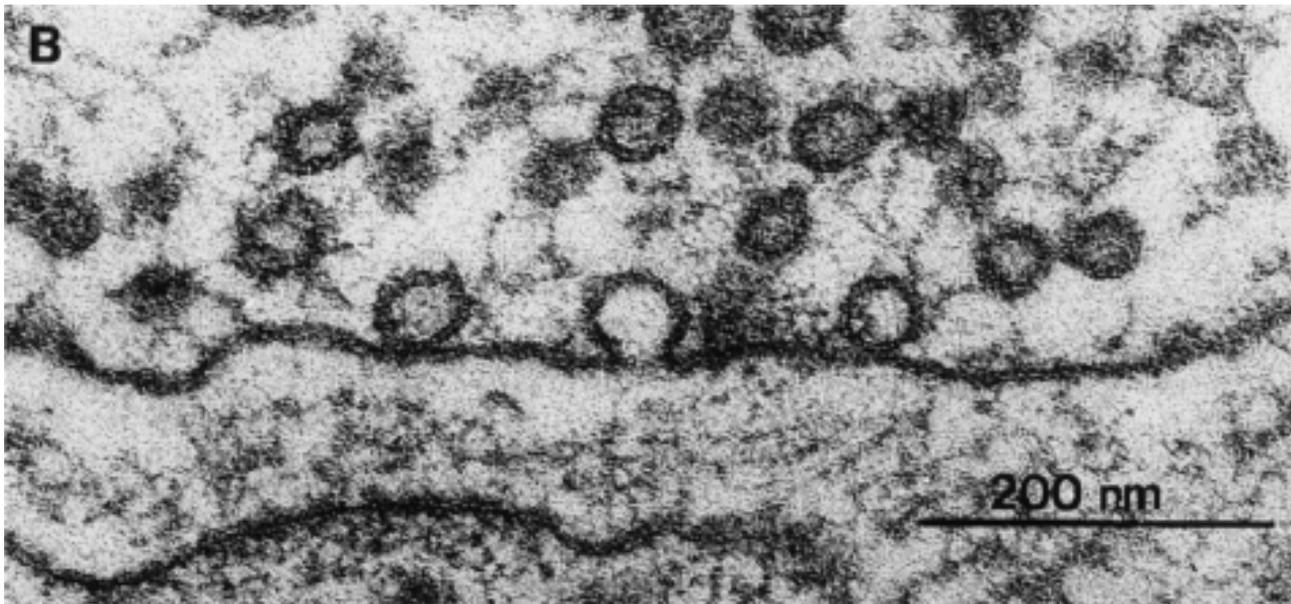


17.3.2006

# Funktionsprinzipien von Synapsen

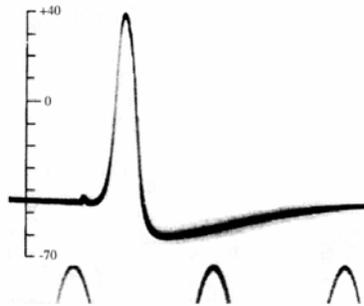
Andreas Draguhn



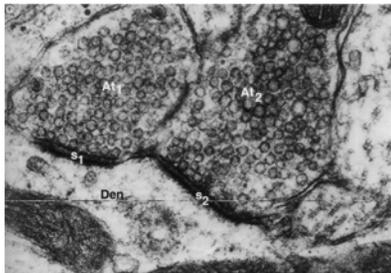
- Aufbau
- Transmitter und präsynaptische Vesikel
- Postsynaptische Rezeptoren
- Funktion einzelner Synapsen
- Prinzipien der Informationsverarbeitung:
  - i - Summation
  - ii - Hemmung und Erregung
  - iii - Plastizität von Synapsen (Ausblick)



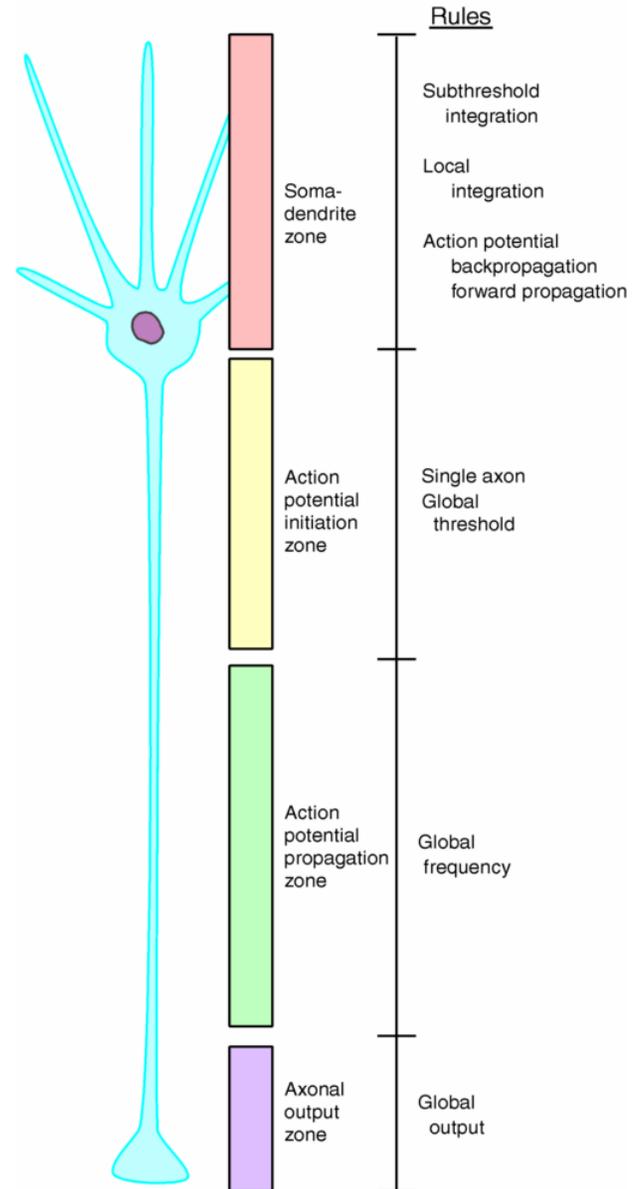
B



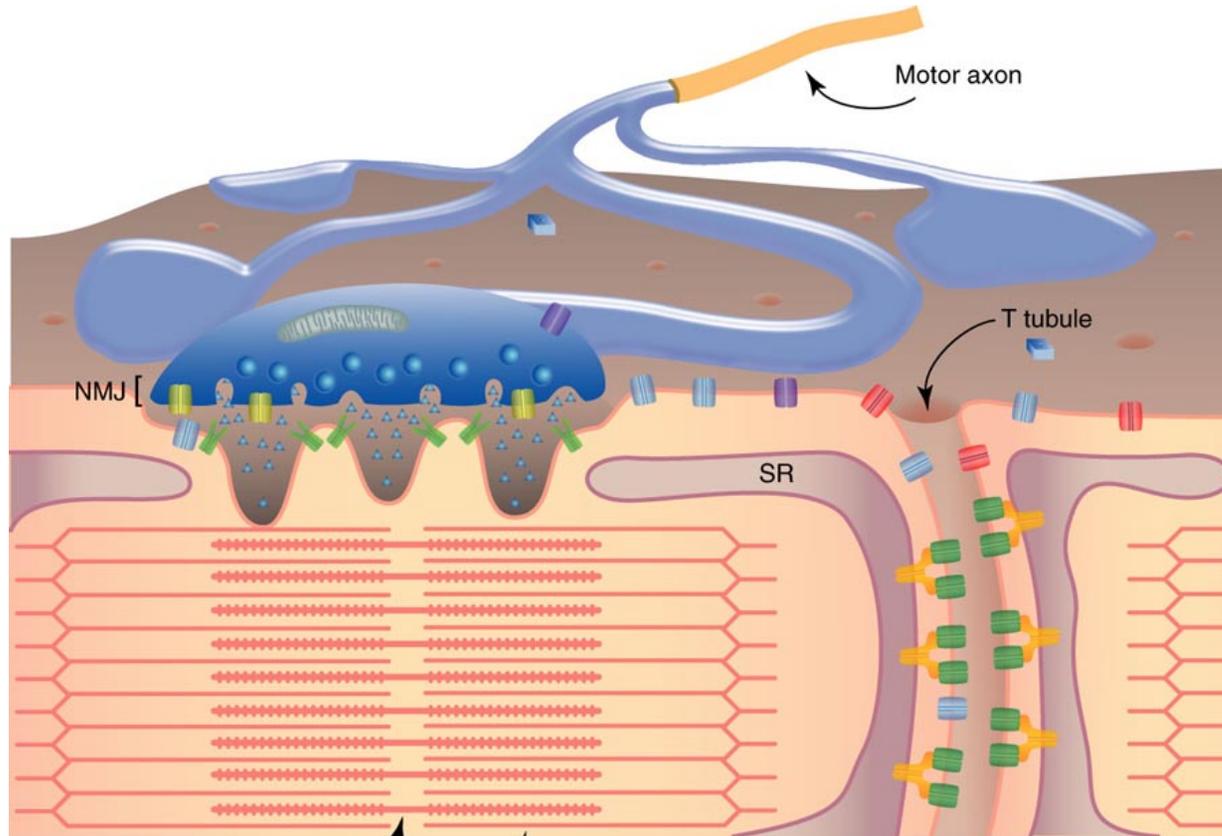
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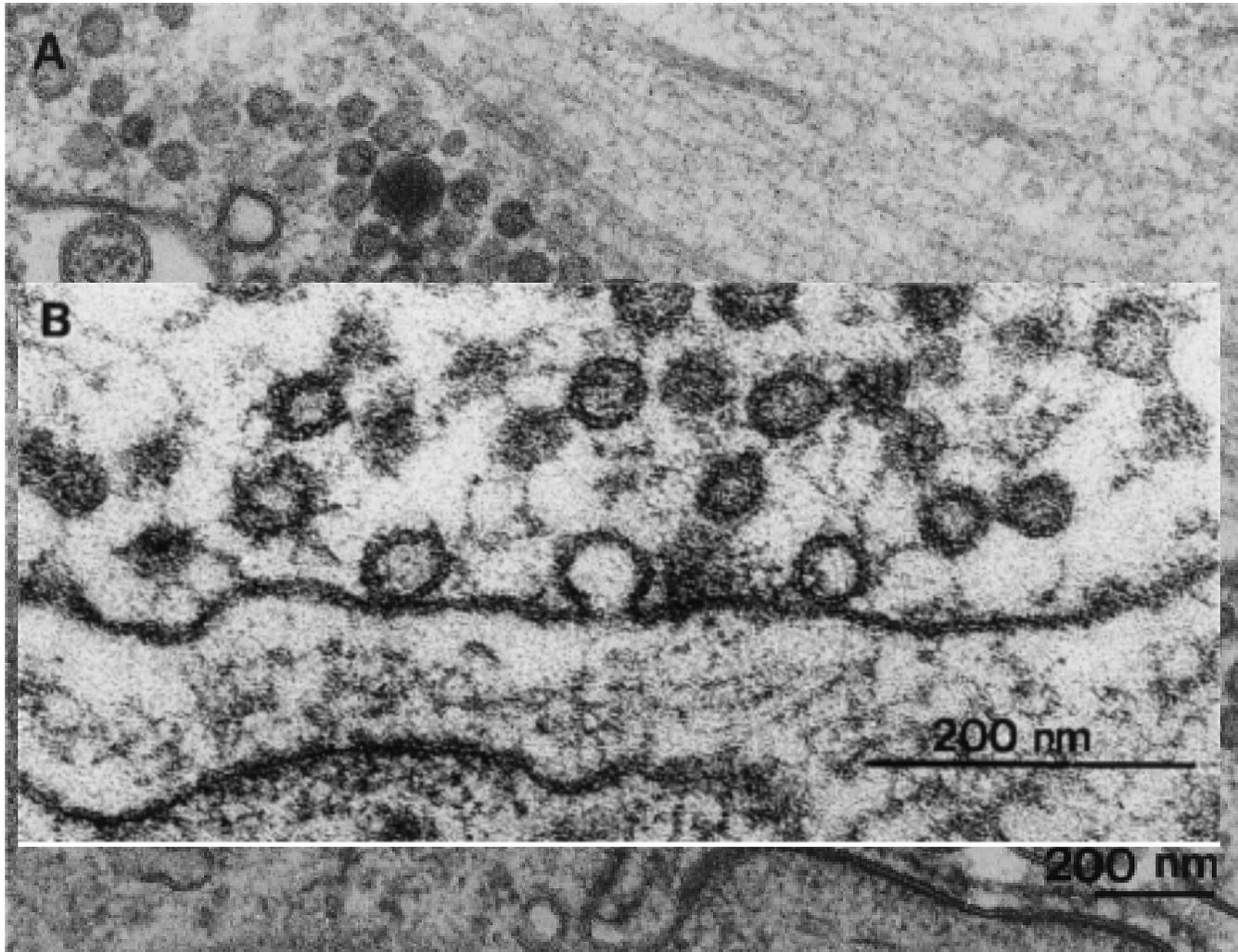


