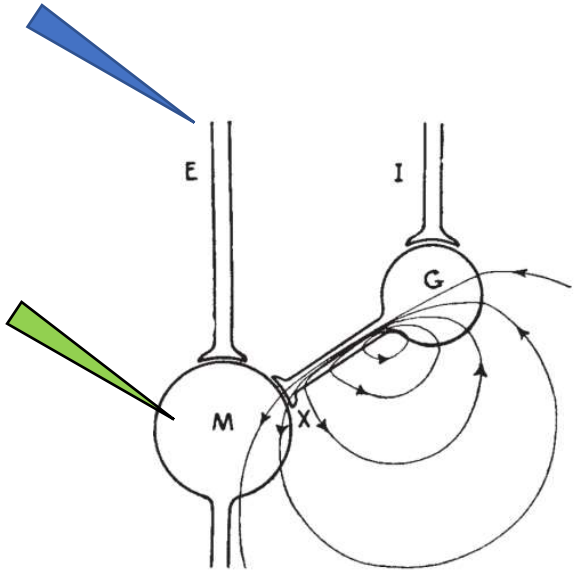
Microelectrode and spinal cord motor neuron. (From Brock LG, Coombs JS, Eccles JC. The recording of potentials from motor-neurones with an intracellular electrode. J Physiol 1952:117:431–60.)

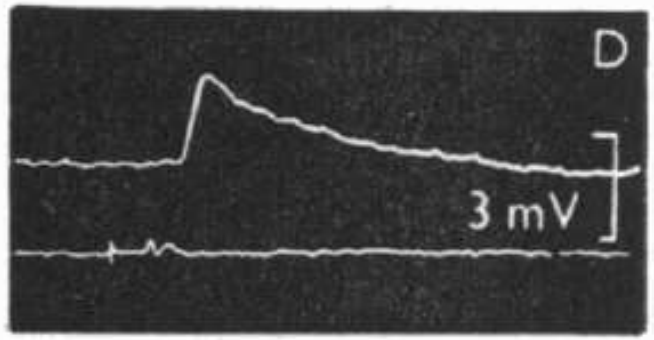
Golgi-cell hypothesis is falsified





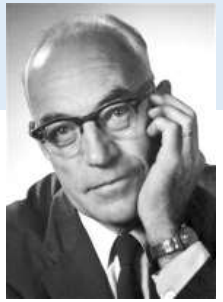






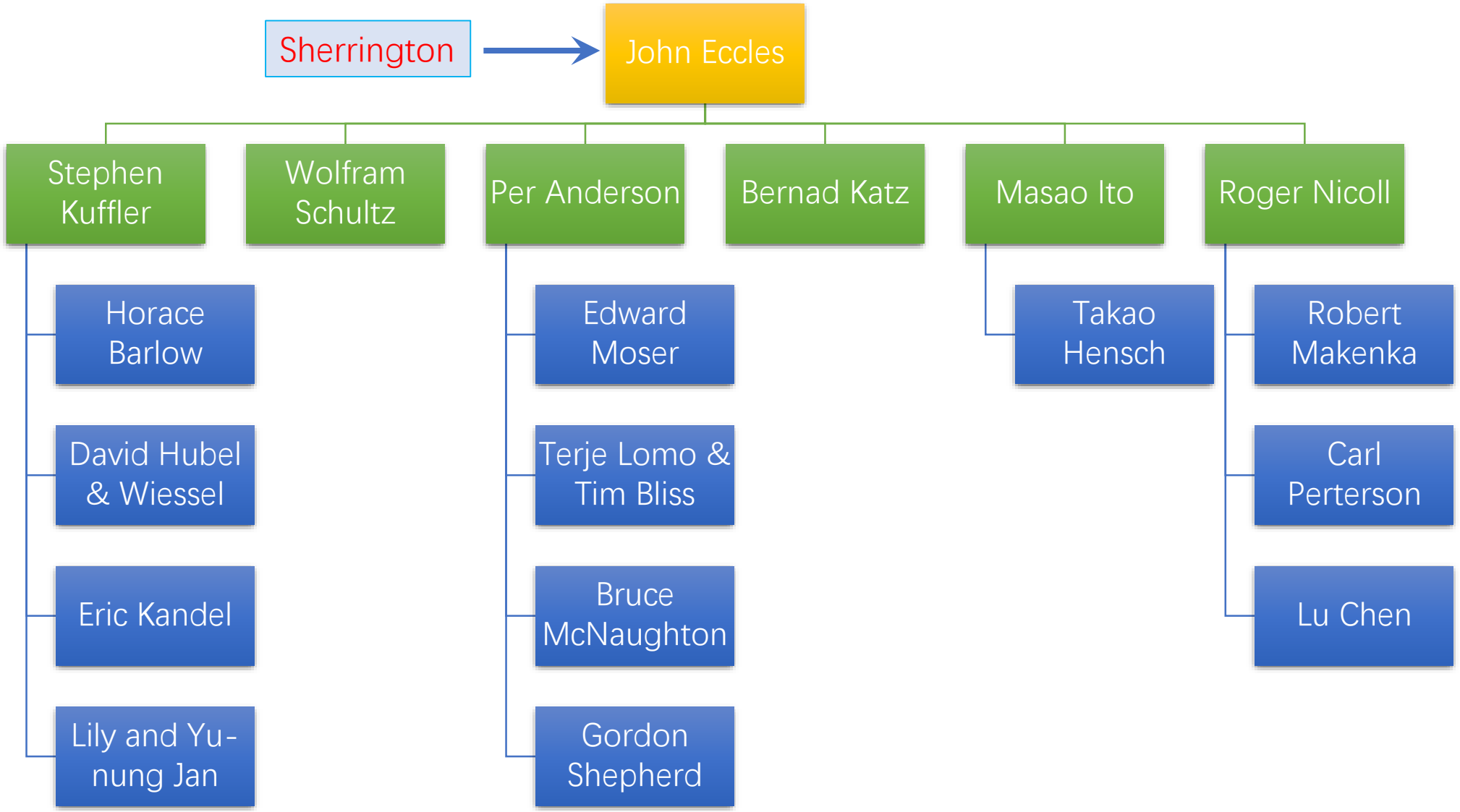
J Physiol 1952:117:431–60

The credit to falsify oneself



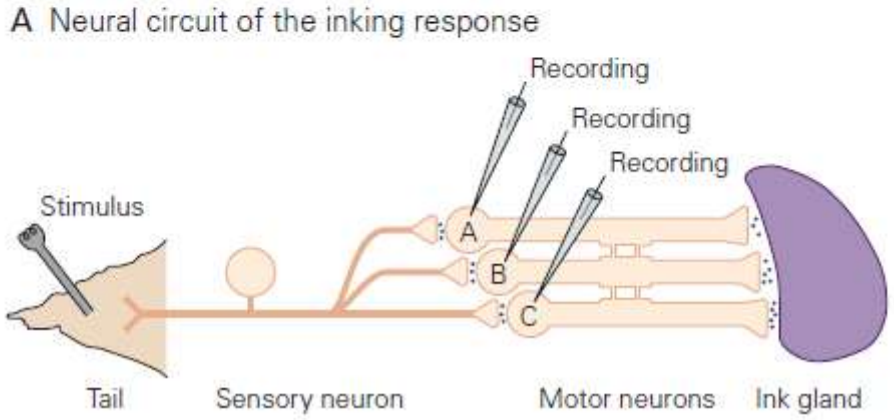
- Eccles and Dale had a long association which began as adversaries, sometimes expressed in tense exchanges. The warmth of their personal relationship and mutual respect is clearly evident in their correspondence. In the closing address at the 1975 Sir Henry Dale Centennial Symposium in Cambridge Eccles remarked, ‘‘It was a great privilege to have been so closely associated with him in those great creative years, first as a sparring partner in opposition and then as a convert. Such great men are infinitely precious in our lives and in our culture.”
- This remarkable experiment demonstrated the tenacity of John Eccles to pursue scientific research even if the outcome could falsify his previously strongly held views. This important chapter in the history of neuroscience demonstrates the collaboration of scientists in different disciplines, establishing the mechanism by which neurons communicate in the CNS.

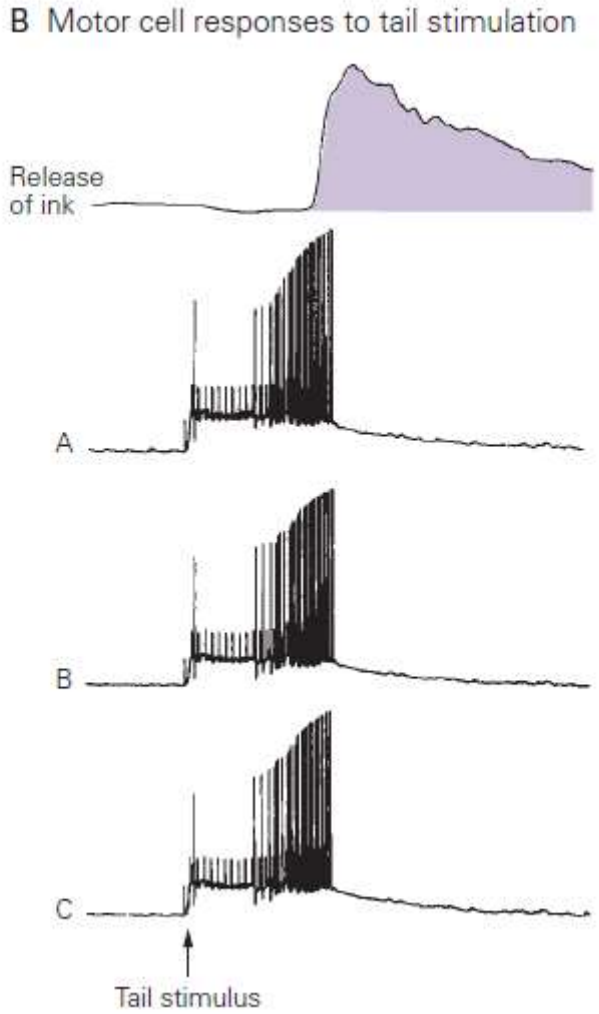
The scientific family tree of John Eccles



What could be electrical synapses good for?

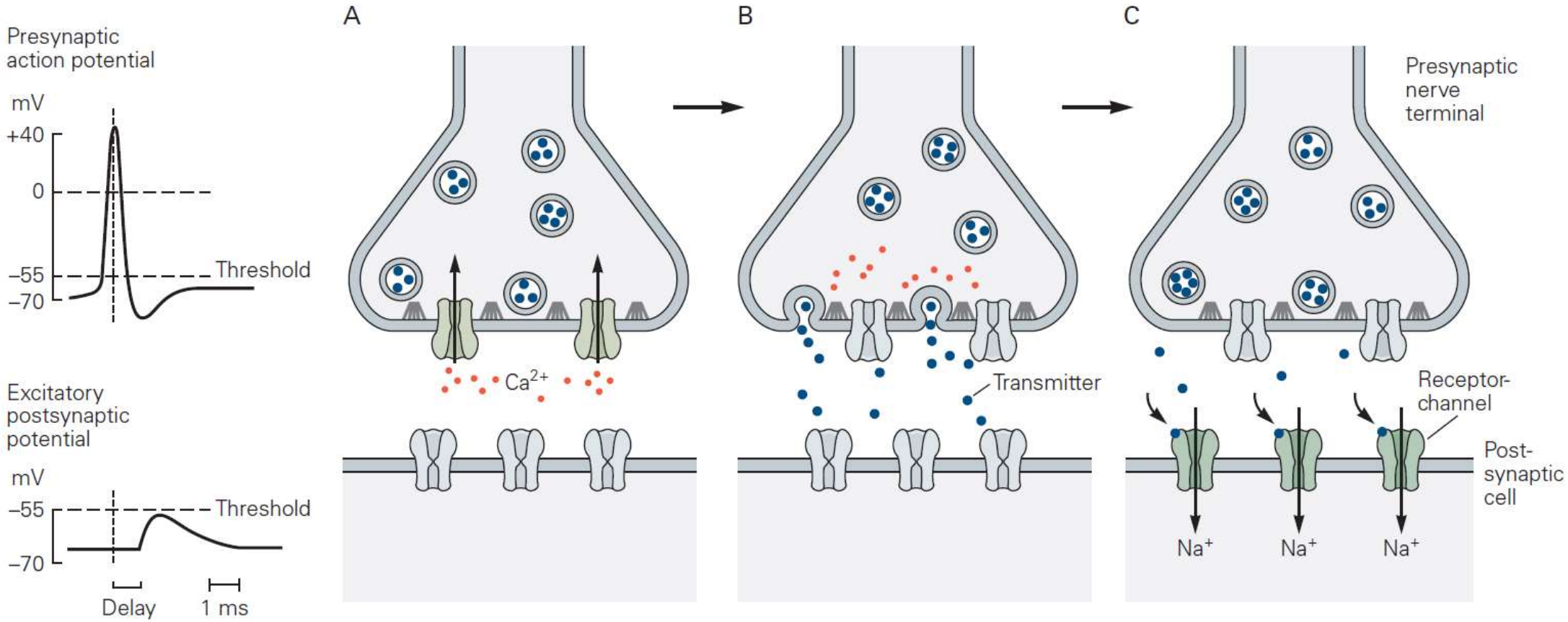
Electrically coupled motor neurons produce synchronous behaviors





Carew and Kandel 1976

Synaptic transmission at chemical synapses

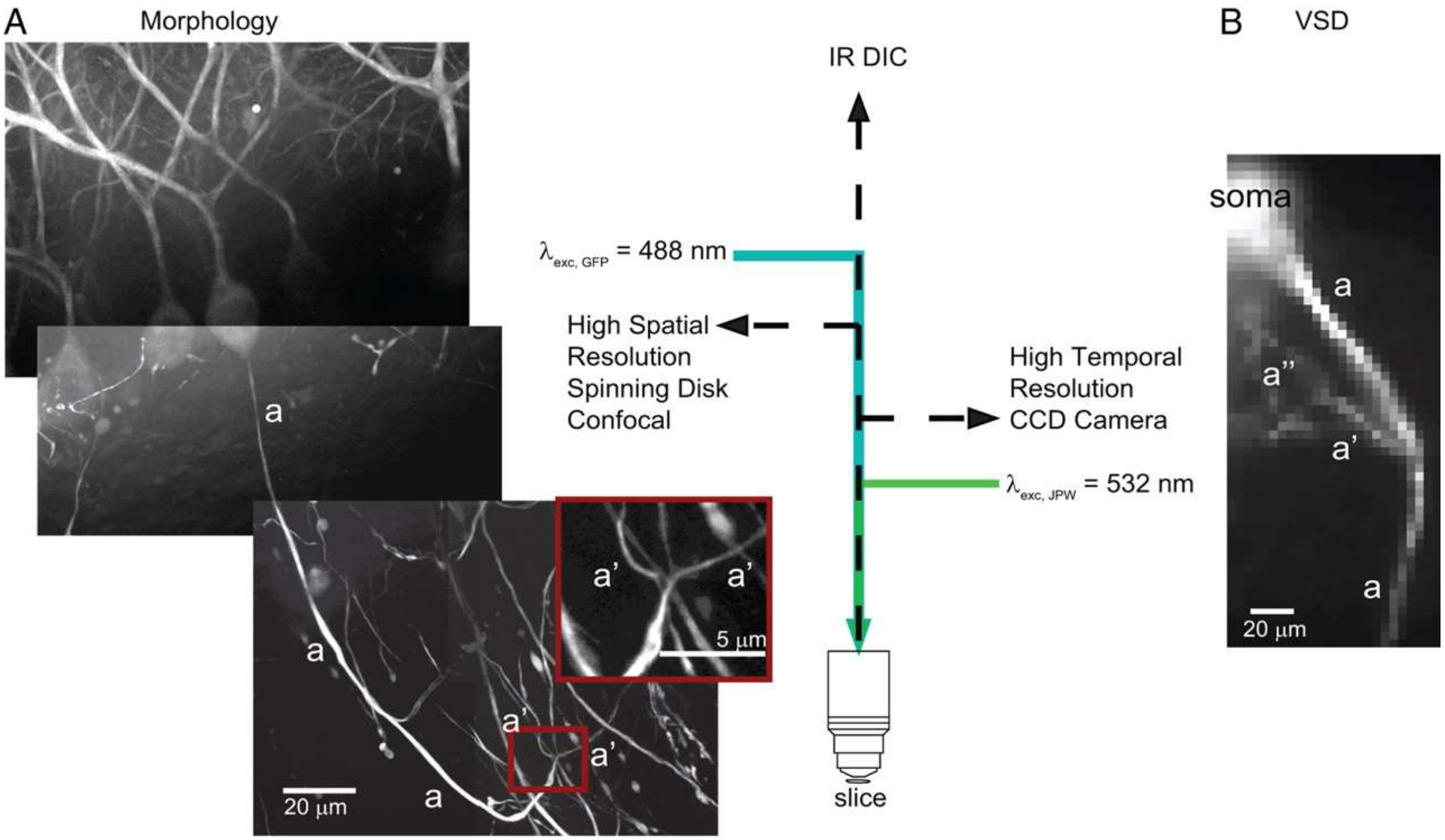


With some exceptions, the synapse consists of three components: (1) the terminals of the presynaptic axon, (2) a target on the postsynaptic cell, and (3) a zone of apposition.