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Thick filament  
Thin filament

	SR calcium release channel		Potassium channel
	ACH		T-tubule voltage gated channel
	ACH receptor		Skeletal muscle chloride channel
	Neuronal voltage gated calcium channel		Skeletal muscle sodium channel



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## Azetylcholin



## Aminosäuren

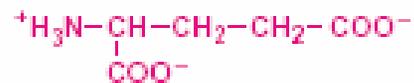
$\gamma$ -amino-Buttersäure (GABA):



Glycin:

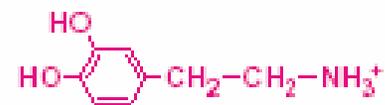


Glutamat:

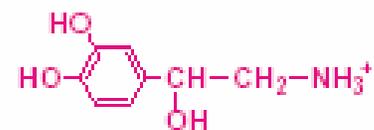


## Monoamine

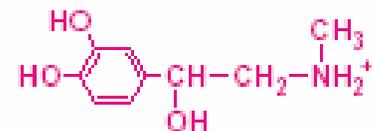
Dopamin:



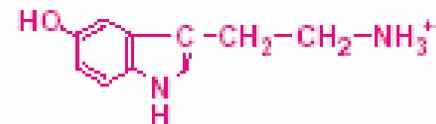
Noradrenalin:



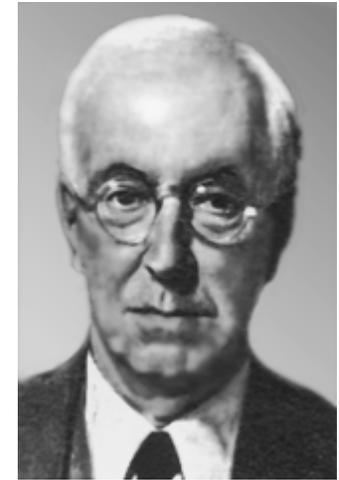
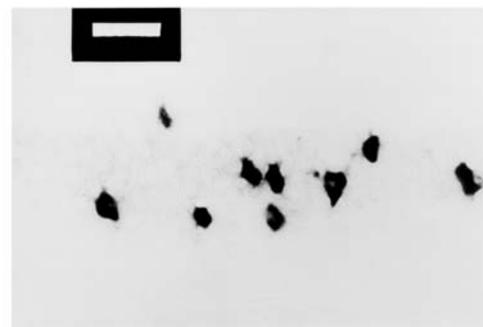
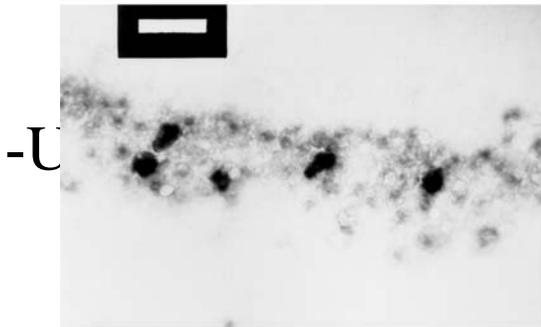
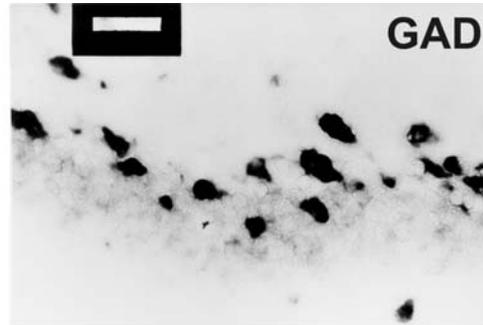
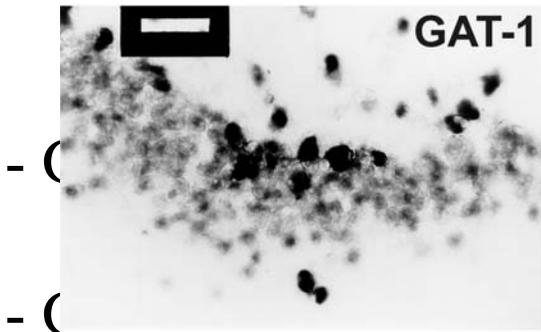
Adrenalin:



Serotonin:

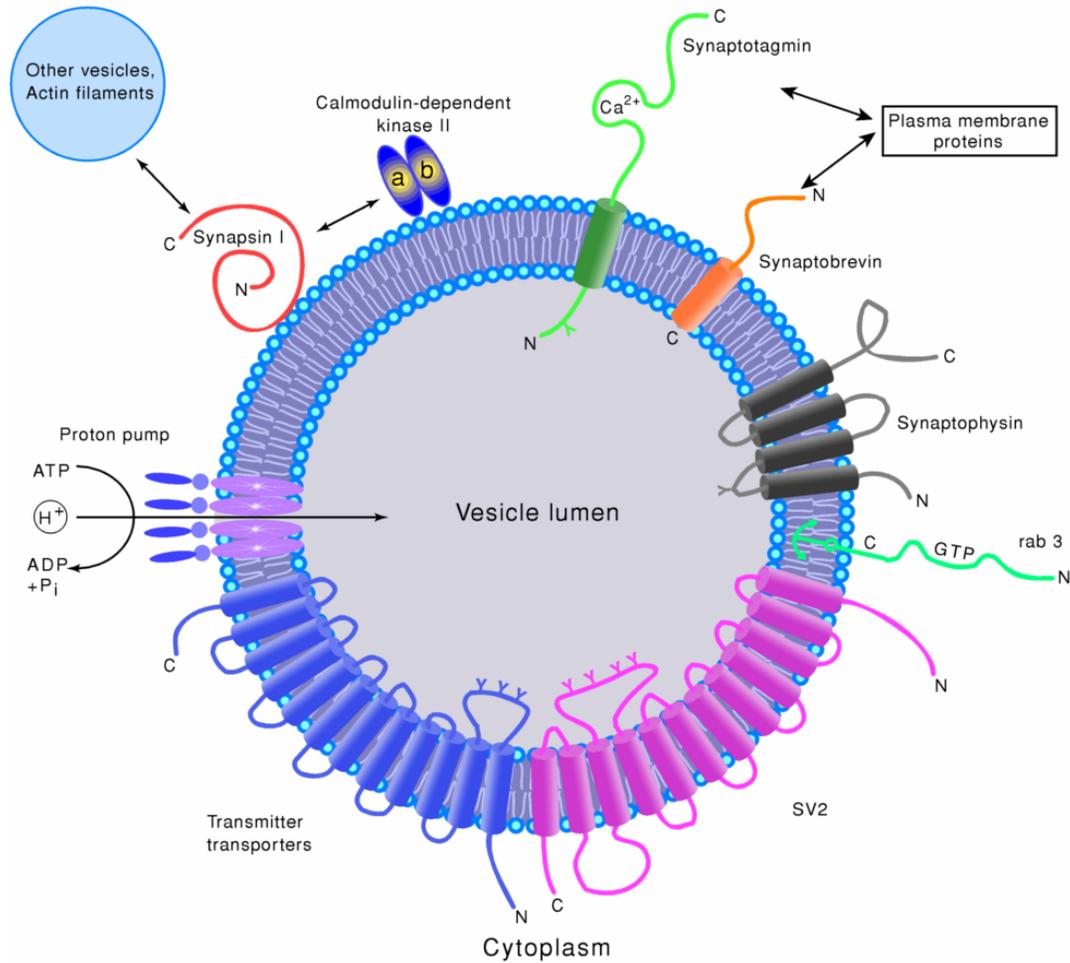


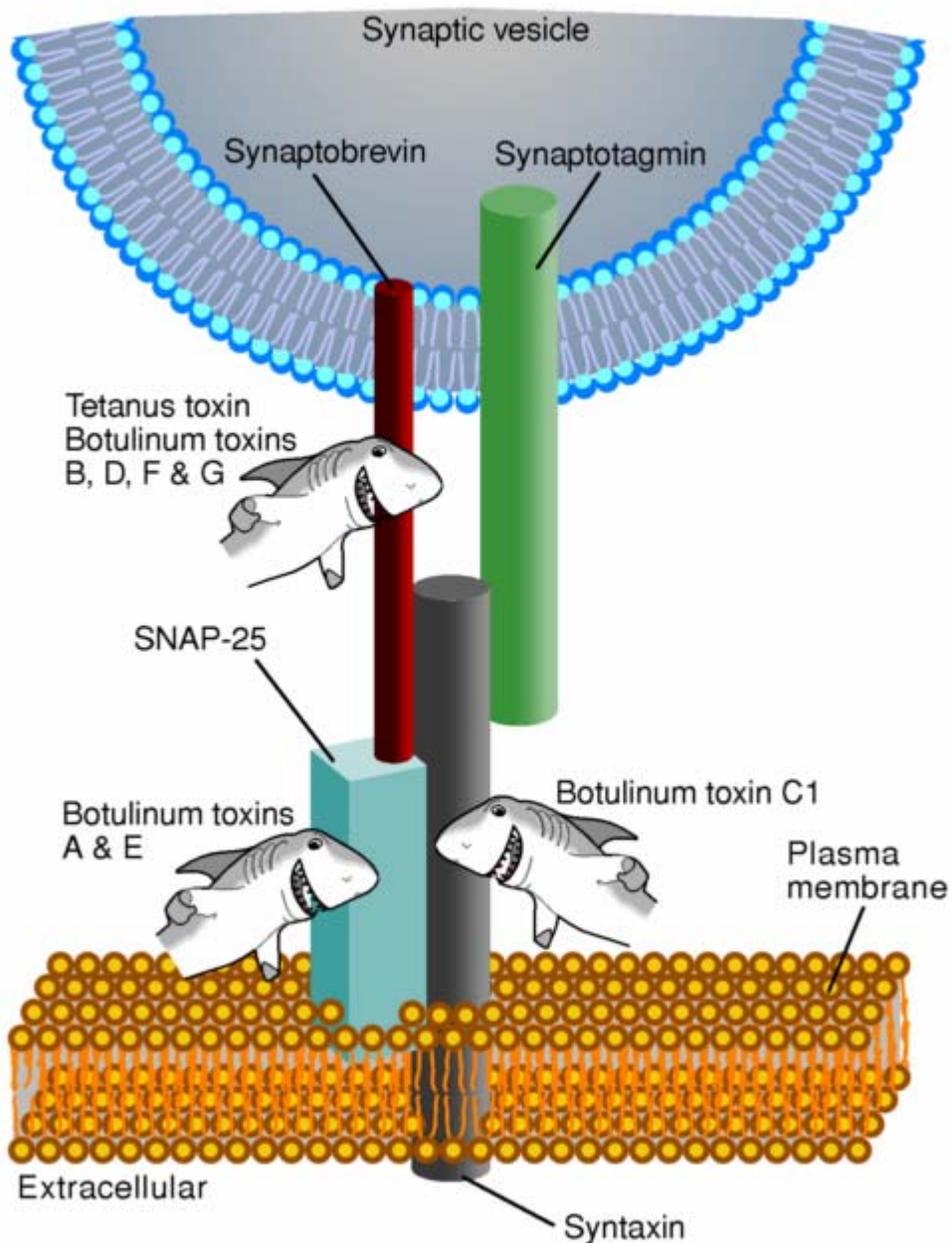
# Das „Dalesche Prinzip“: eine Zelle – ein Transmitter



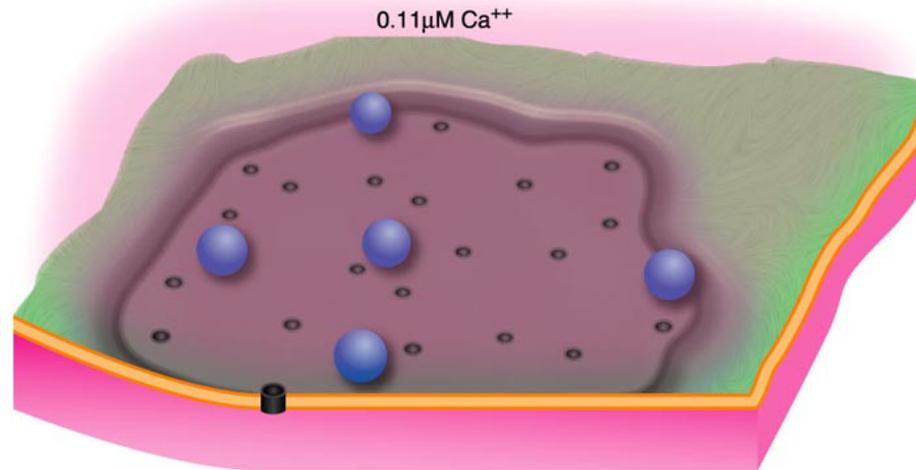
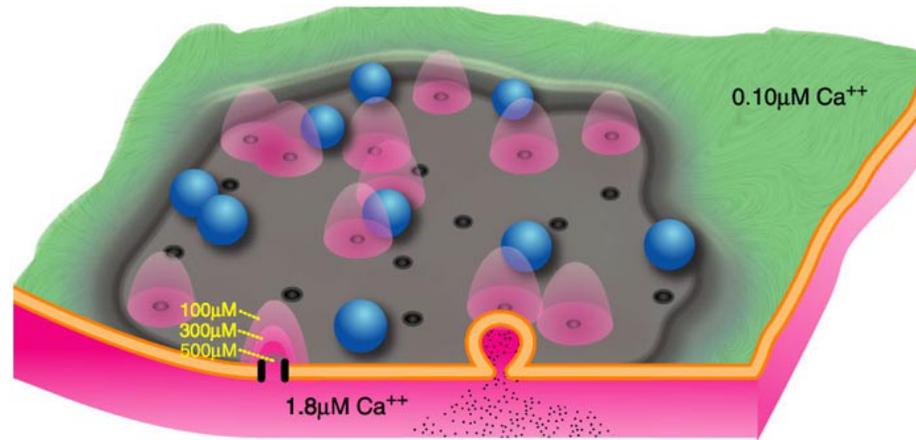
Sir Henry Dale  
1875 – 1968  
Nobelpreis 1936

FIG 7.4

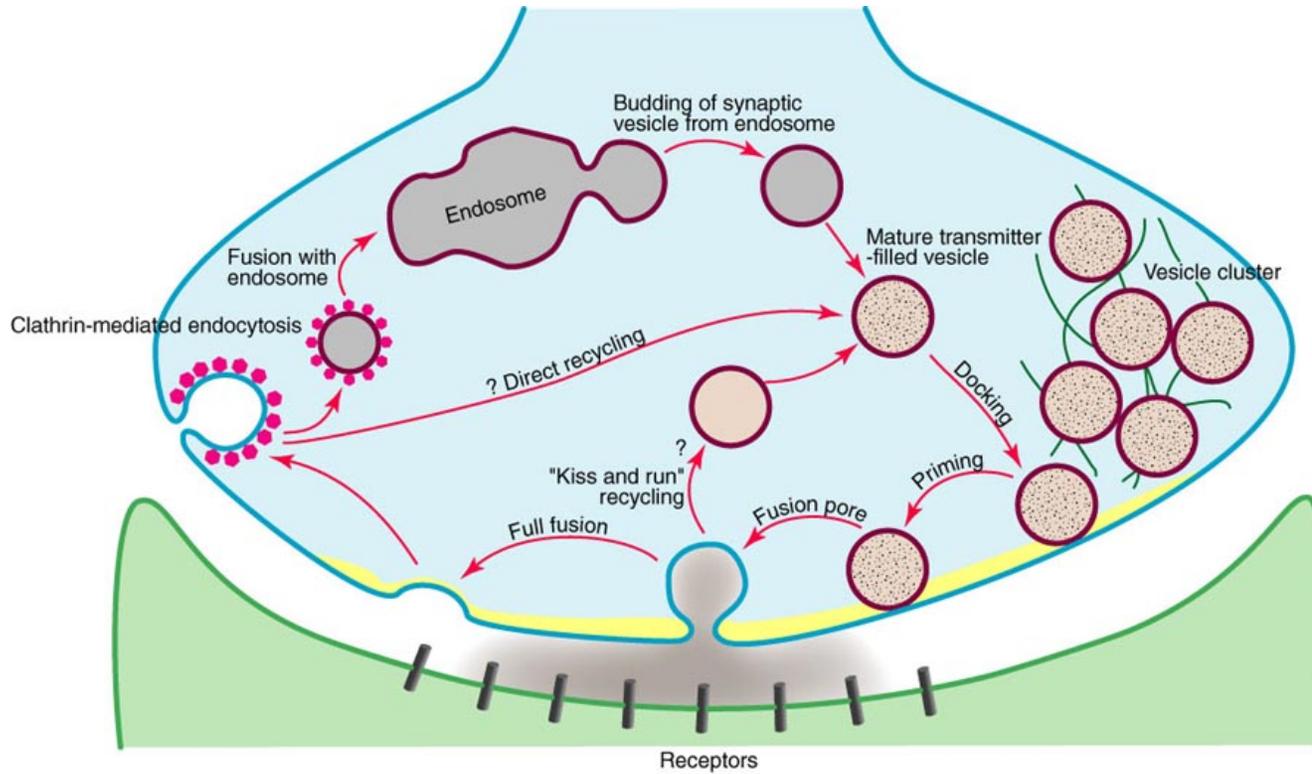




# Ca<sup>2+</sup>-abhängige Freisetzung



# Der Vesikelzyklus

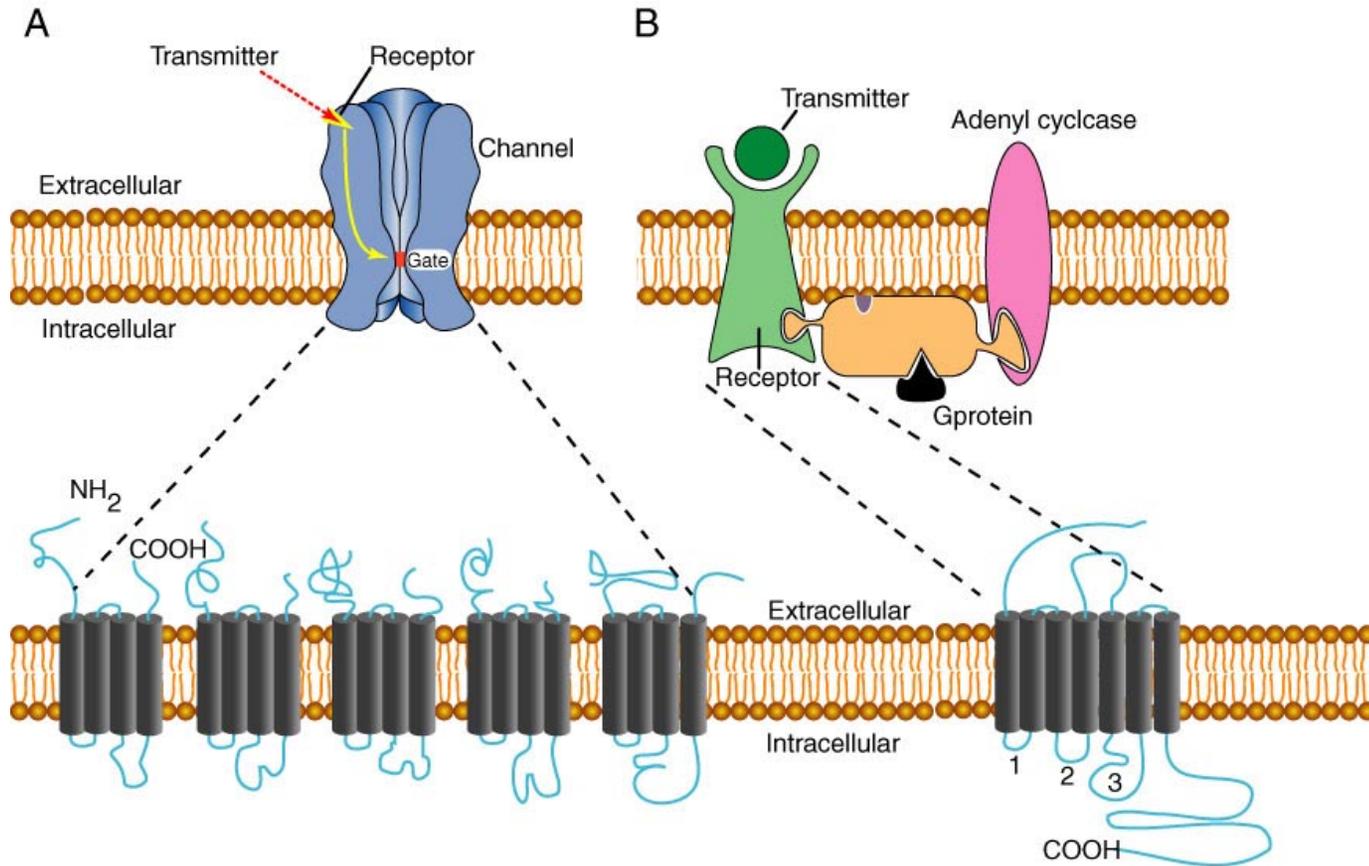


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Readily releasable pool – reserve pool