1) Action potential generated
2) Propagate into axon terminals
3) Transmitter release
4) Synaptic response

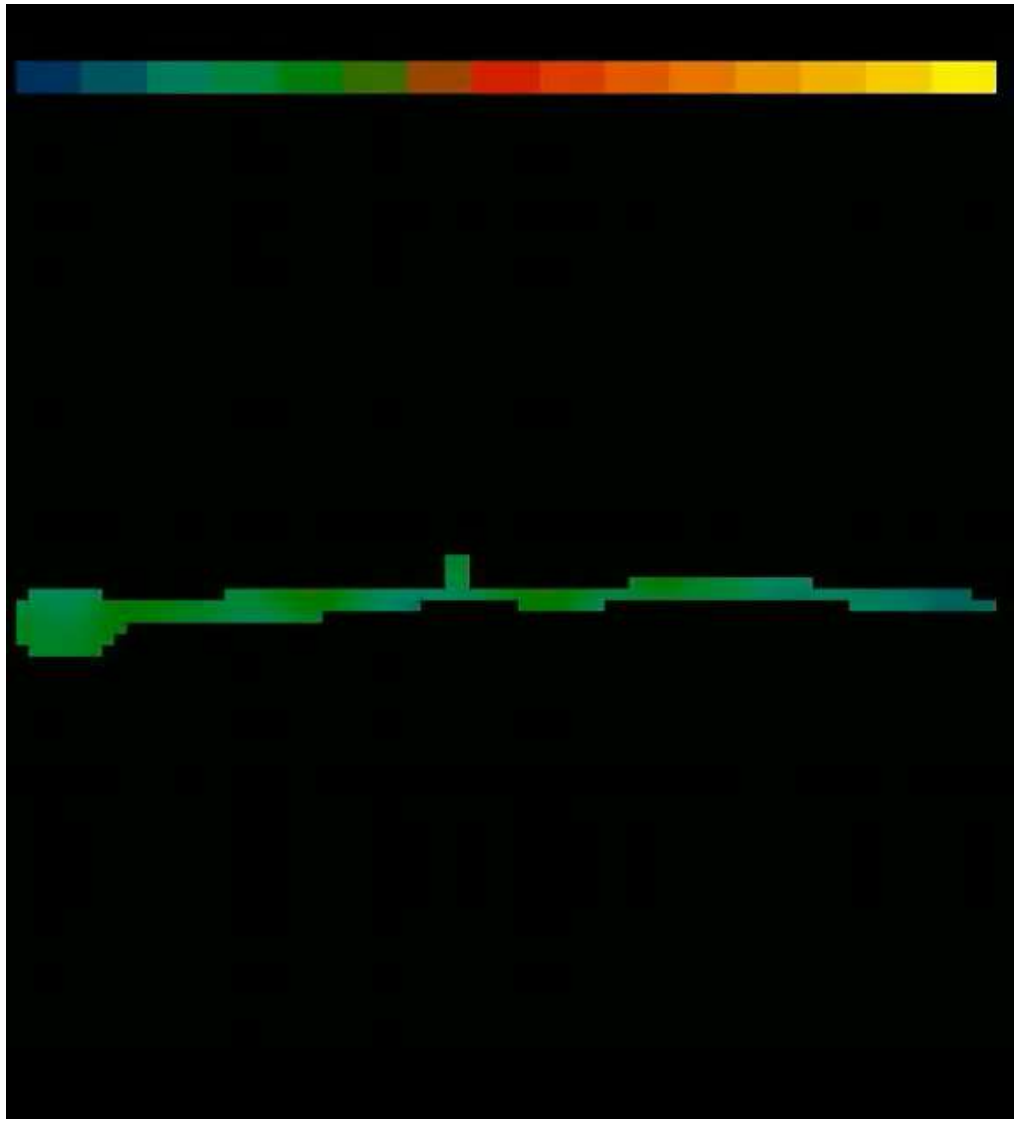
- How is action potential generated?

How is Action potential generated?



Journal of Neuroscience 19 May 2010, 30 (20) 6891-6902

Action potentials initiate in the Purkinje cell axon initial segment



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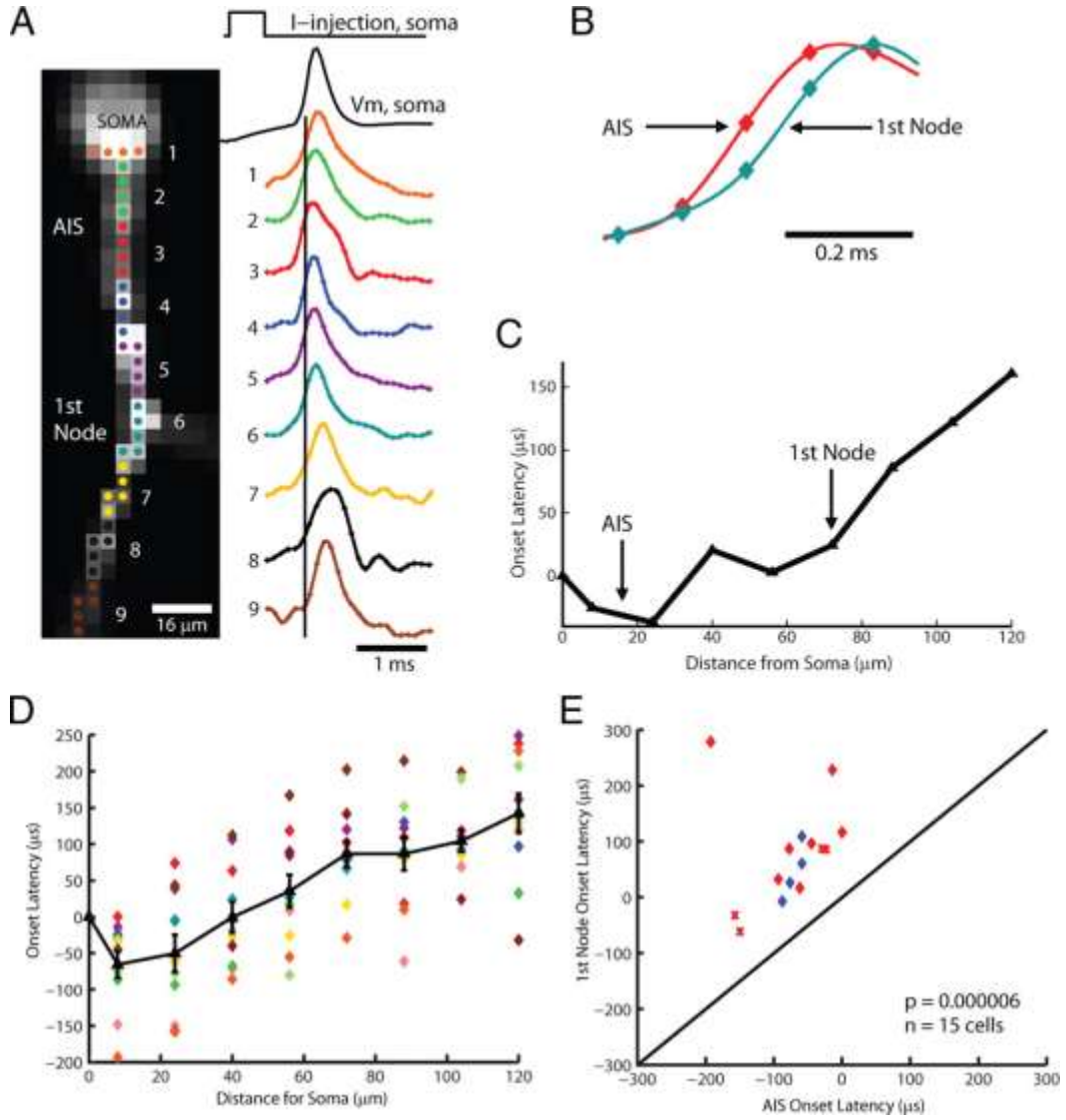

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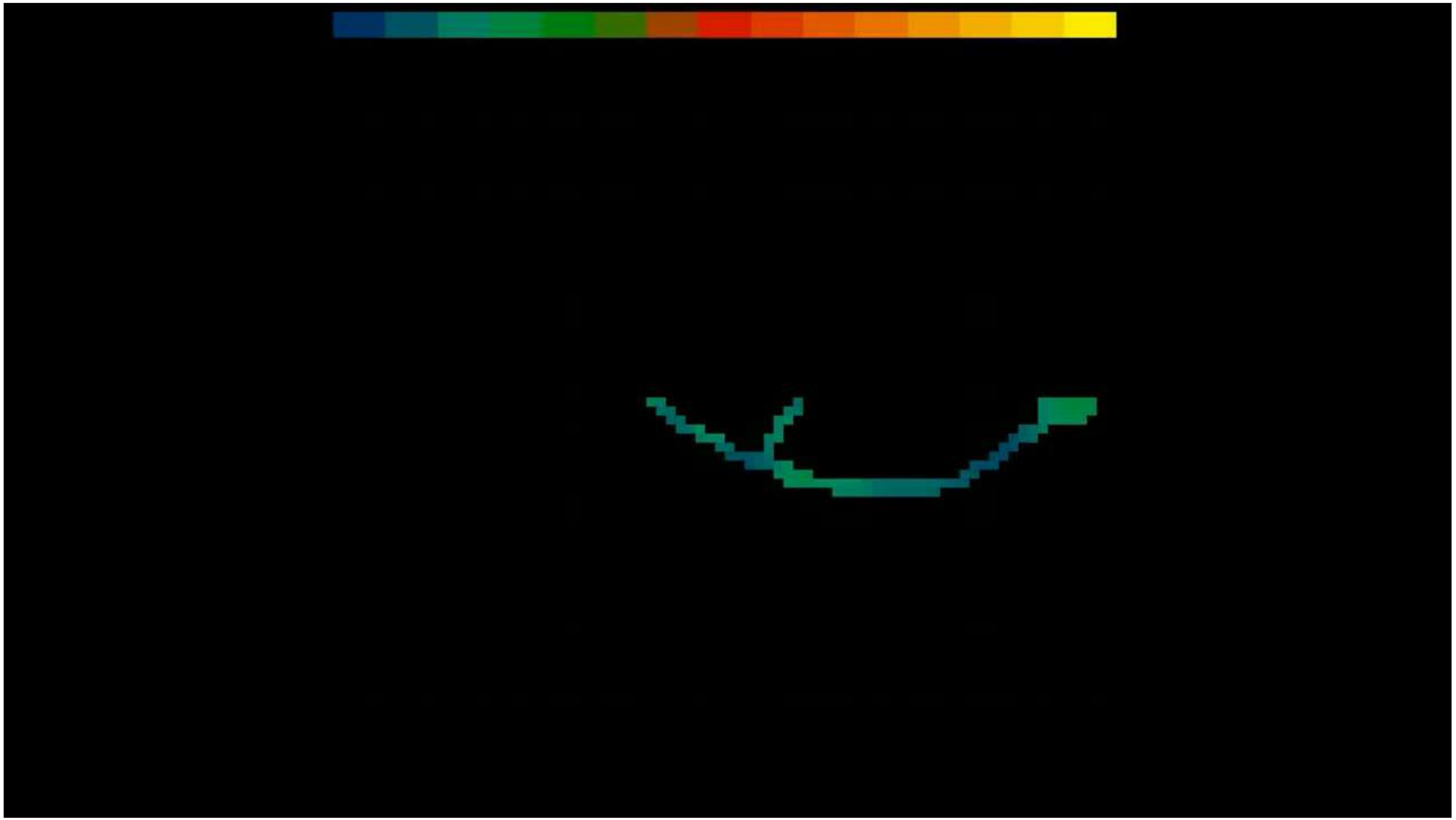
Action potentials propagate into branches