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# Postsynaptische Rezeptoren



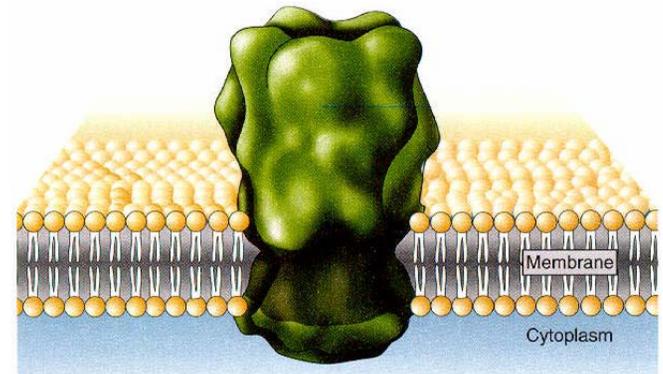
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Grundtypen: Ionenkanäle und GPCR

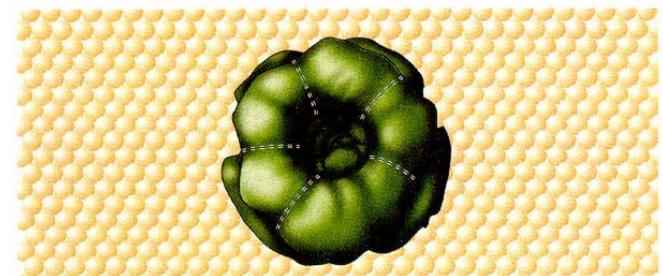
- Porenbildende Proteine
- “gating“:  $E_M$  oder Liganden
- passive Leitung des Stroms!
- Ionenselektivität

Hemmung / Erregung

Calcium-Einstrom

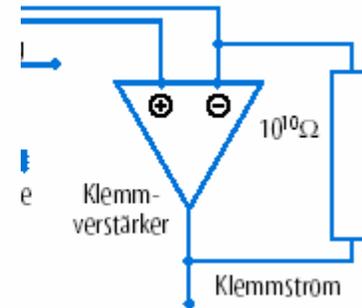
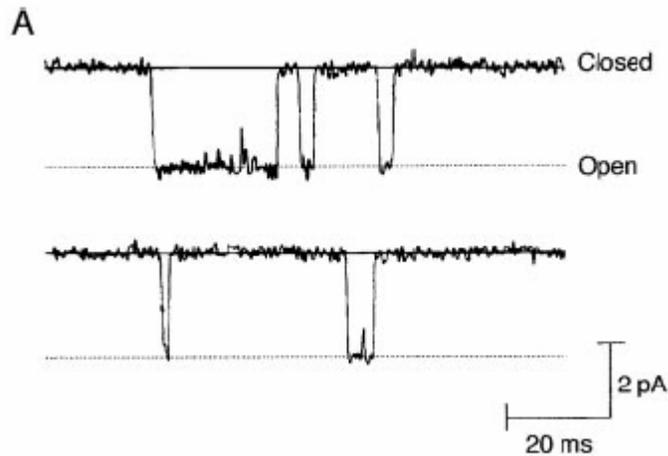


(a)



(b)

# Untersuchung des Verhaltens einzelner Ionenkanäle mit Hilfe der **patch clamp** Technik



B. Sakmann aus  
Neuron Vol. 25,  
S1–S55, 2000, Cell Press

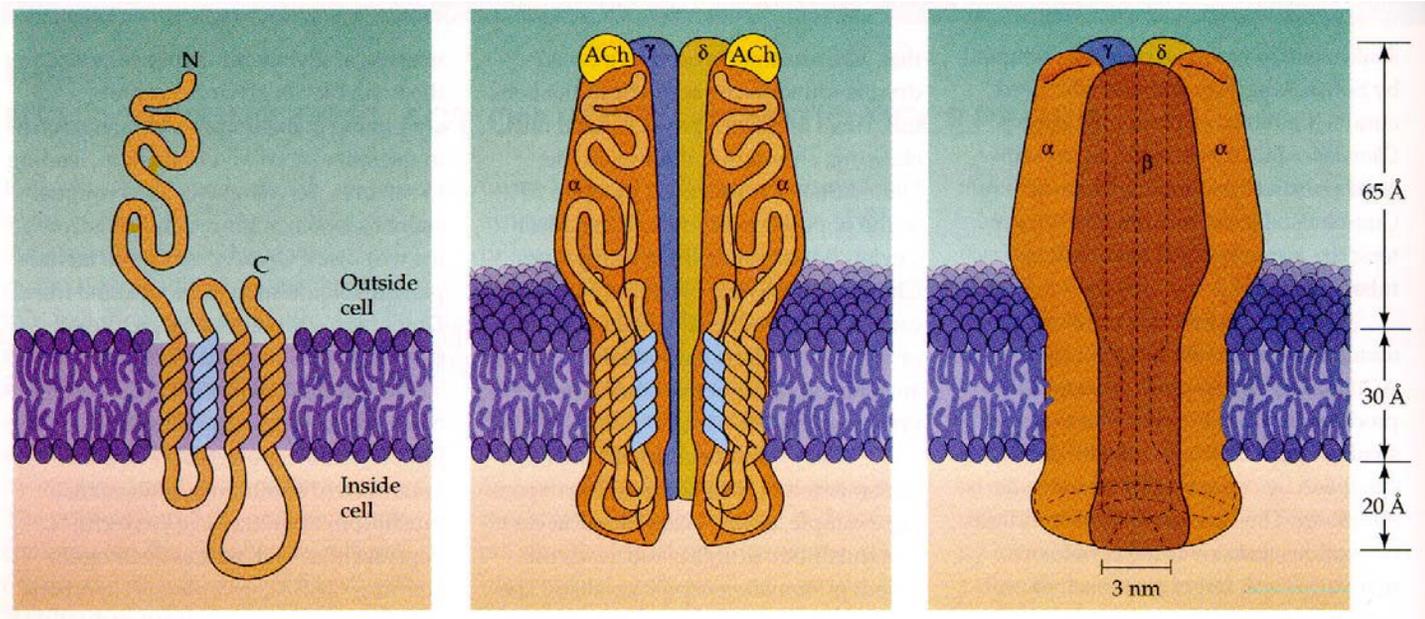


Erwin Neher  
Nobelpreis 1991



Bert Sakmann  
Nobelpreis 1991

# Molekulare Physiologie der Ionenkanäle (1): Struktur-Funktions-Beziehungen



Untereinheit mit  
Transmembrandomänen

Schnitt durch die Ach-  
bindenden Untereinheiten

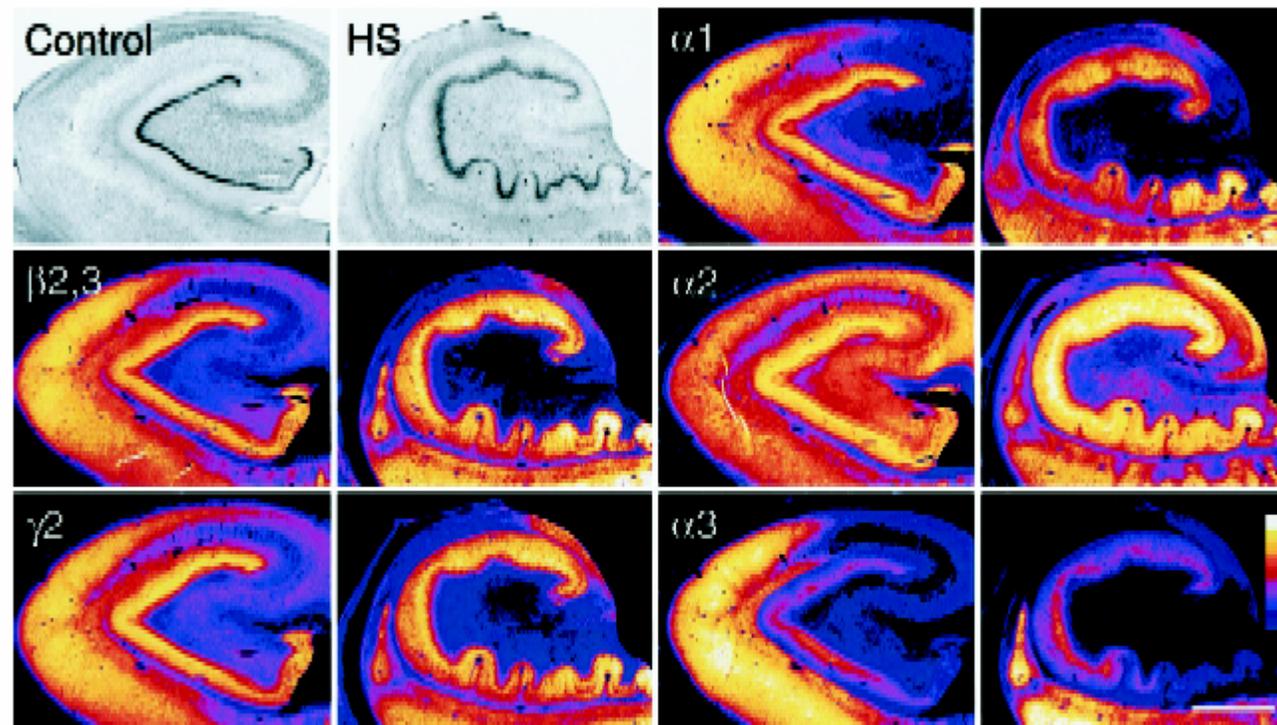
Rezeptor als Ganzes aus  
fünf Untereinheiten



## Selective Alterations in GABA<sub>A</sub> Receptor Subtypes in Human Temporal Lobe Epilepsy

Fabienne Loup,<sup>1</sup> Heinz-Gregor Wieser,<sup>2</sup> Yasuhiro Yonekawa,<sup>3</sup> Adriano Aguzzi,<sup>4</sup> and Jean-Marc Fritschy<sup>1</sup>

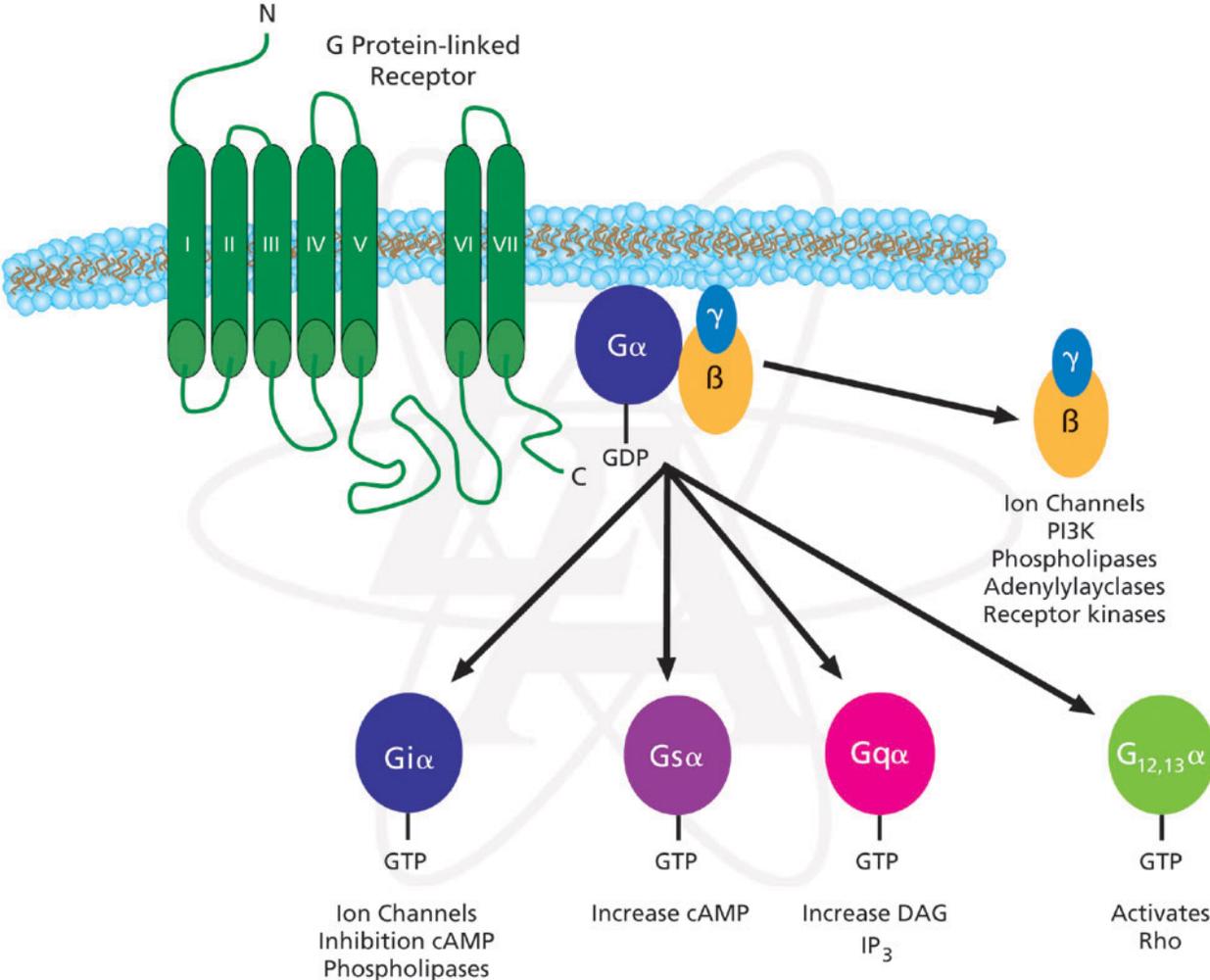
<sup>1</sup>Institute of Pharmacology, University of Zurich, and Departments of <sup>2</sup>Neurology, <sup>3</sup>Neurosurgery, and <sup>4</sup>Neuropathology, University Hospital Zurich, 8057 Zurich, Switzerland



**Figure 2.** Cytoarchitecture and regional distribution of the major GABA<sub>A</sub> receptor subunits in the hippocampus from a control (autopsy, *first and third columns*) and a TLE patient with HS (*second and fourth columns*). Optical density of staining is color-coded according to a normalized scale showing the strongest signal in white and the background in dark blue. In both specimens, adjacent sections were stained for the subunits  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$ ,  $\beta 2,3$ , and  $\gamma 2$ , and for Nissl. In the control, Nissl staining shows a normal distribution of neuronal cell somata. Labeling for the  $\beta 2,3$ - and  $\gamma 2$ -subunits is largely similar, whereas each  $\alpha$ -subunit has a differential distribution pattern. In TLE with HS, Nissl staining reveals prominent cell loss in CA1, CA3, and dentate hilus with relative sparing of the dentate granule cell layer and granule cell dispersion. The CA2 and partly CA3 pyramidal cell layer is not shown in this section, but is visible in those stained for the  $\alpha$ -subunits. The decrease in GABA<sub>A</sub> receptor subunit immunoreactivity parallels cell loss in CA1, CA3, and dentate hilus, whereas staining is increased or decreased in a subunit-specific manner in CA2 and dentate gyrus. The magenta spots in the dentate hilus represent surviving mossy cells. Scale bar, 2 mm.

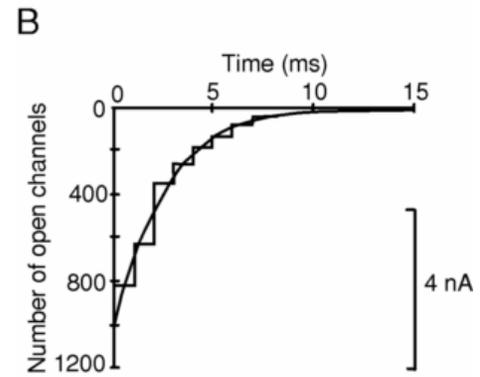
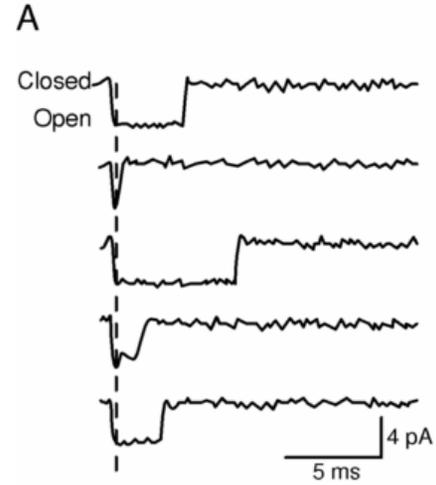
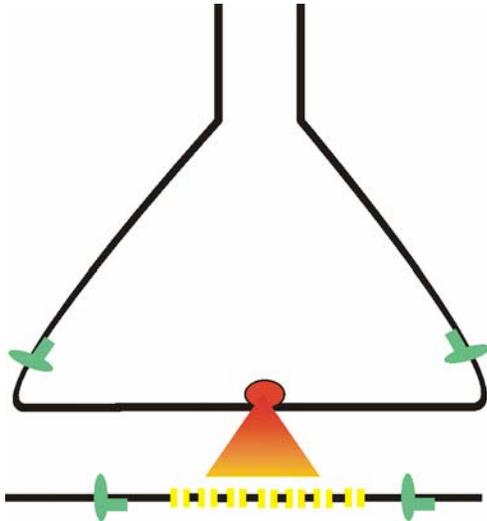
# Diversity of G Protein-Coupled Receptor Signal Transduction Pathways

SIGMA-ALDRICH



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# „Quanten“

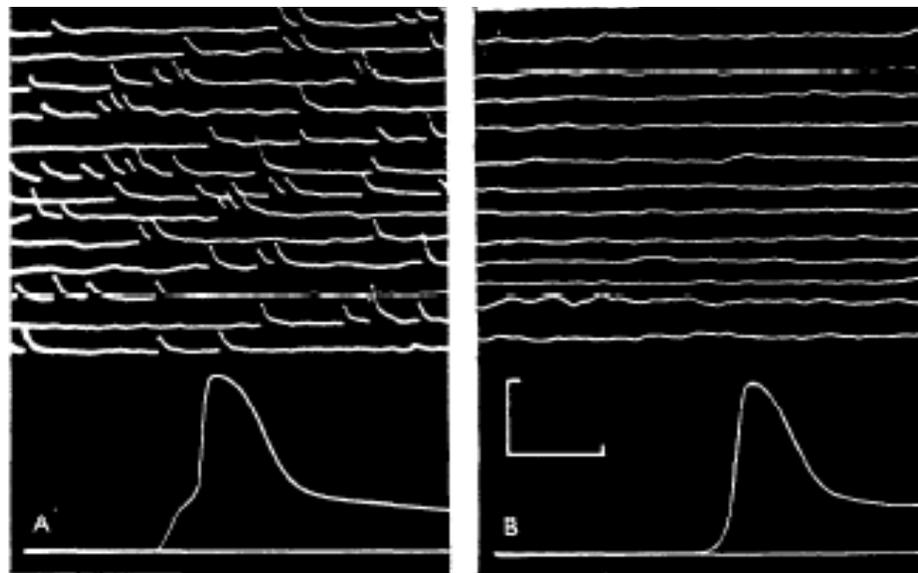


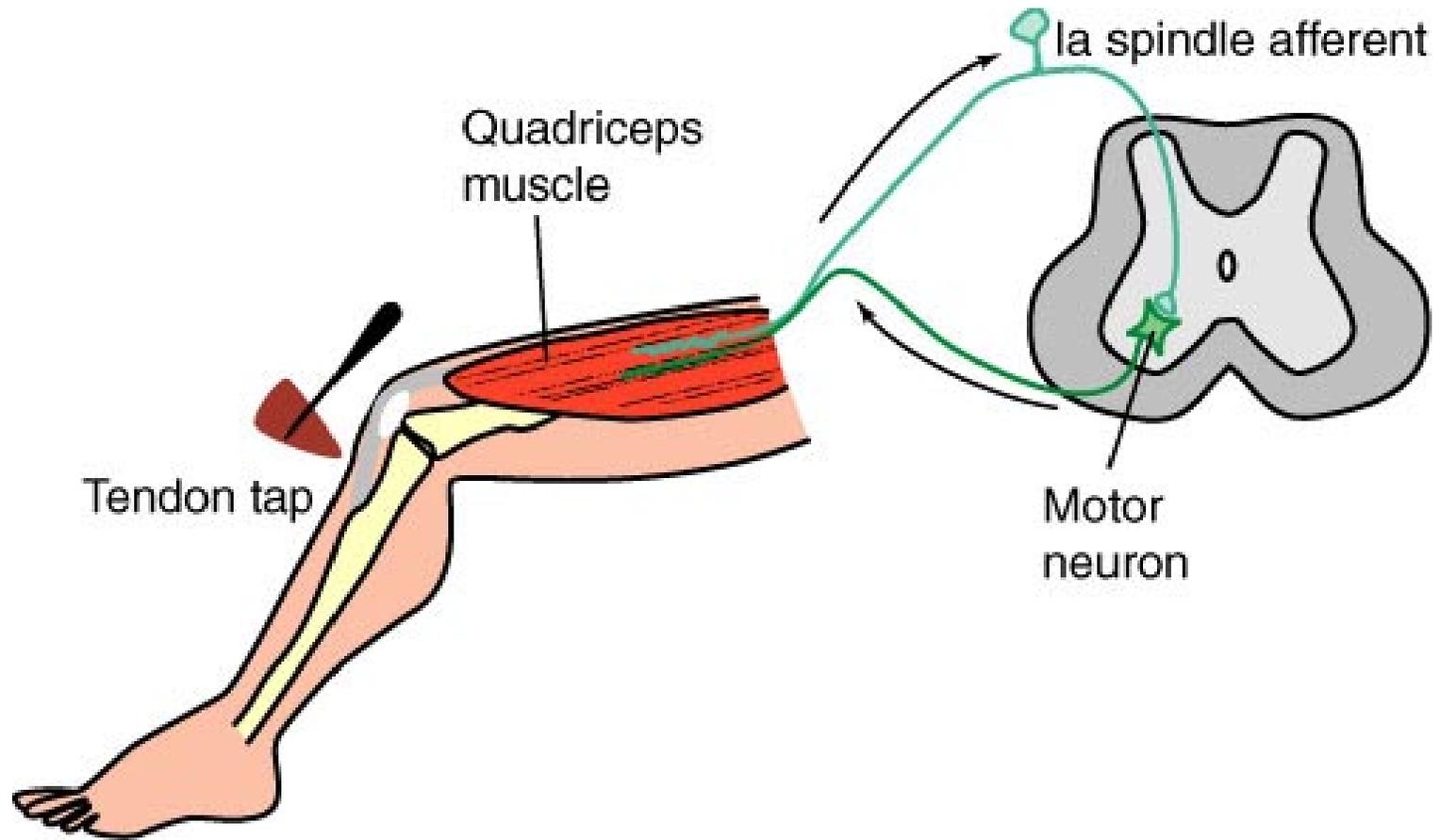
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B. KATZ