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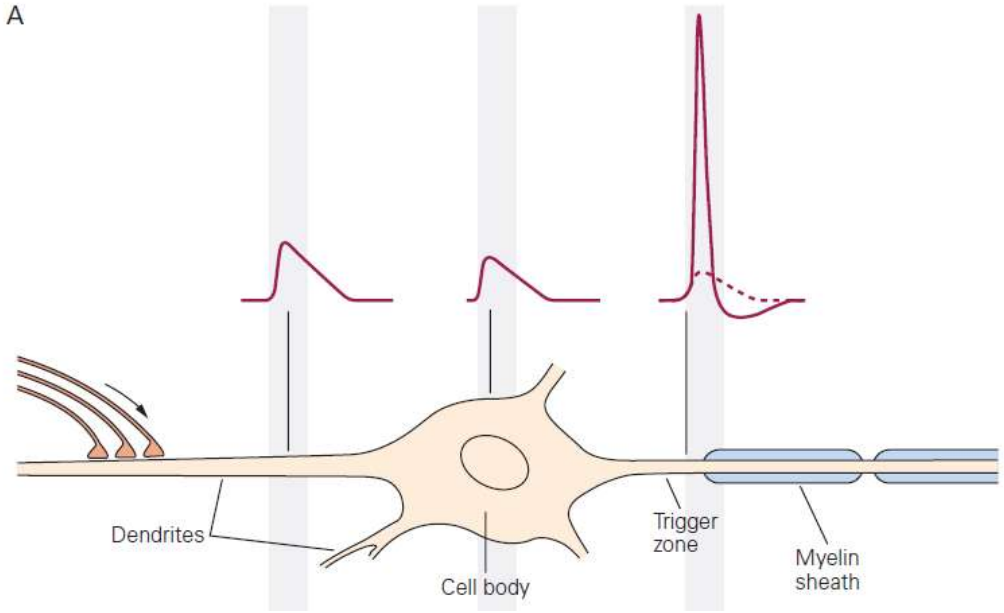
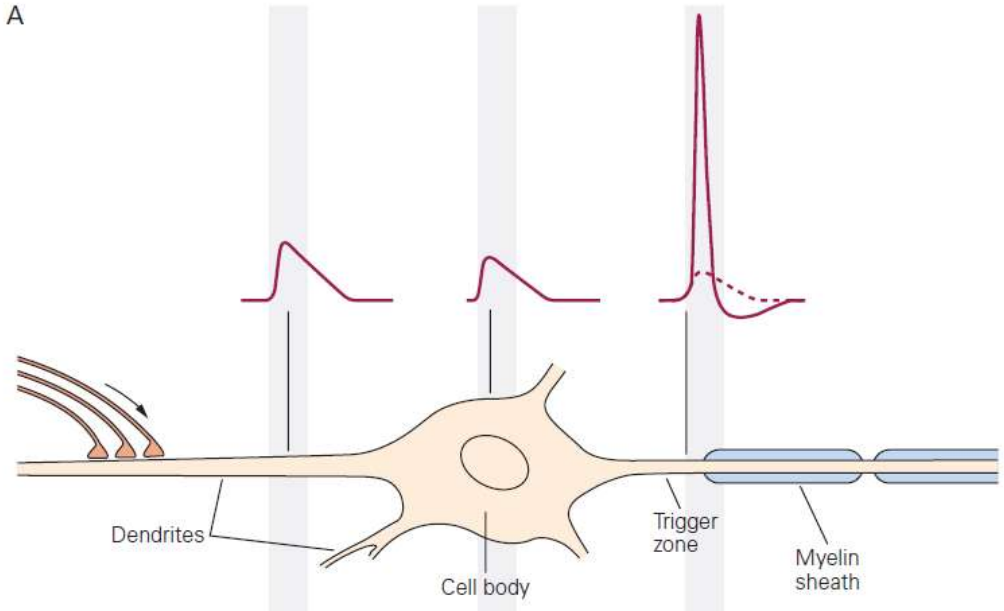
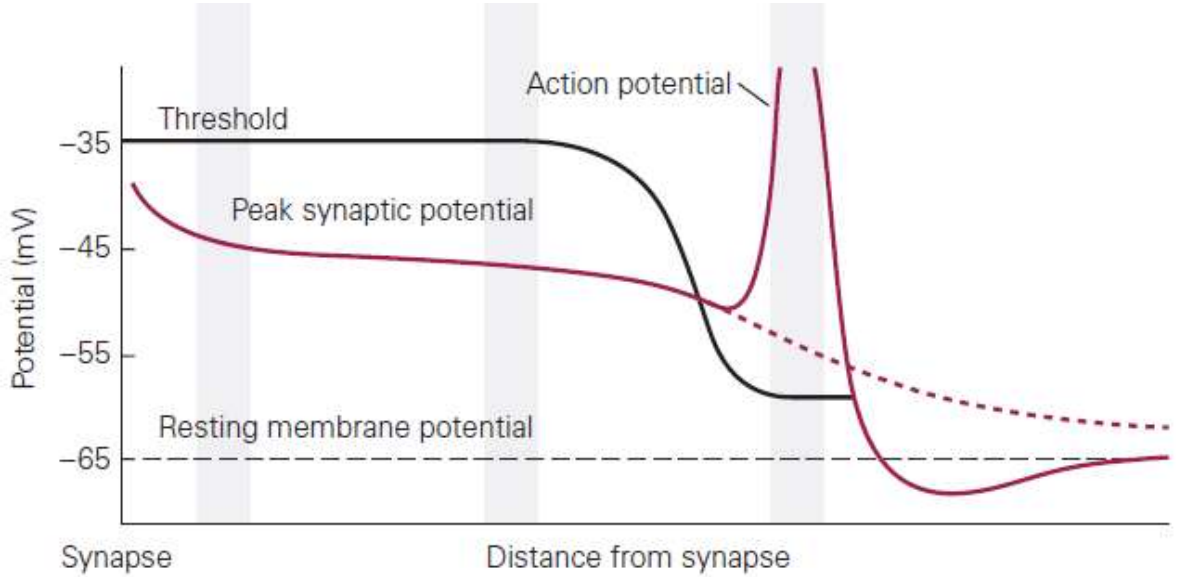
Action potential at the axon initial segment

Why?

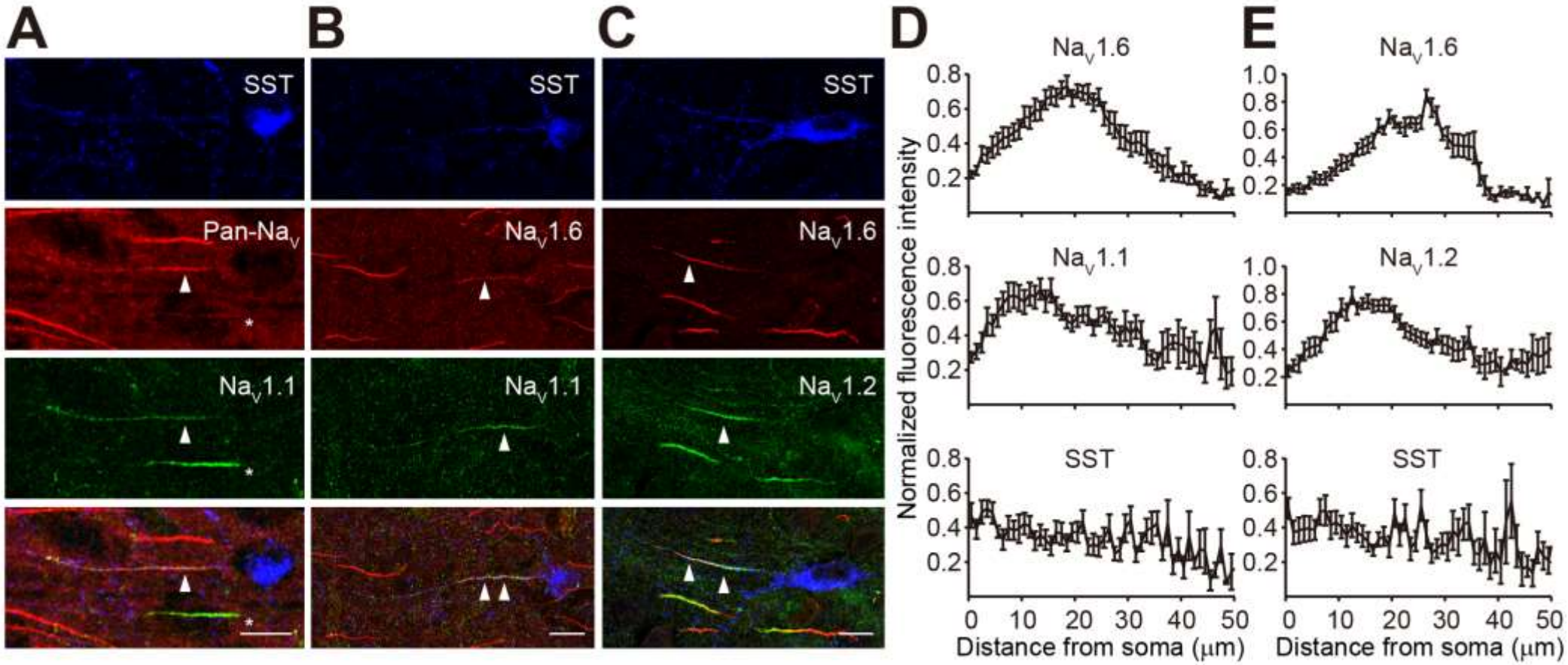


Action potential at the axon initial segment



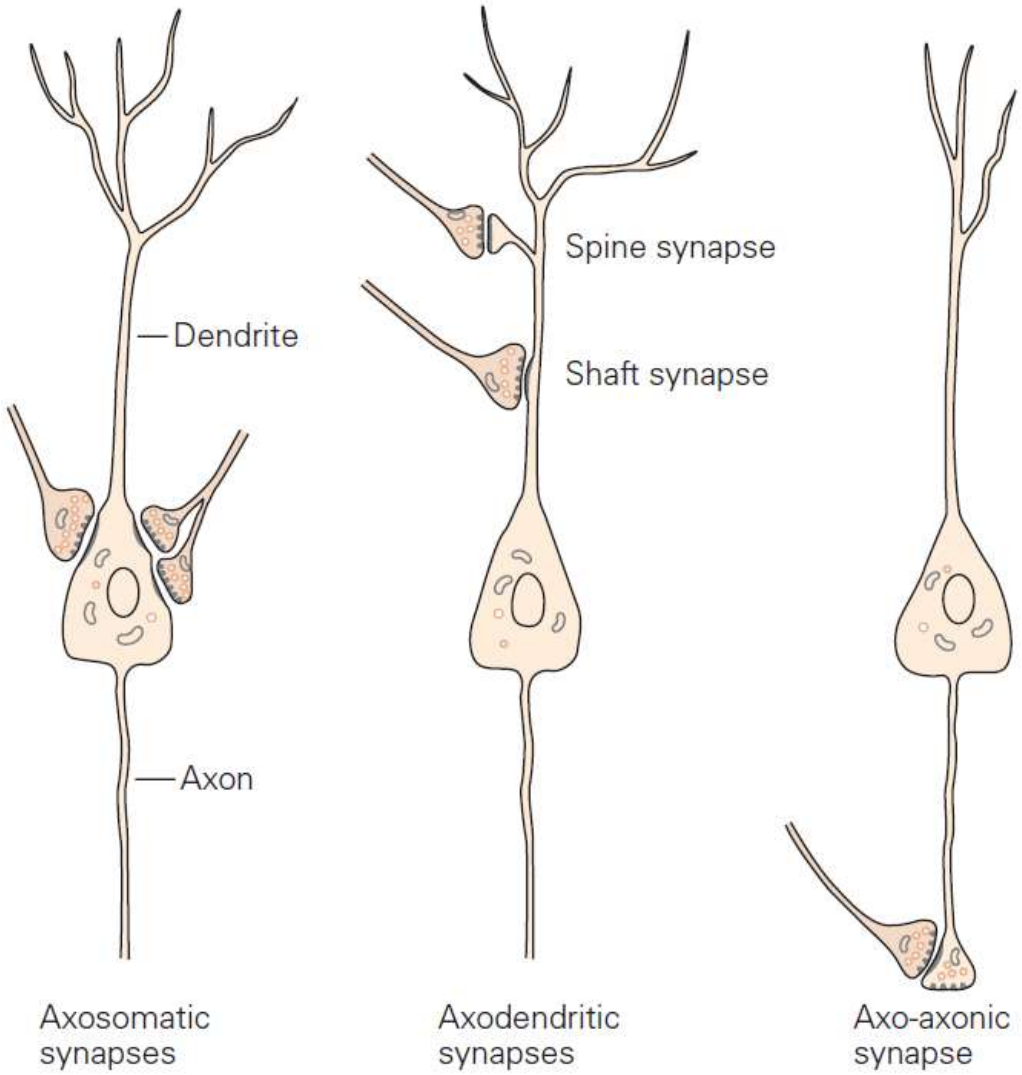


NaV1.2 was found accumulated at AIS of SST



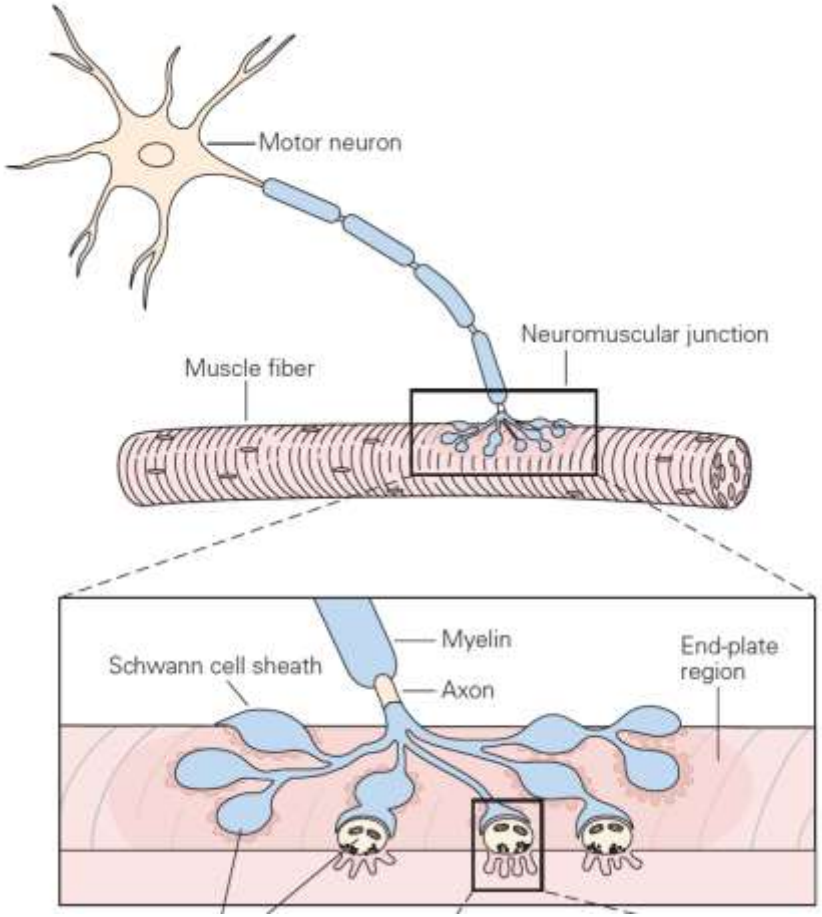
Yousheng Shu Lab, 2014

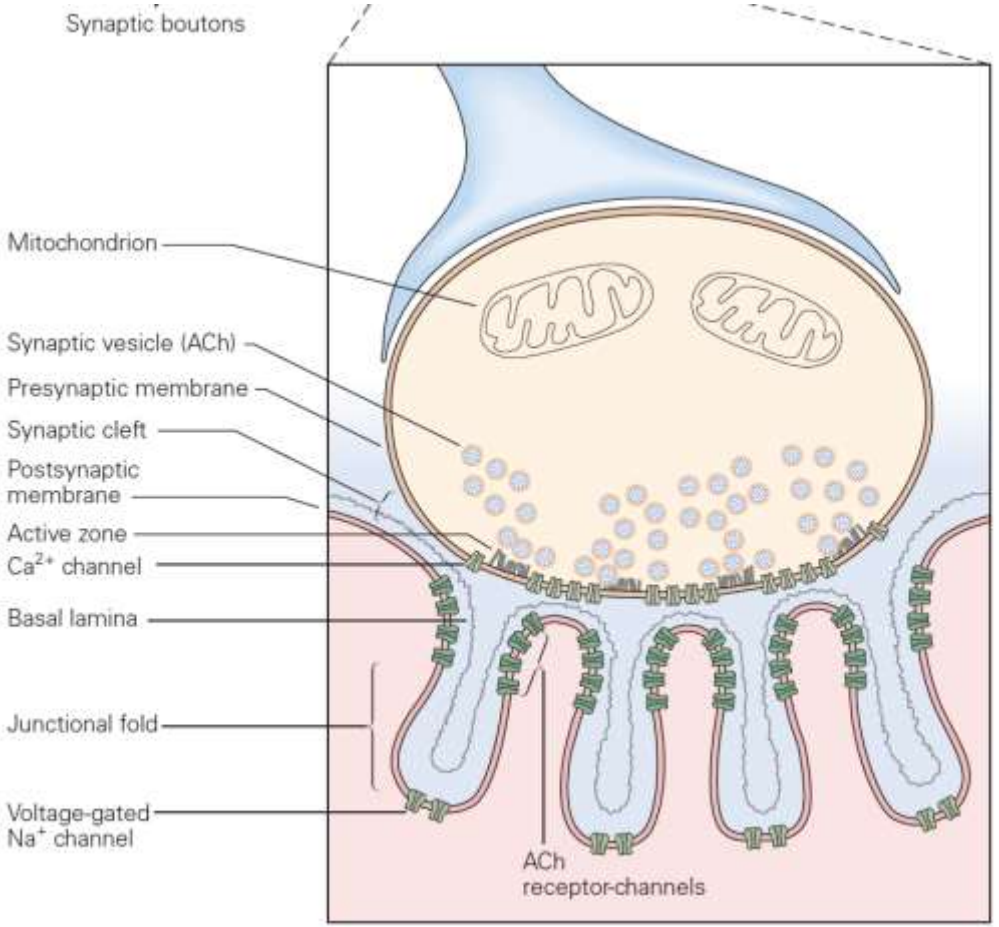
Synaptic contact can occur on the cell body, the dendrites, or the axon of the postsynaptic cell