On the quantal mechanism of neural  
transmitter release

*Nobel Lecture, December 12, 1970*





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Die nmj ist ein Schalter  
 – hier wird nicht “verrechnet“

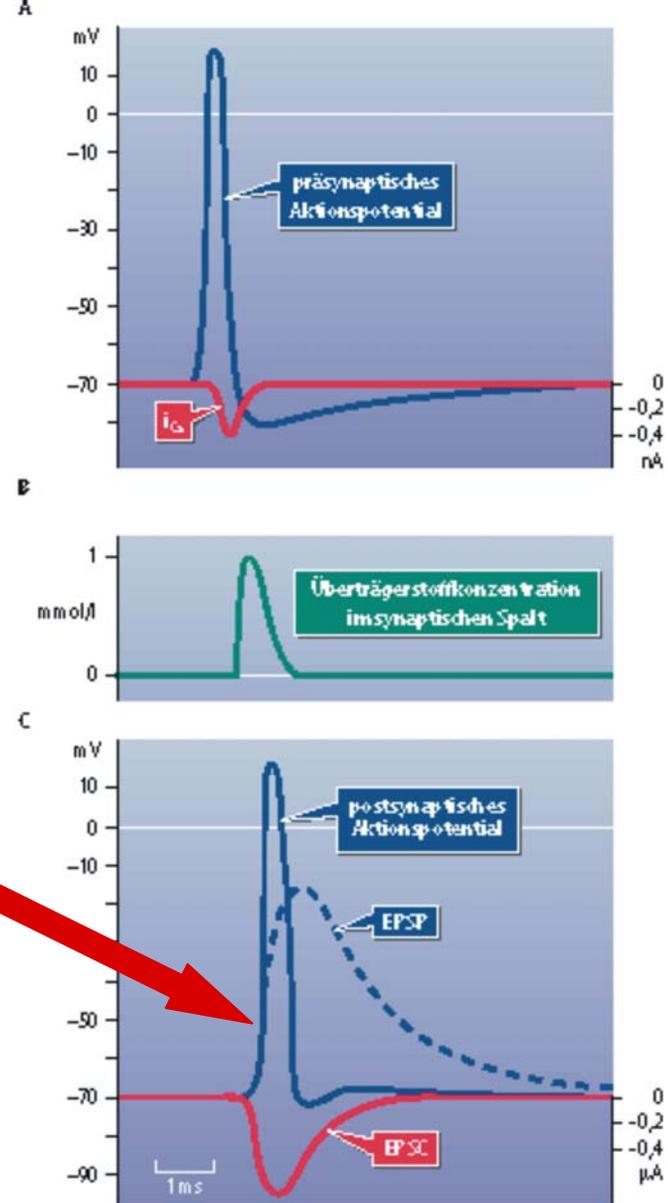
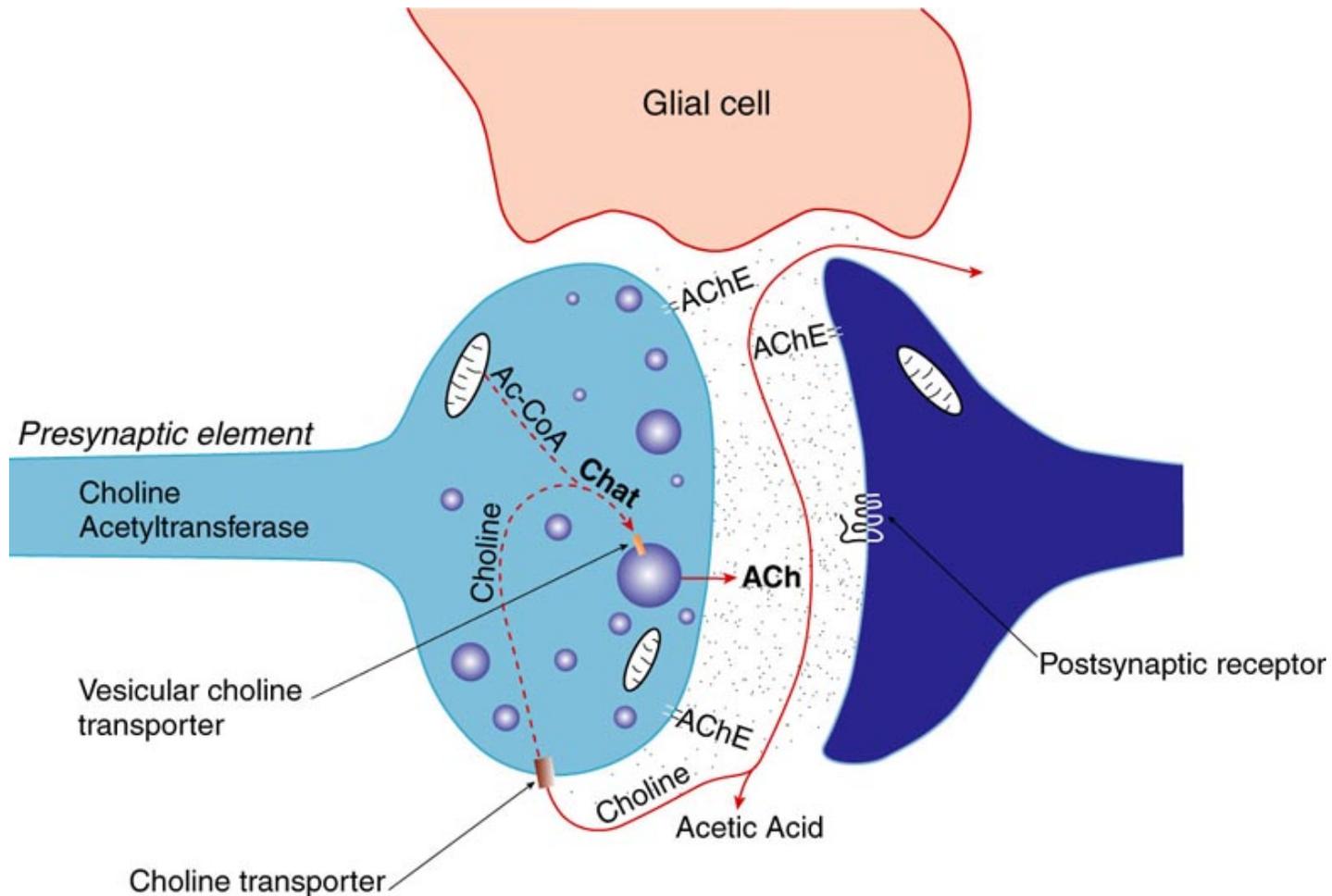
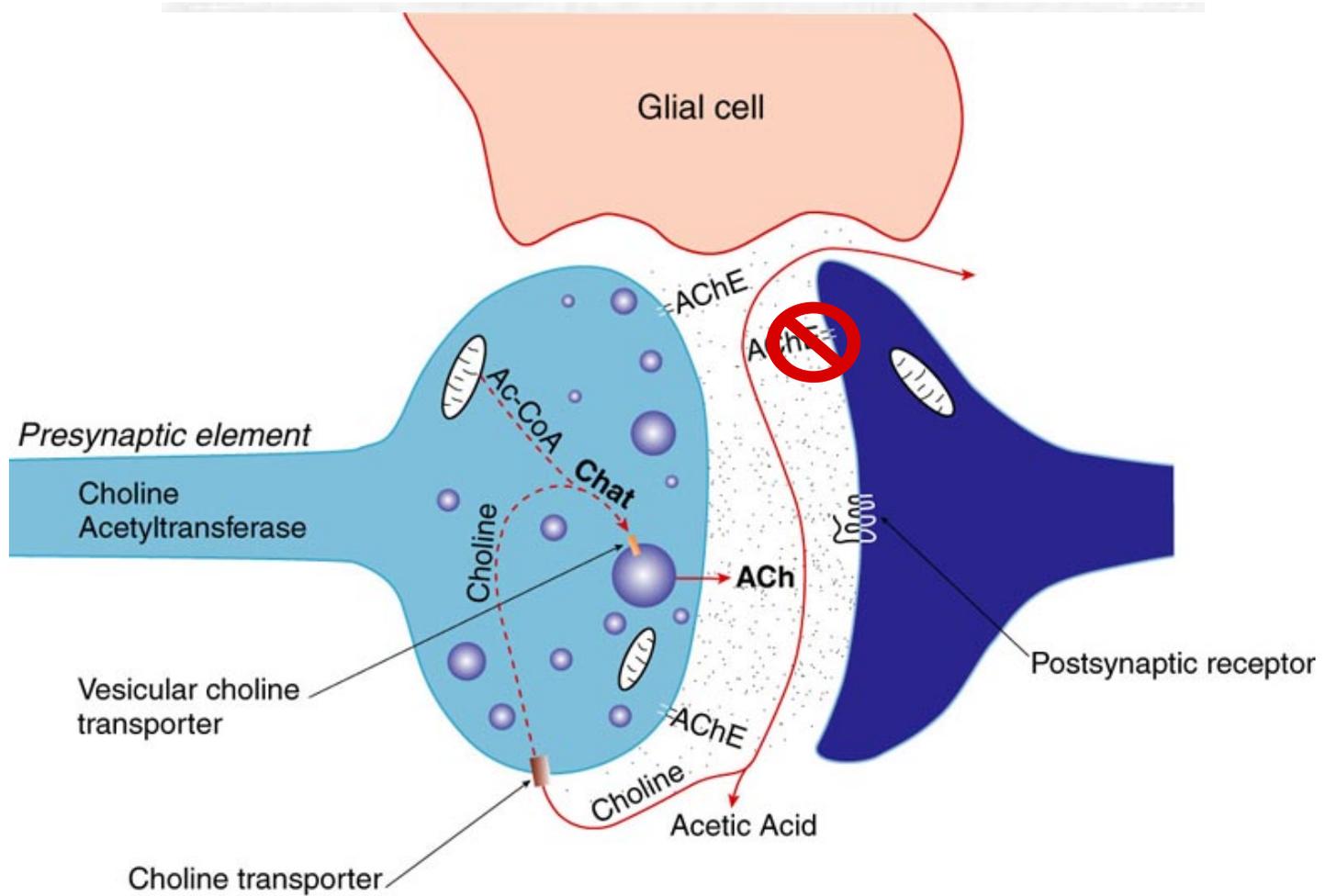


Abb. 3-14 aus Schmidt/Thews: Physiologie des Menschen 27. Auflage 1997  
 Kapitel 3: J. Dudek: Erregungsübertragung von Zelle zu Zelle