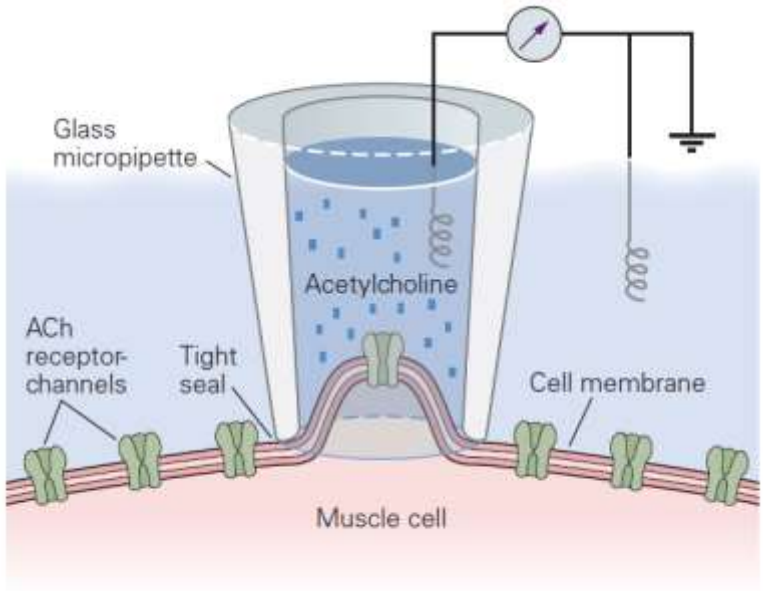
- How is the transmitter released?

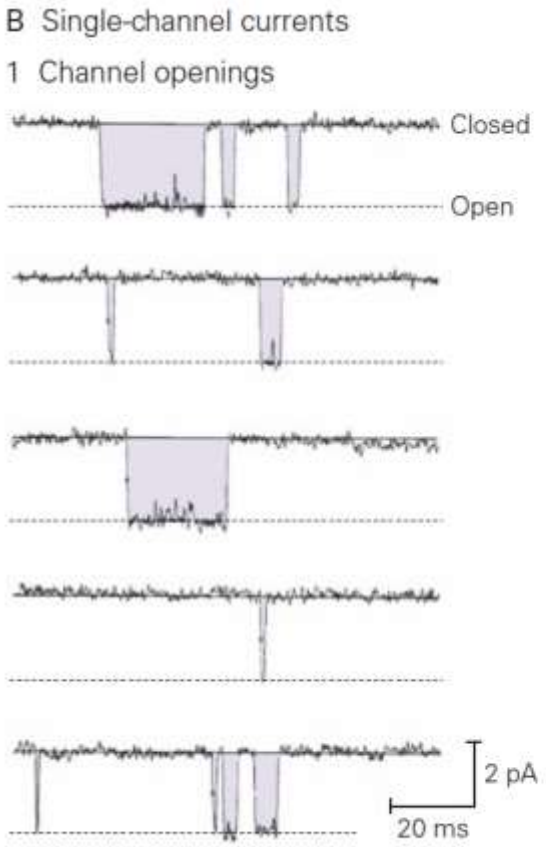
Neuromuscular junction

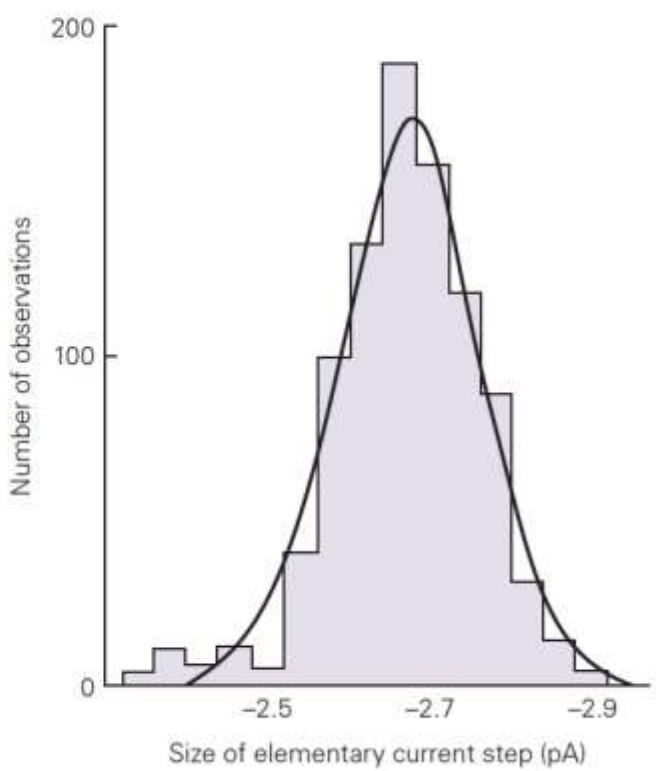




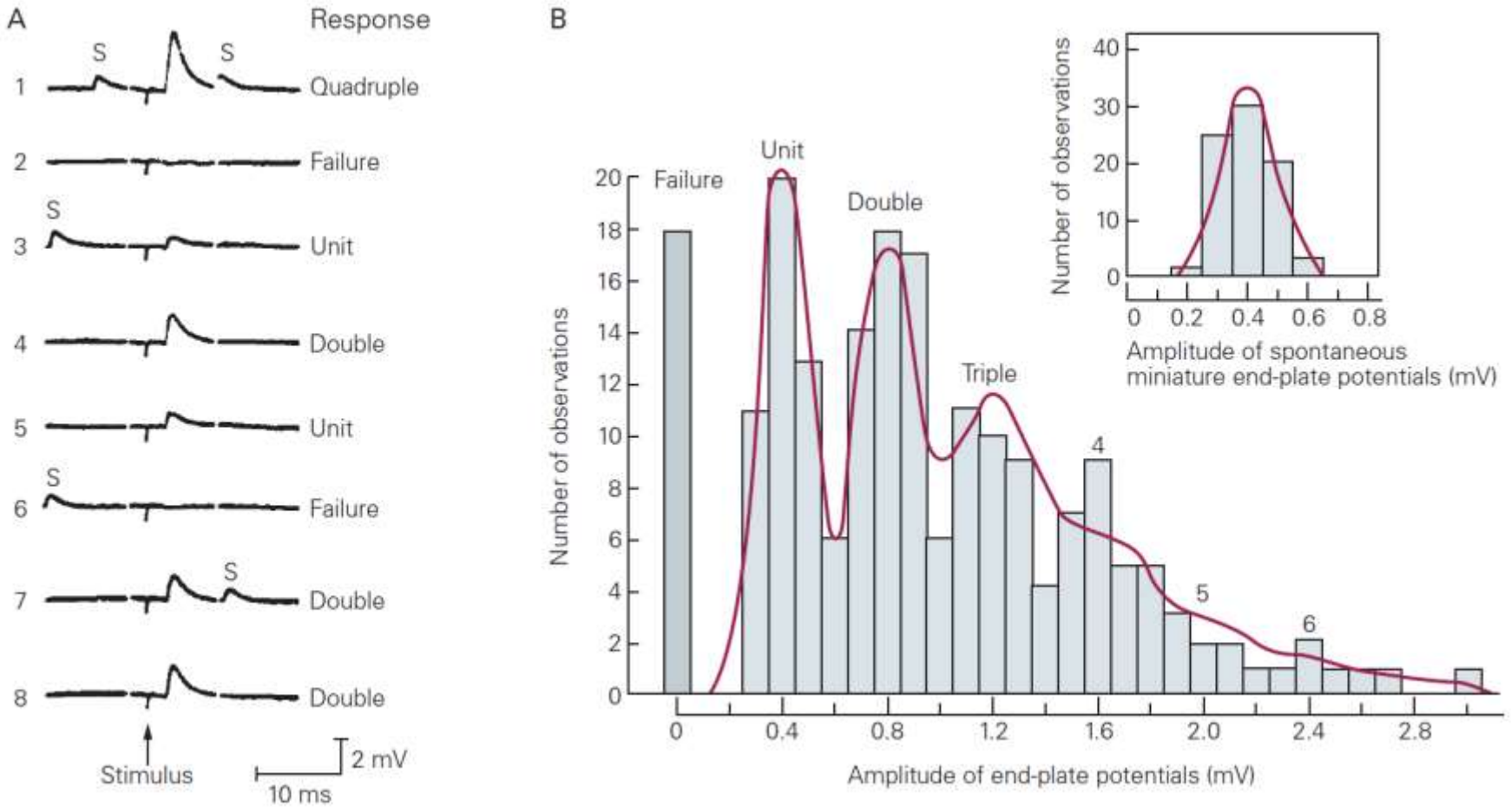
Modern neuroscience on synaptic transmission





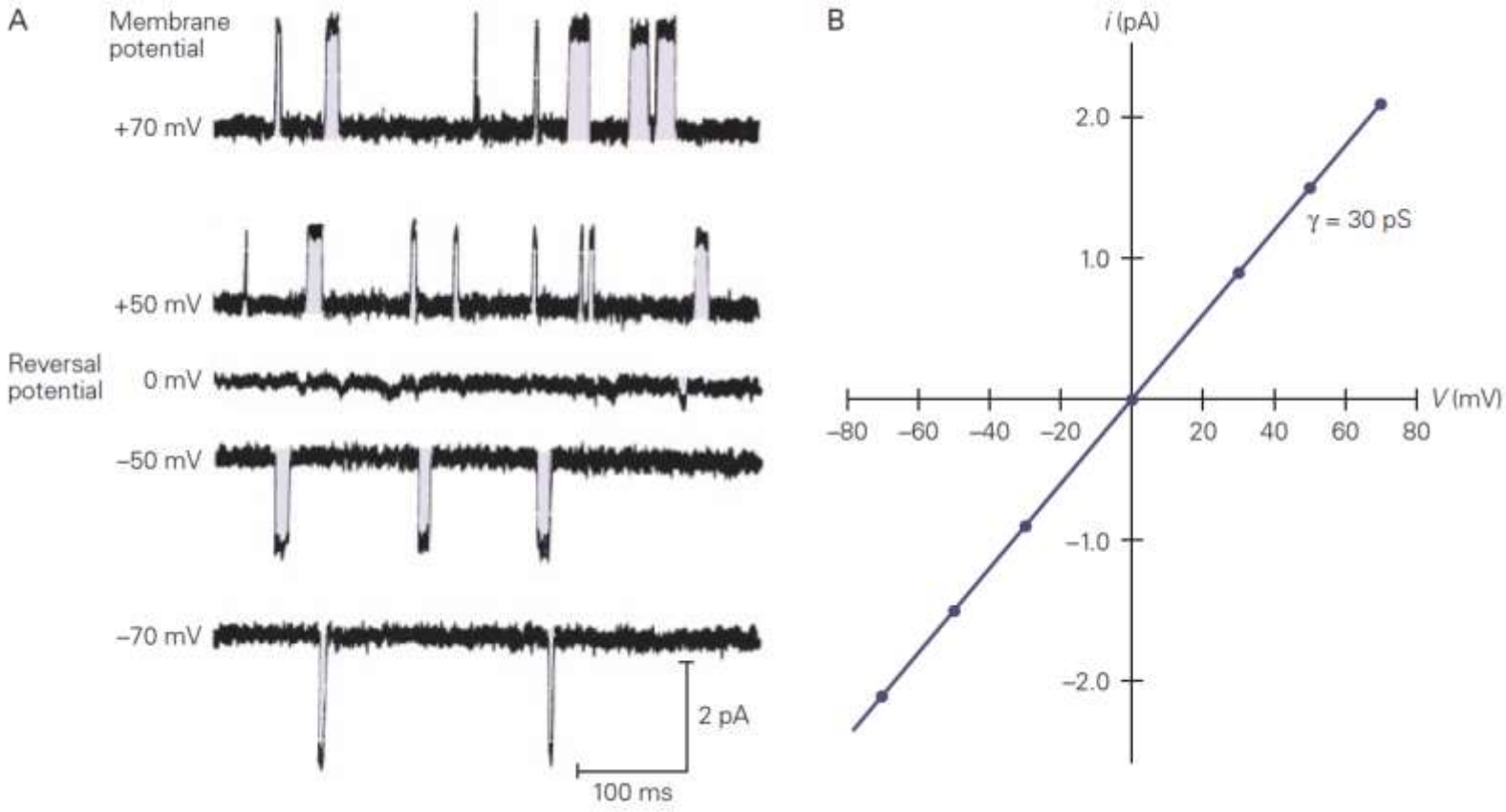


Quantal release in synaptic transmission



each vesicle stores one quantum of transmitter

Reversal potential



$$E = n \cdot p \cdot a.$$

The release of a quantum of transmitter is a random event.

Release probability (p)
Quantal size (a)
Numbers of readily releasable quanta (n)

- How exactly is the transmitter released upon action potential?
- How is the electrical signal transformed into chemical signal?