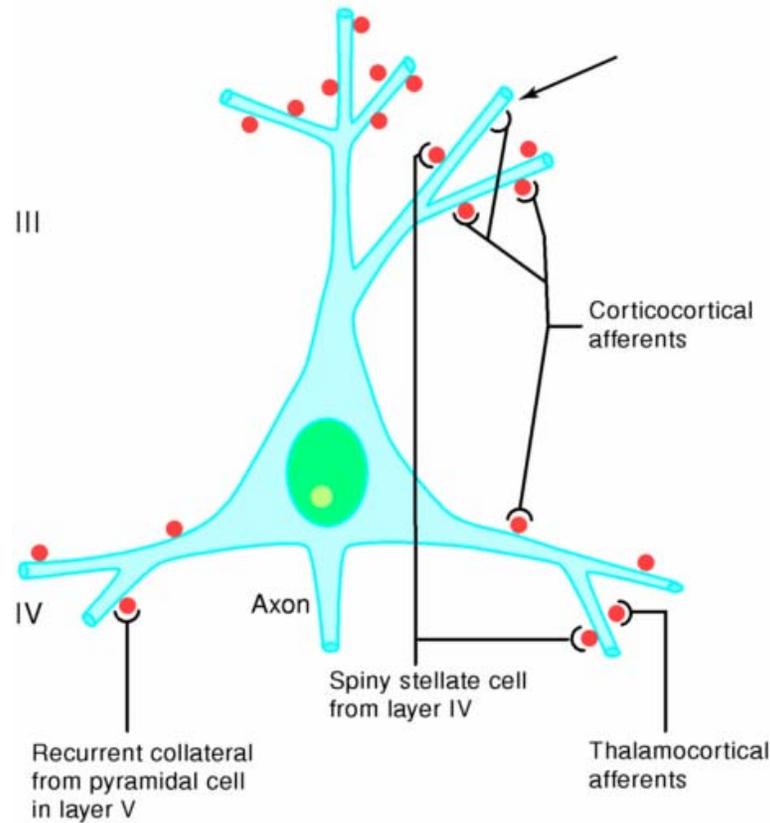


# Beendigung synaptischer Potentiale: Cholinesterase (CHE)





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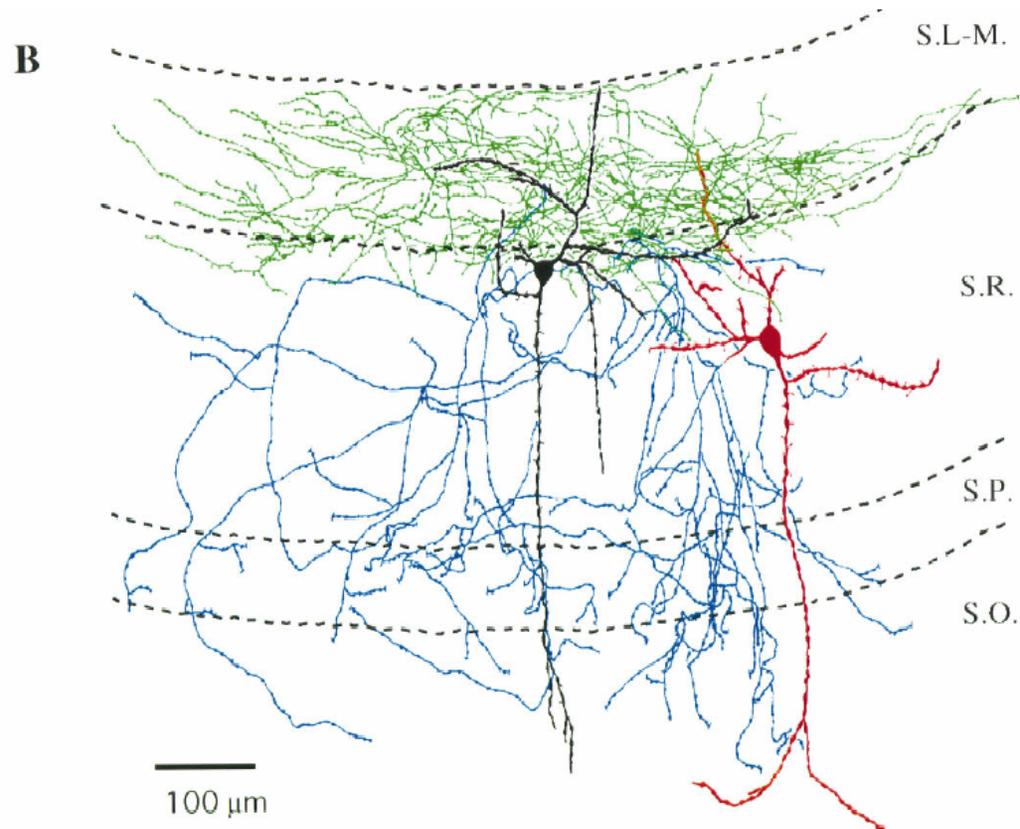


Mehrere tausend (bis  $x \cdot 10^4$ ) Synapsen enden an einzelnen Neuronen  
 Unterschiedliche Transmitter, Lokalisation und Effizienz  
 Überlagerung der Eingänge → Informationsverarbeitung

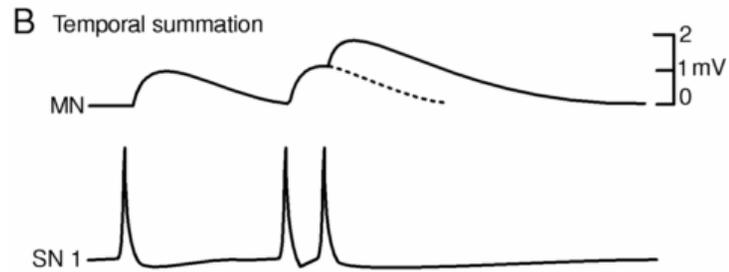
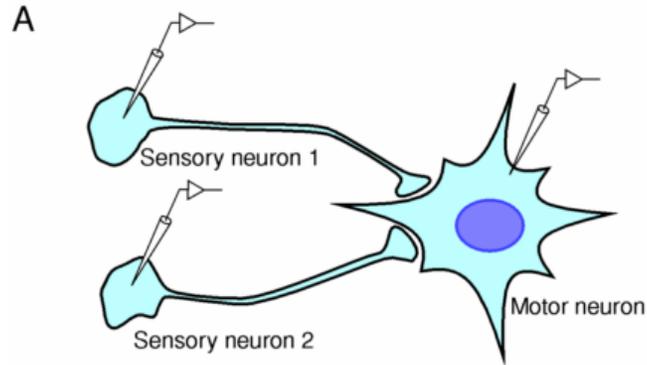
## Synaptic Communication among Hippocampal Interneurons: Properties of Spontaneous IPSCs in Morphologically Identified Cells

Norbert Hájos and Istvan Mody

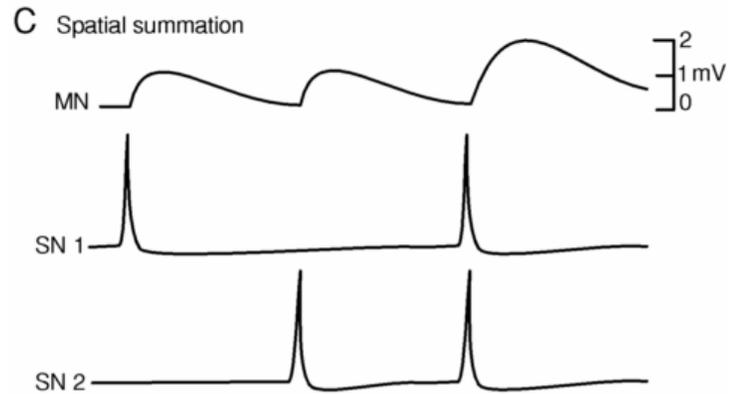
*Departments of Neurology and Physiology, Reed Neurological Research Center, University of California, Los Angeles,  
School of Medicine, Los Angeles, California 90095-1769*