Nobel Prize on synaptic transmission

The Nobel Prize in Physiology or Medicine 2013

© Nobel Media AB. Photo: A. Mahmoud

James E. Rothman

Prize share: 1/3

© Nobel Media AB. Photo: A. Mahmoud

Randy W. Schekman

Prize share: 1/3

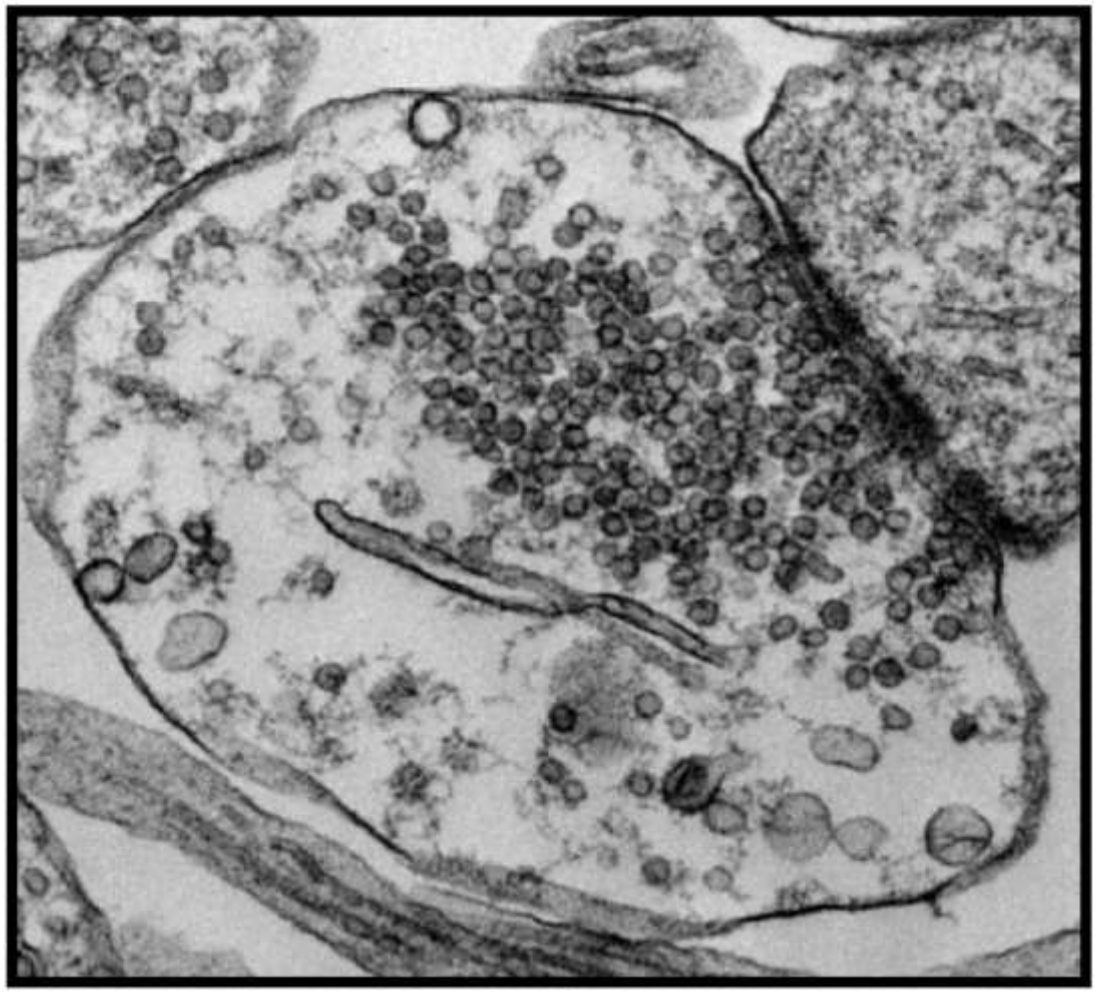
© Nobel Media AB. Photo: A. Mahmoud

Thomas C. Südhof

Prize share: 1/3

Randy Schekman discovered a set of genes that were required for vesicle traffic. **James Rothman** unravelled protein machinery that allows vesicles to fuse with their targets to permit transfer of cargo. **Thomas Südhof** revealed how signals instruct vesicles to release their cargo with precision.

Three Processes Govern Neurotransmitter Release

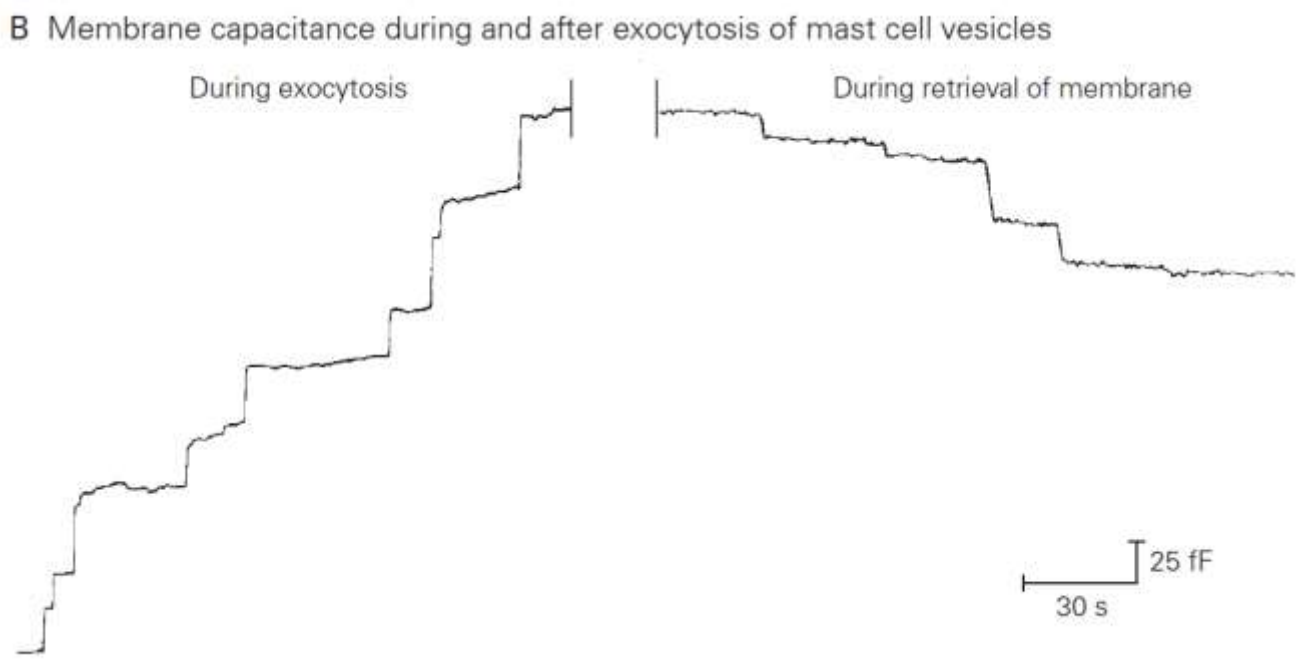


1. Synaptic vesicle fusion

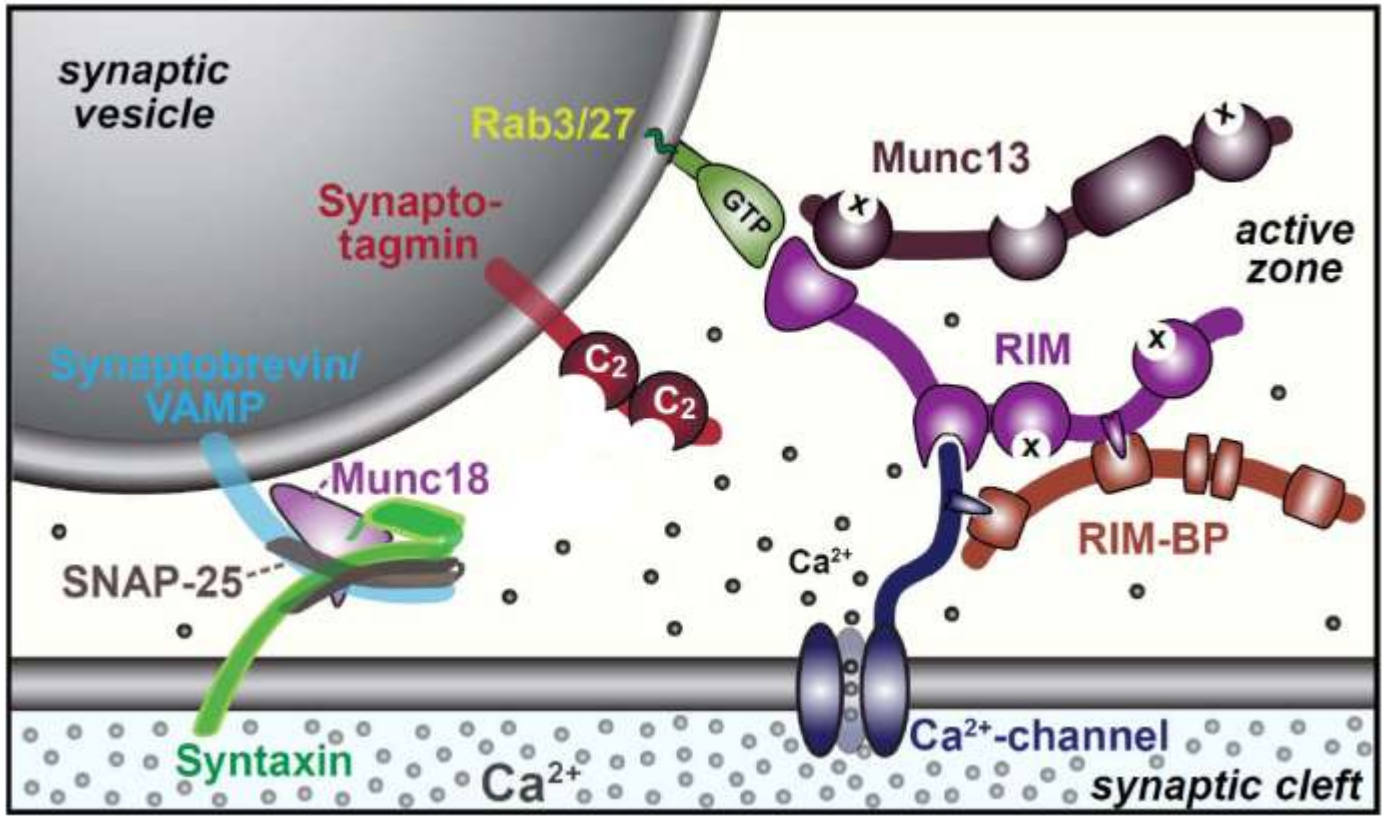
2. Ca2+-triggering of fusion
Very fast: ~0.1 msec
Cooperative: ~5 Ca2+-ions

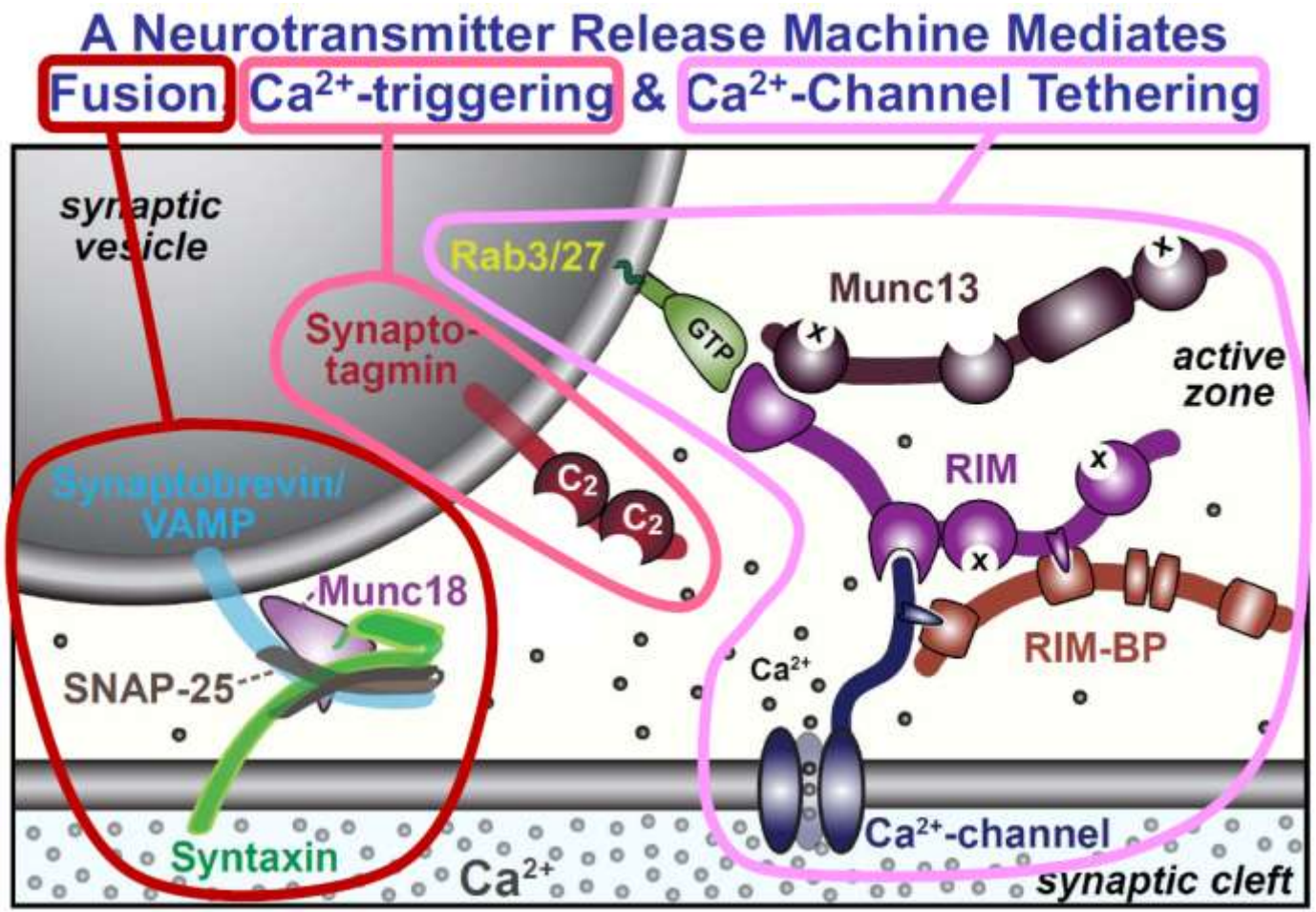
3. Localized Ca2+-influx

Exocytosis for synaptic vesicle fusion



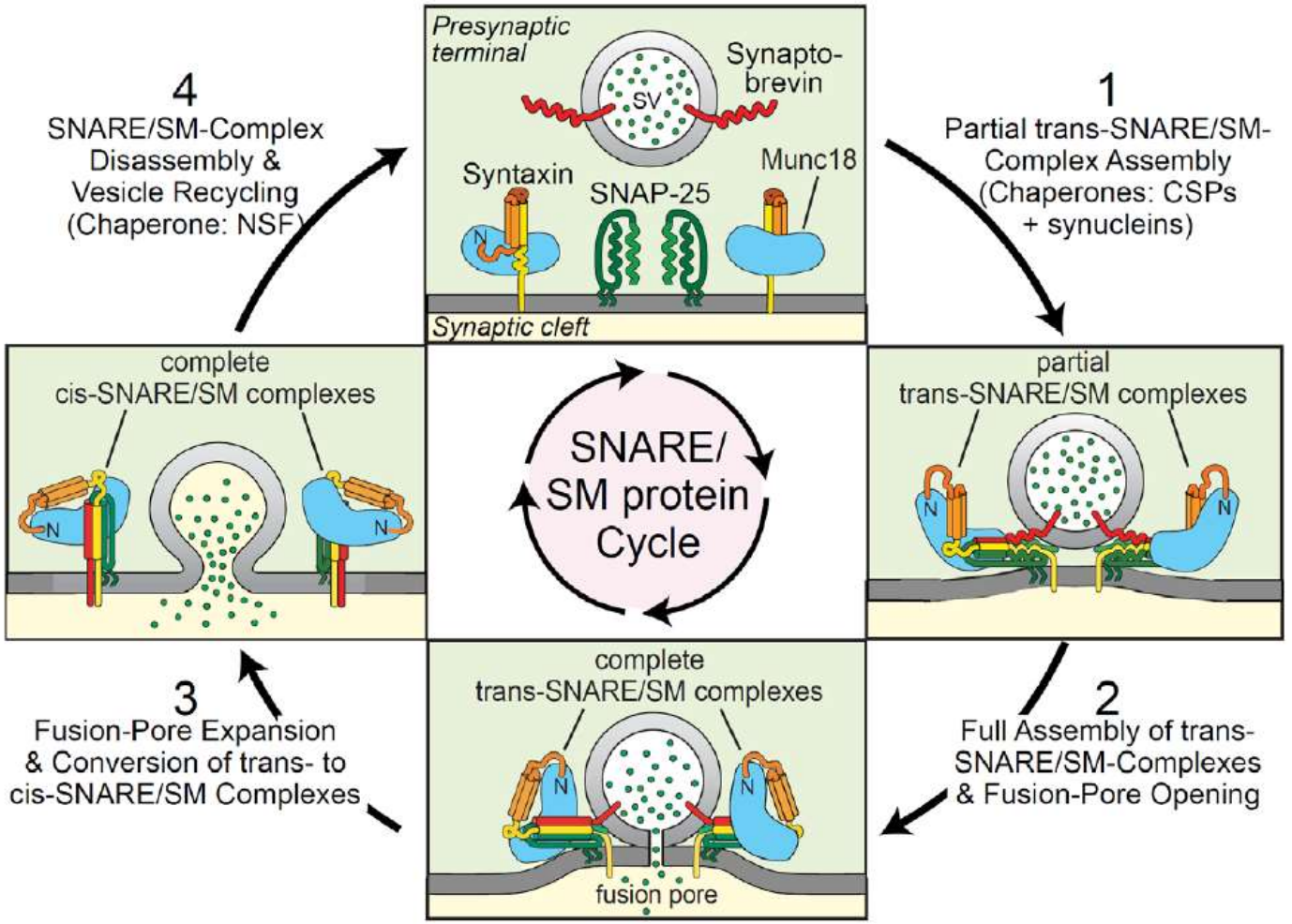
A Neurotransmitter Release Machine Mediates Fusion, Ca2+-triggering & Ca2+-Channel Tethering





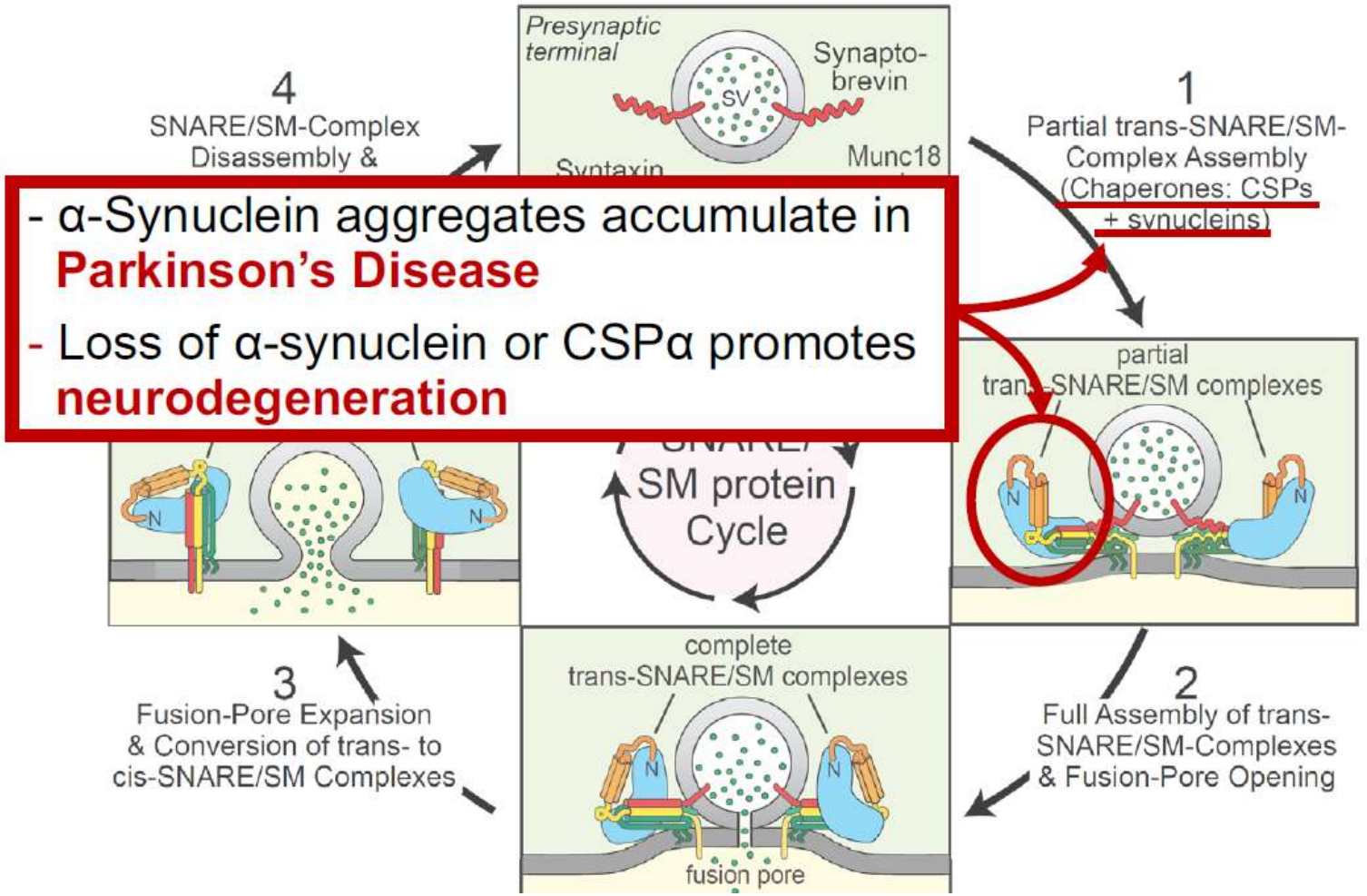
Thomas Südhof

SNARE/SM Protein Complex Assembly Drives Fusion



Thomas Südhof

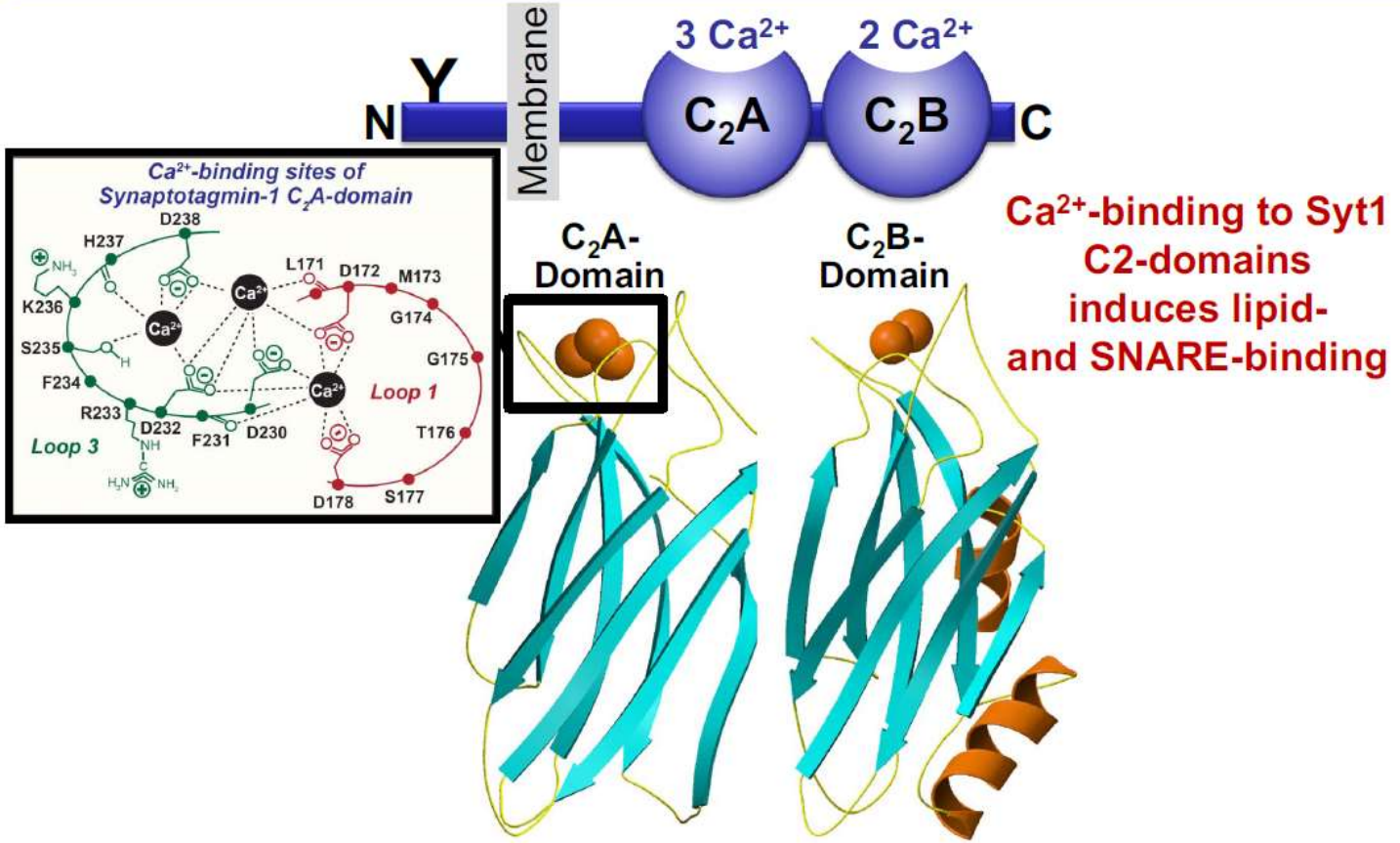
SNARE/SM Protein Complex Assembly Drives Fusion



- α-Synuclein aggregates accumulate in **Parkinson's Disease**
- Loss of α-synuclein or CSPα promotes **neurodegeneration**

Thomas Südhof

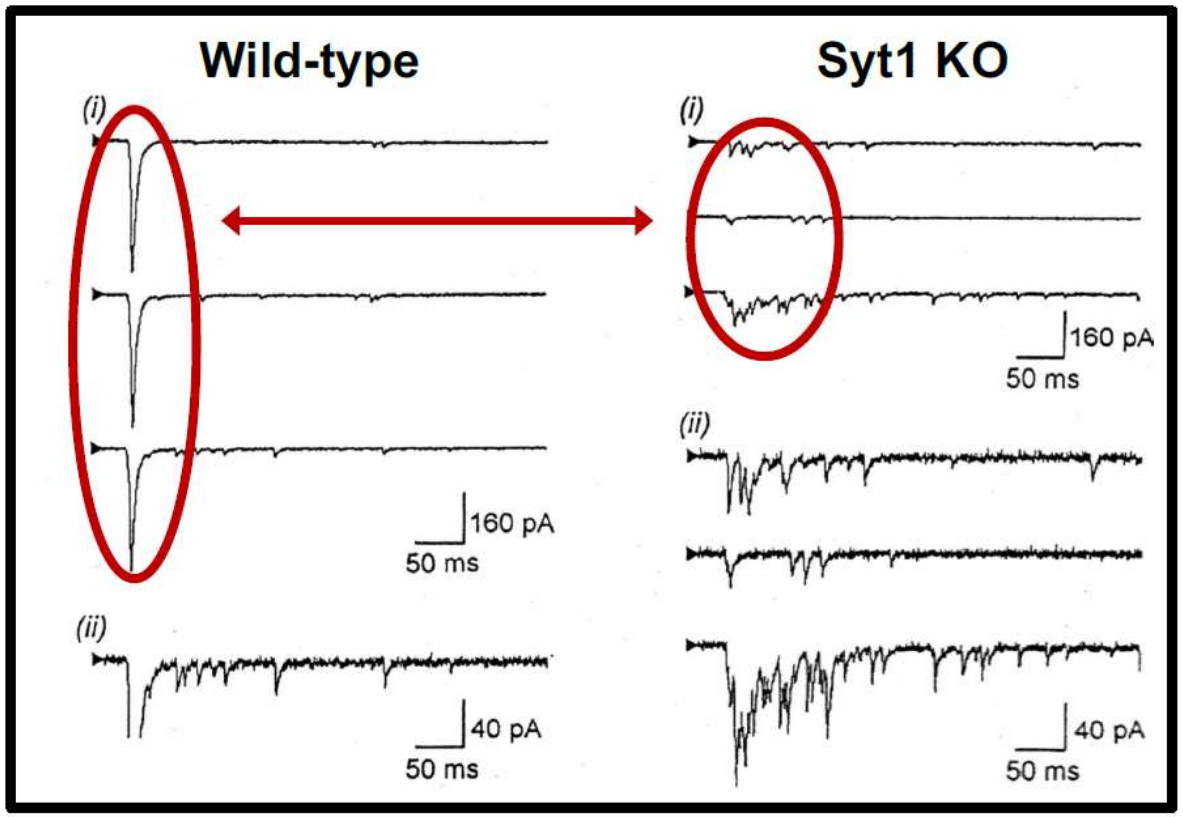
Architecture of Synaptotagmin-1 Ca^{2+}-Binding Sites



Perin et al., Nature 1990; Brose et al., Science 1992; Davletov & Südhof, 1993;
Li et al., Nature 1995; Sutton et al., Cell 1995; Chen et al., Neuron 2001

Thomas Südhof

Synaptotagmin-1 is Essential for Ca^{2+}-Triggered Neurotransmitter Release



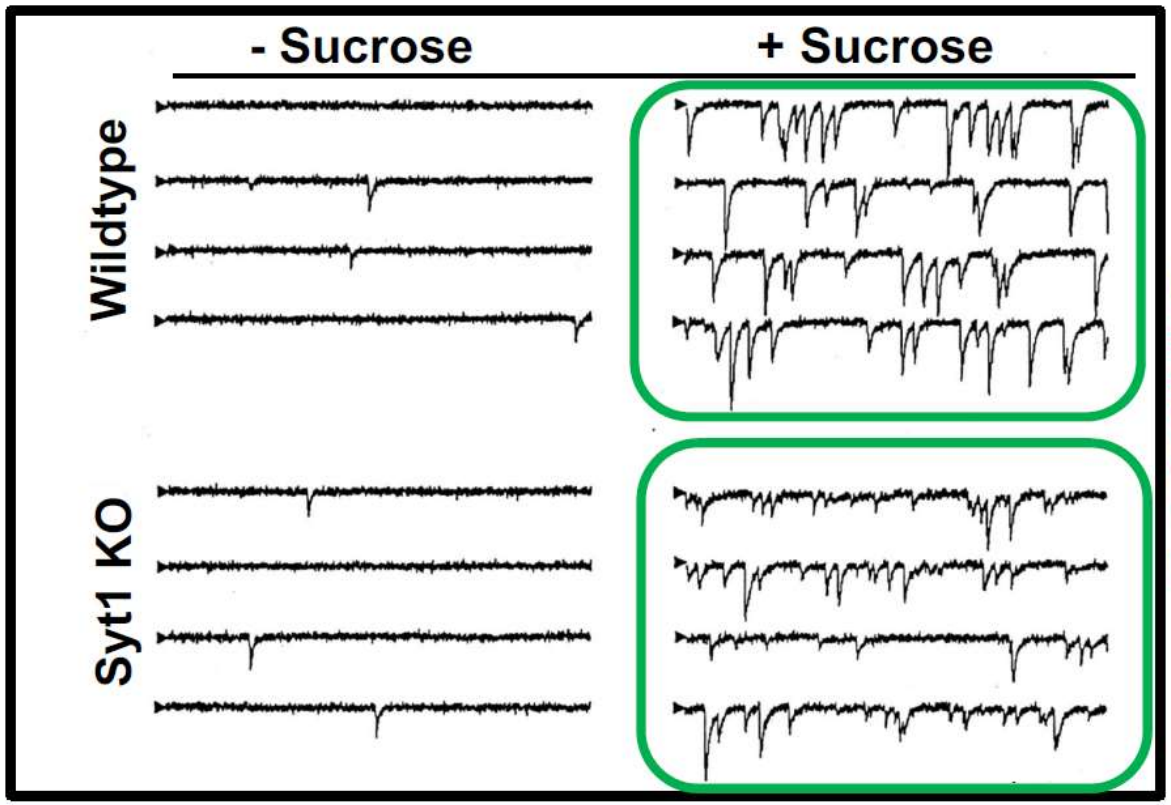
Release stimulated by isolated action potentials

Fast Ca^{2+}-triggered release is gone …

Geppert et al., Cell 1994

Thomas Südhof

Synaptotagmin-1 is Not Essential for Sucrose-Stimulated Neurotransmitter Release



Hypertonic sucrose stimulates release by a Ca^{2+}-independent mechanism

Synaptotagmin is ONLY required for Ca^{2+}-triggered fusion

Geppert et al., Cell 1994

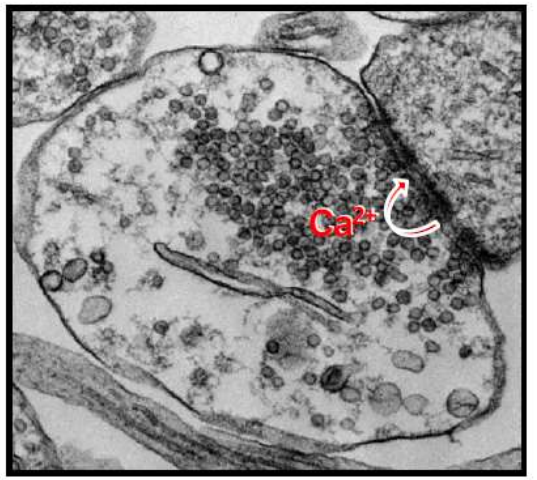
Thomas Südhof

Three Processes Govern Neurotransmitter Release

1. Synaptic vesicle fusion

2. Ca^{2+}-triggering of fusion
   - Very fast: ~0.1 msec
   - Cooperative: ~5 Ca^{2+}-ions

3. Localized Ca^{2+}-influx

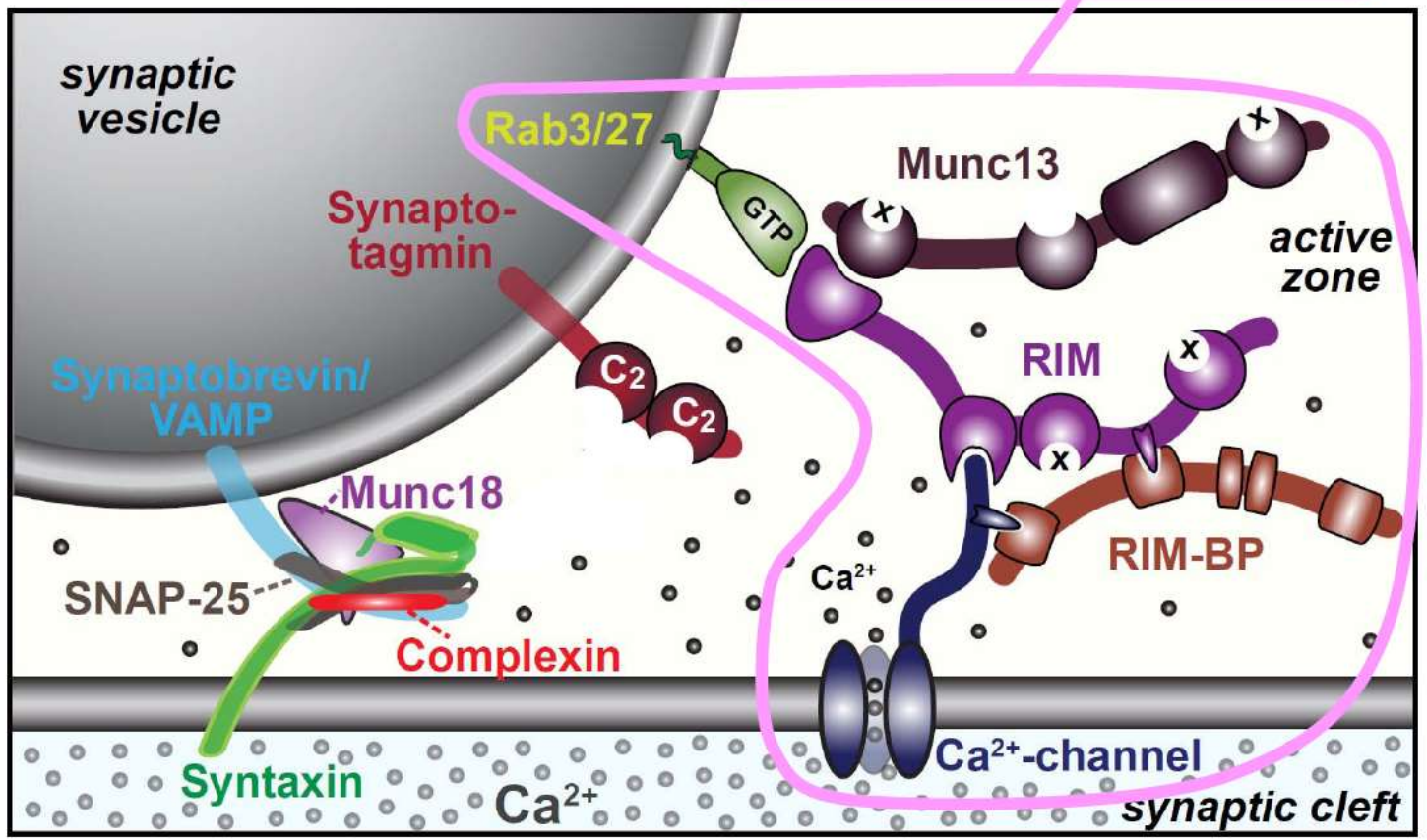


Without localized Ca^{2+}-influx at the active zone, action potentials and release become uncoupled, and release is desynchronized and decelerated

The importance of localized Ca^{2+}-influx cannot be overestimated – like in real estate, location is everything!

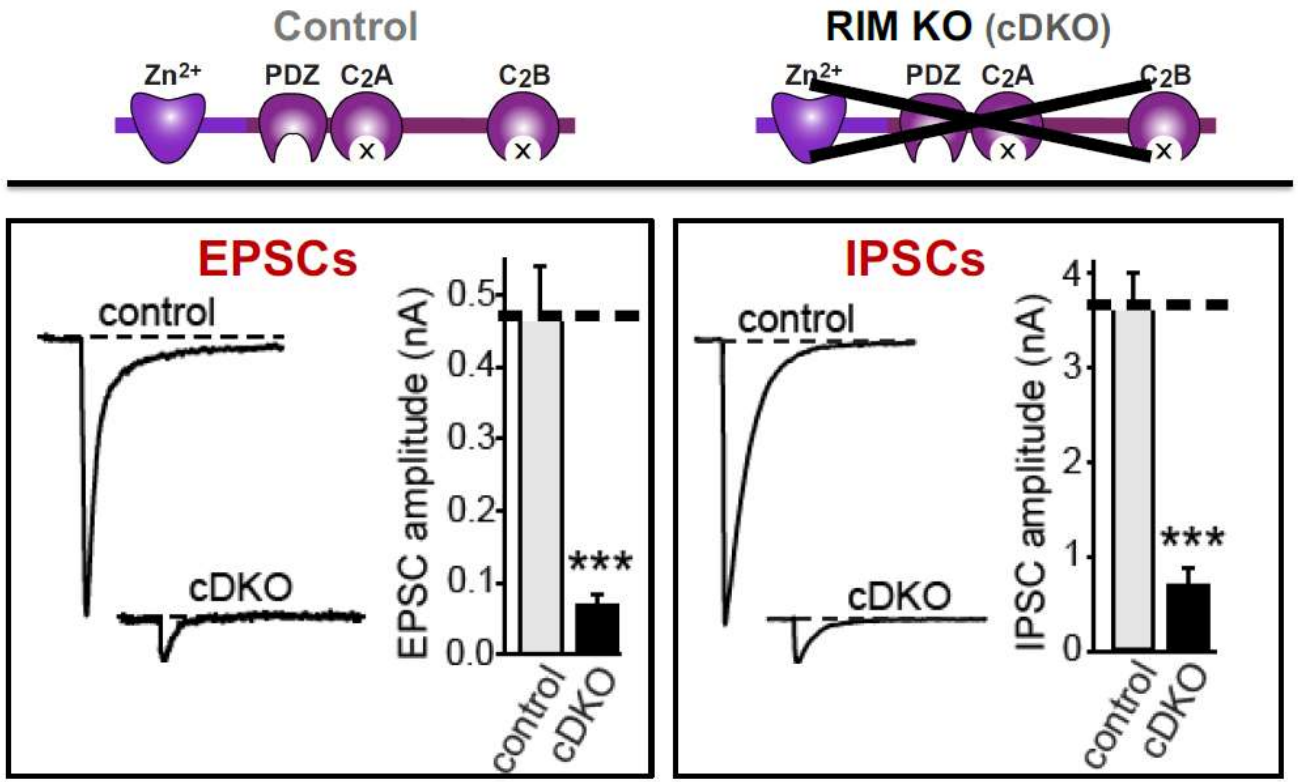
Thomas Südhof

A Neurotransmitter Release Machine Mediates Fusion, Ca^{2+}-triggering & Ca^{2+}-Channel Tethering



Thomas Südhof

Deletion of RIM Severely Impairs Release

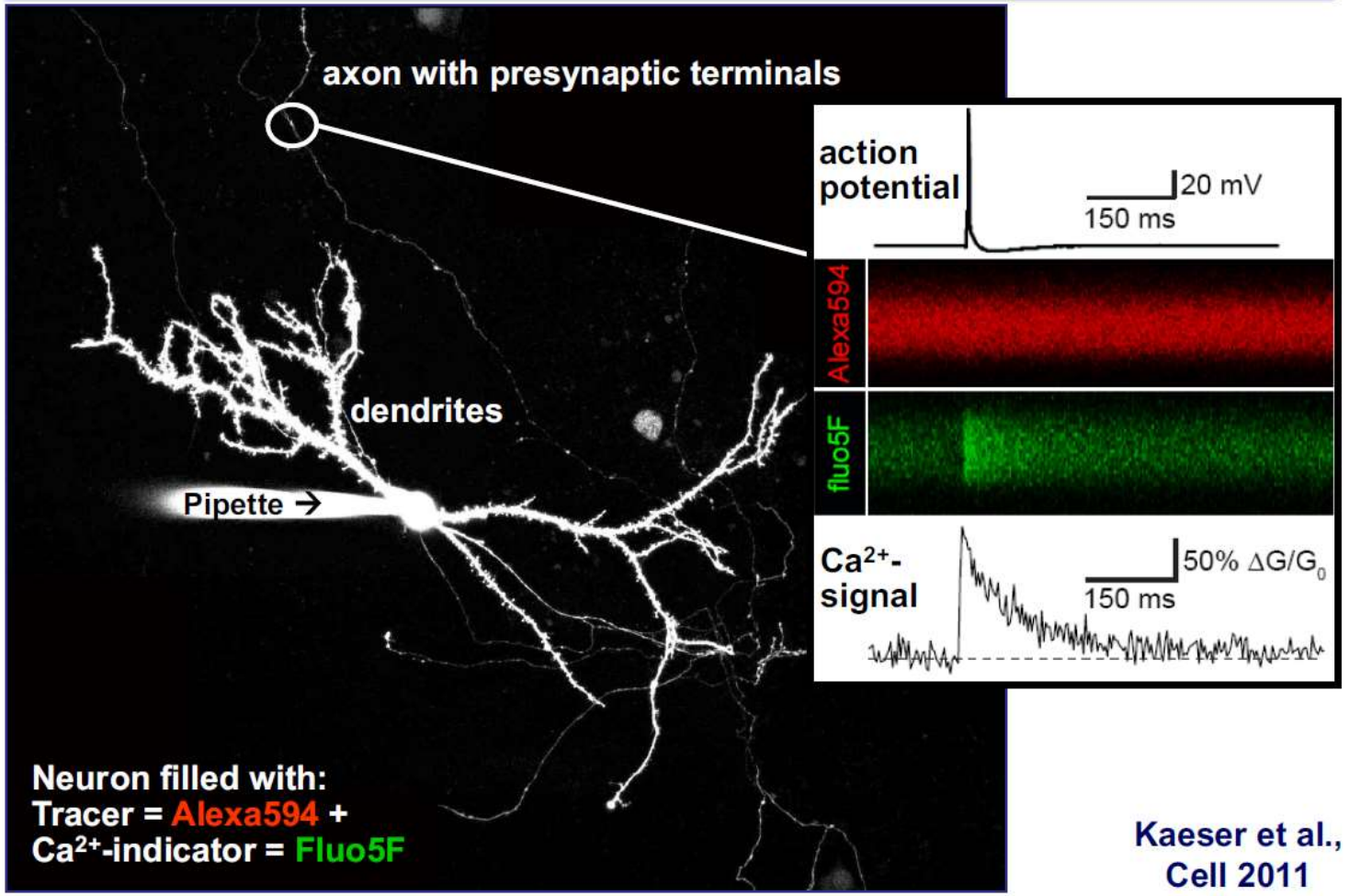


Is release impaired because of a defect in Ca^{2+}-influx?

Kaeser et al., Cell 2011; Deng et al., Neuron 2011; Han et al., Neuron 2011

Thomas Südhof

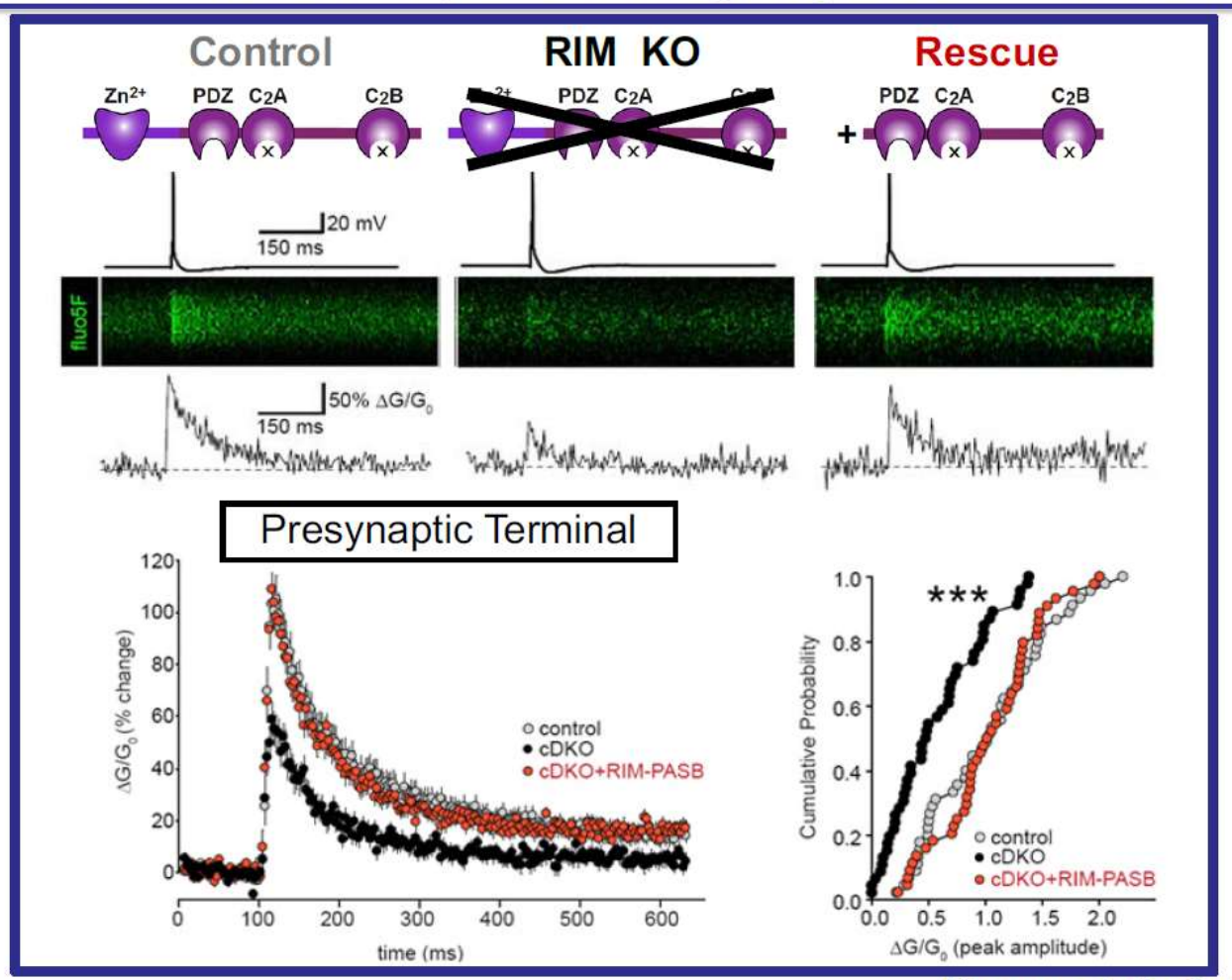
Measurement of Ca^{2+}-Transients in Hippocampal Neurons



Kaeser et al., Cell 2011

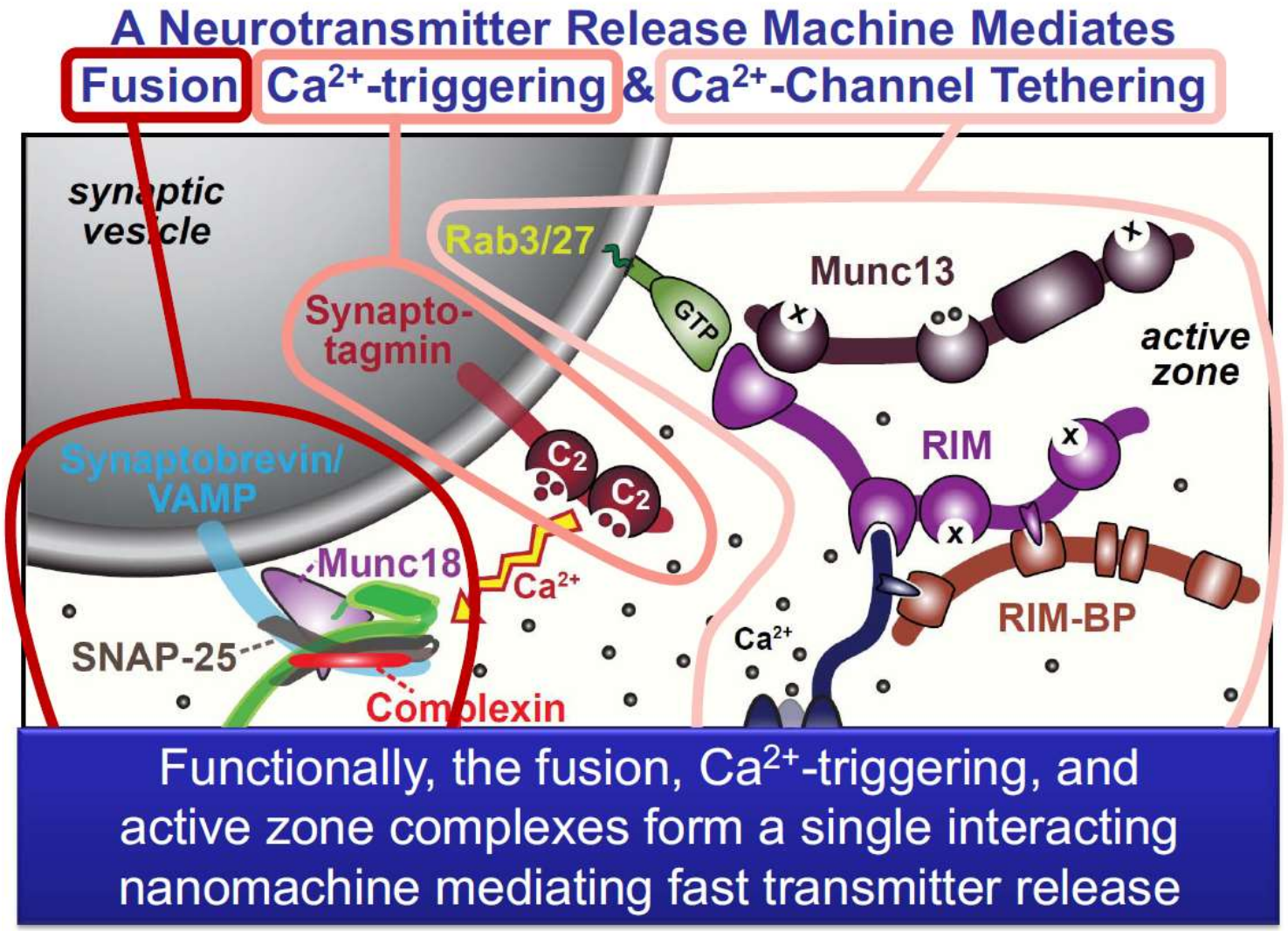
Thomas Südhof

RIM Deletion Impairs Presynaptic Ca^{2+}-Influx



Kaeser et al., Cell 2011

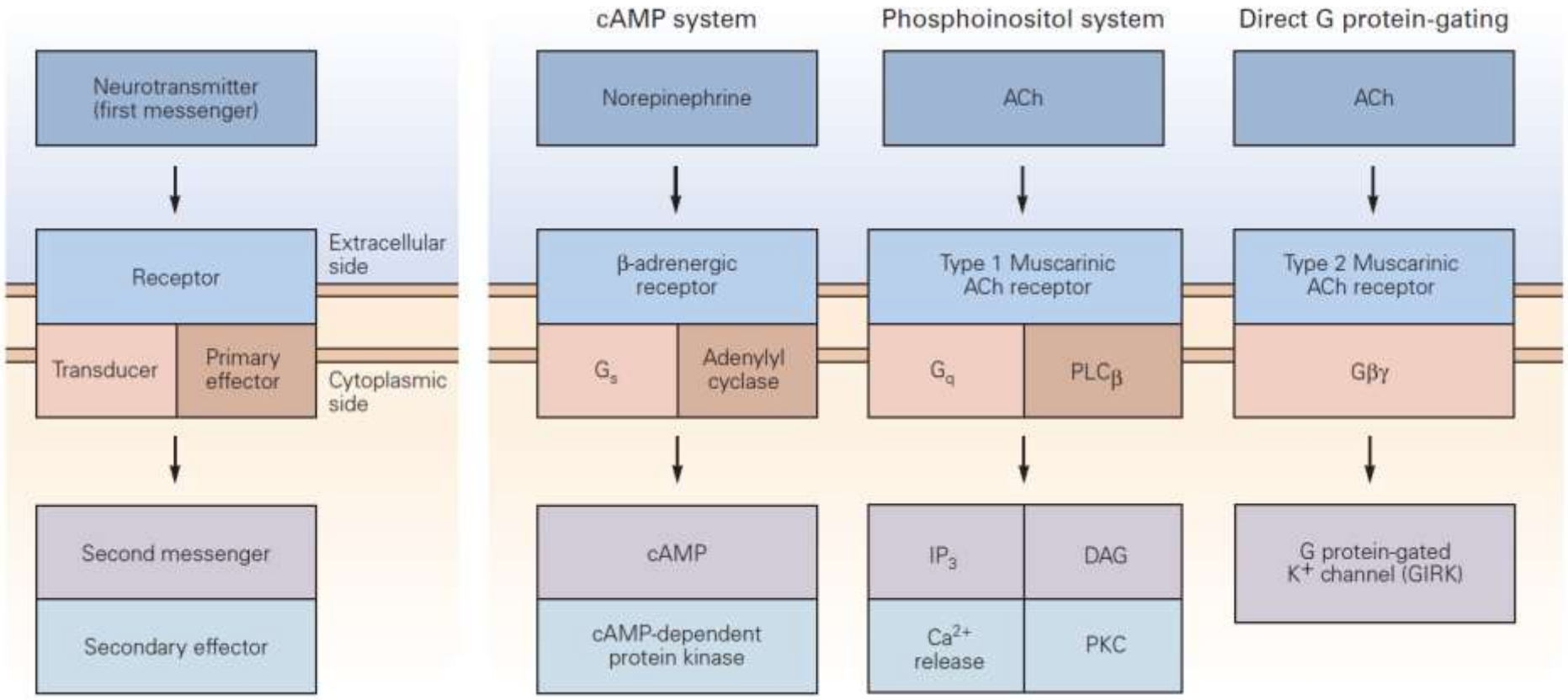
Thomas Südhof



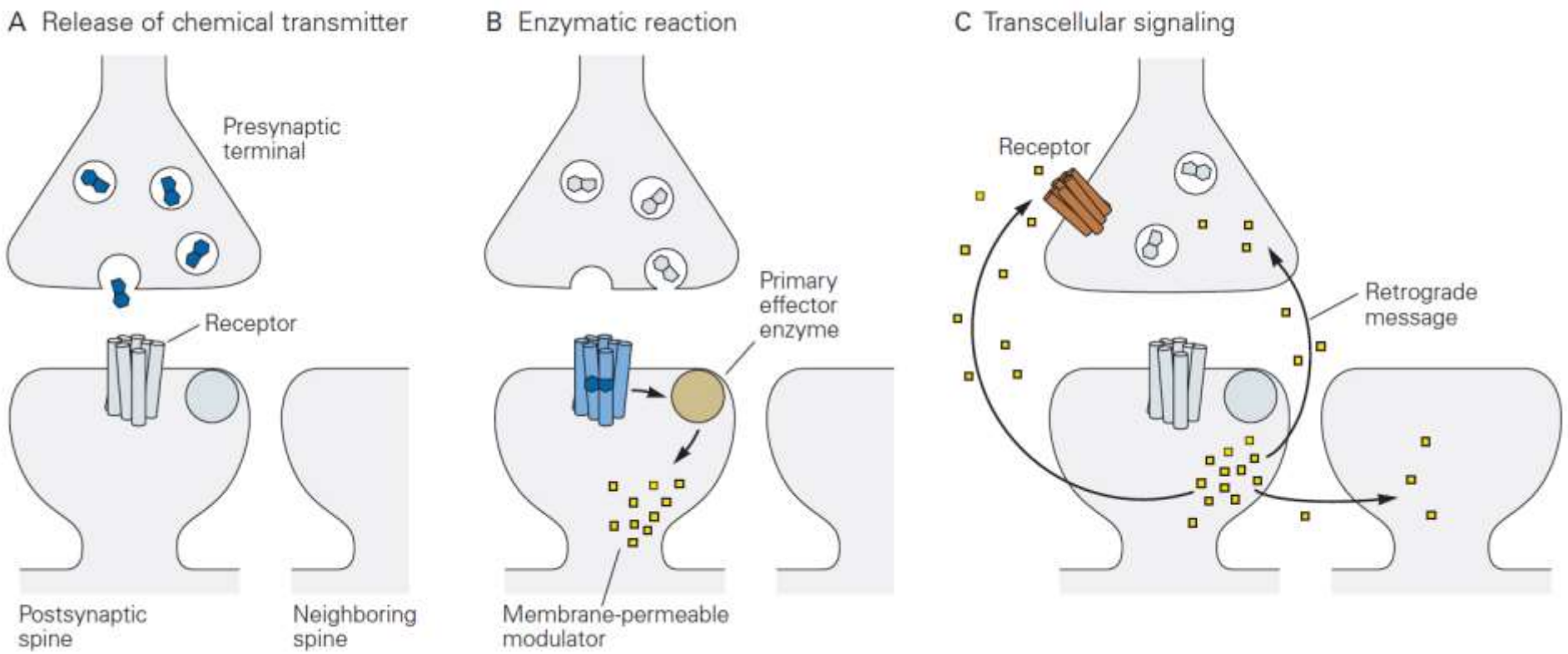
Thomas Südhof

- Synapse and beyond

Modulation of Synaptic Transmission: Second Messengers



Transcellular signaling can occur from the postsynaptic neuron to the presynaptic neuron



Nonsynaptic interactions

- **Ephapses**
  - When two nerve trunks are placed together, impulses in one can alter the excitability of the other. This is called an ephapsea.
- **Summed field potentials**
  - strong activation of a population of neurons, with processes oriented as parallel dipoles, can modulate the excitability of the constituent neurons.
- **Presynaptic autoreceptors**
  - Synaptic receptors on the presynaptic terminal
- **Nonvesicular and Ca2+-independent neurotransmitter release**
  - There is a low level of depolarization of the postsynaptic membrane at the neuromuscular junction that is nonquantal in nature, due to slow leak of ACh from the presynaptic terminal.
- **Slow actions of neuropeptides and neurohormones**
  - Where is the border between synaptic and nonsynaptic actions?
- **Diffuse neurotransmitter actions and volume conduction**
  - Many receptors seem to be localized at a distance from the sites of secretion of their transmitters.
- **Gaseous messengers**
  - Gaseous messenges such as CO and NO extend the scope and nature of a synapse

- Science

Thomas Südhof on Scientific progress

- *... It is important to note, however, that the nature of our studies was not revolutionary. In my career, no single major discovery changed the field all at once. Instead, our work progressed in incremental steps over two decades. I think this is a general property of scientific progress in understanding how something works – a single experiment rarely explains a major question, but usually a body of work is required. In contrast, scientific progress in developing tools normally advances in spurts, and often a single flash of genius creates a completely new method (e.g., see monoclonal antibodies, patch clamping, PCR, or shRNAs, to name a few). ...*

https://www.nobelprize.org

Thomas Südhof & Lu Chen

Radical progress in biology is rare

- *The closest our work came to inducing a radical change in the field was probably the identification of synaptotagmins as calcium-sensors for fusion, and of Sec1/Munc18-like proteins (SM-proteins) as membrane fusion proteins, but both hypotheses took decades to develop and to become accepted by the field – in fact, the SM-protein hypothesis was only recently adopted by others, 20 years after we proposed it, and is still in flux.*

The Südhof laboratory in Dallas in 1995

Personal take by Thomas Südhof

- *I at least have learned most from personal contacts, not from reading the literature or listening to talks. Although reading books or papers provided me with an indispensable background of facts, I learned how to think, how to assess a subject, and how to value a perspective from insightful comments of others.* ***Thus, for a scientific career the most important elements are good teachers and mentors, and a great environment – not only during early years as student and postdoc, but throughout the entire career of a scientist.*** *...*
- *I would advise everybody to* ***make career choices primarily based on the people involved****, not on the geographic location of a place or the fashionableness of the subject or the techniques. I believe this is true for all stages of a career.*

END

Neurobiology course, 2018/10

Chun XU