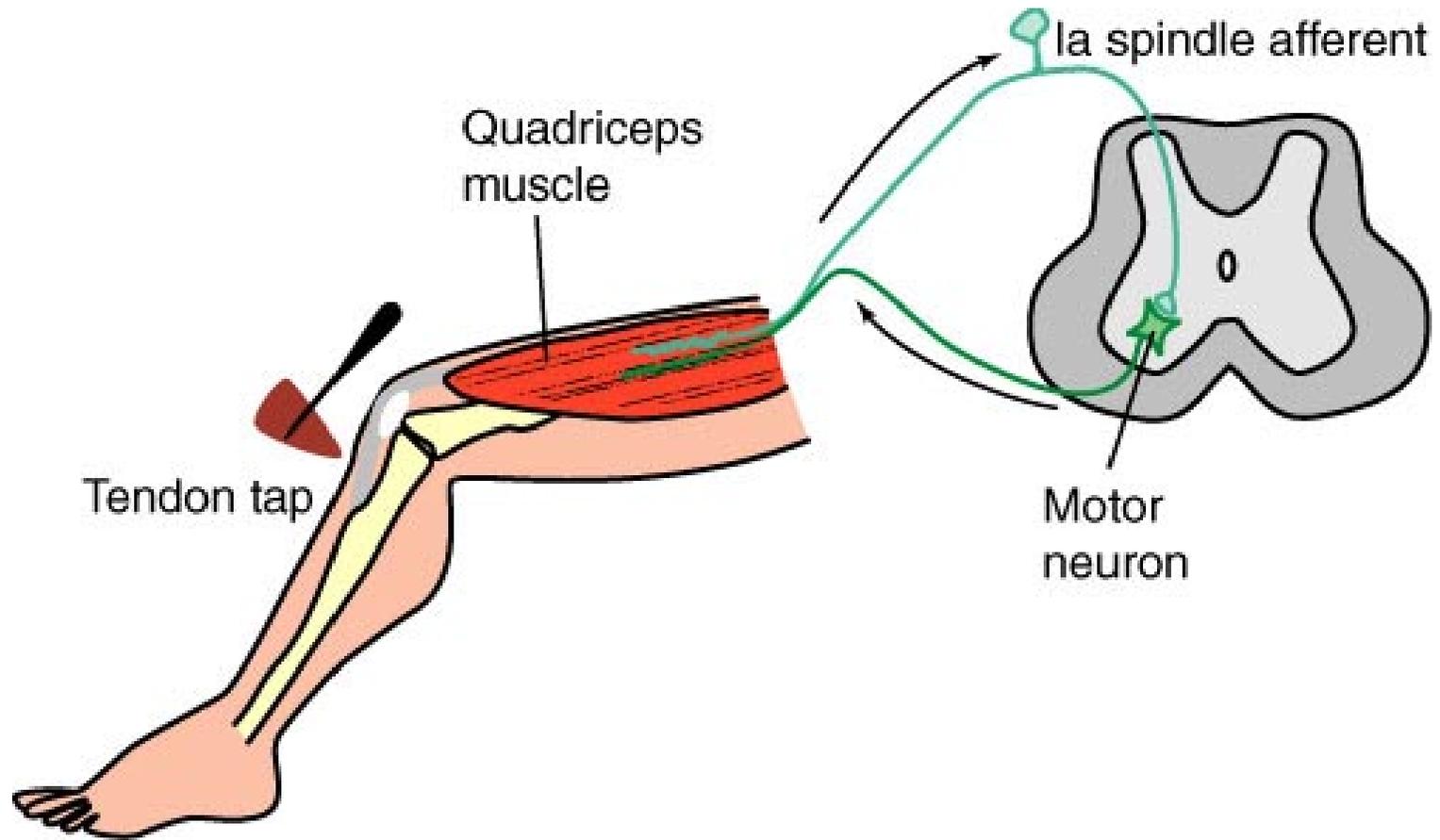
# Summation



zeitlich

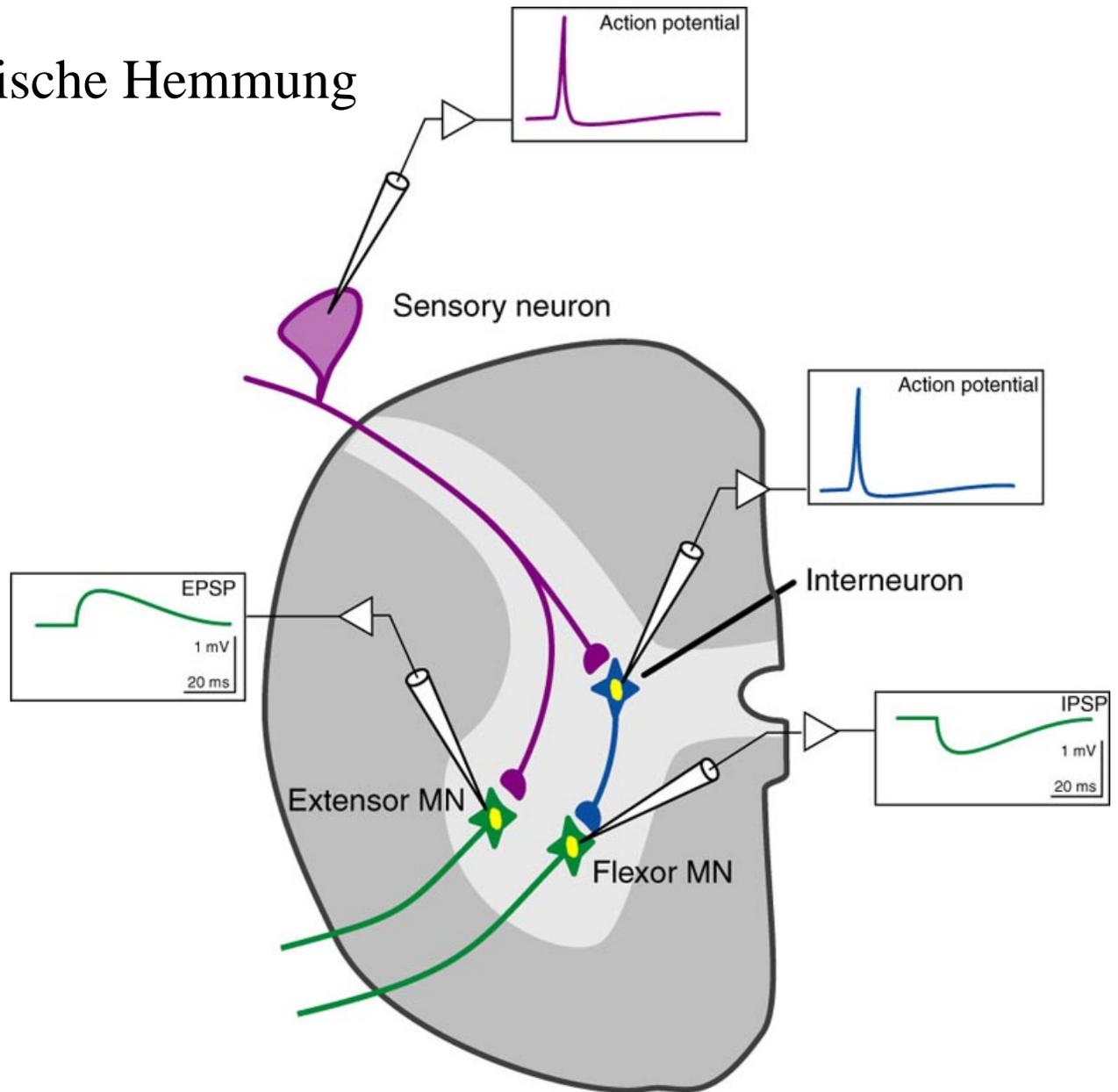


räumlich

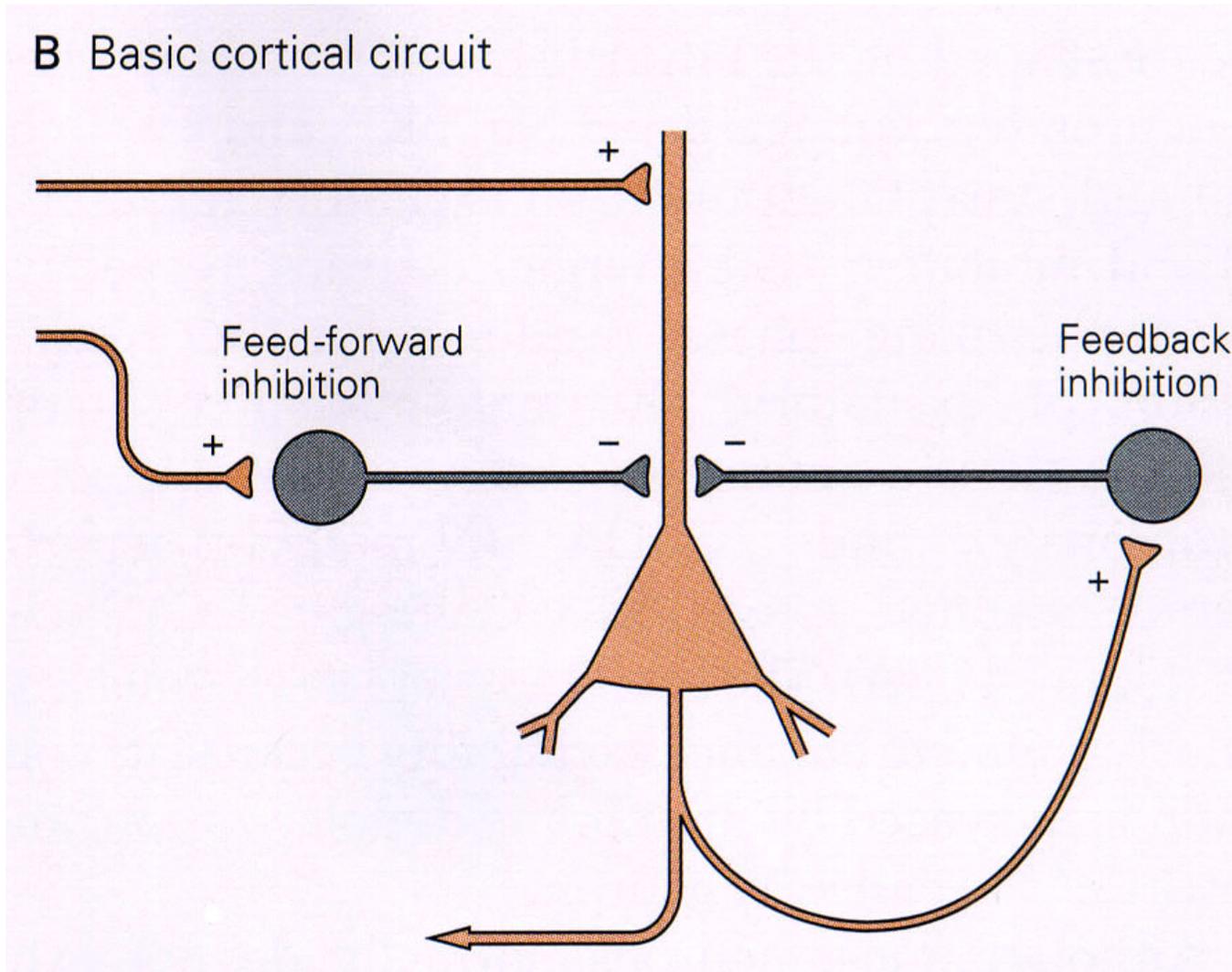


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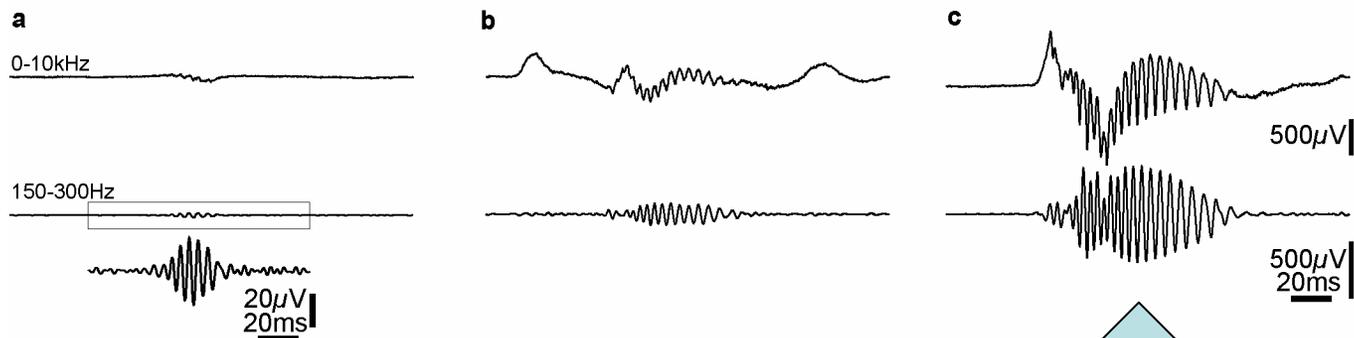
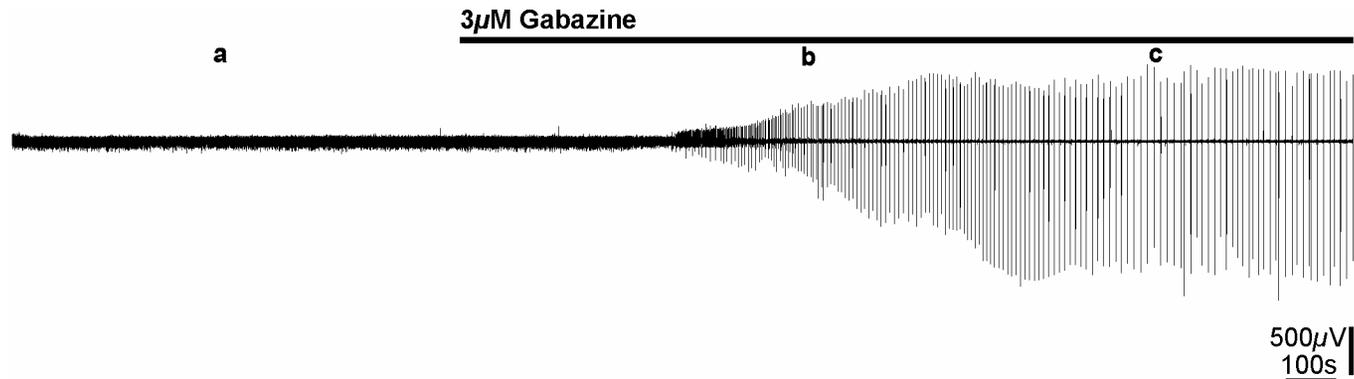
# synaptische Hemmung



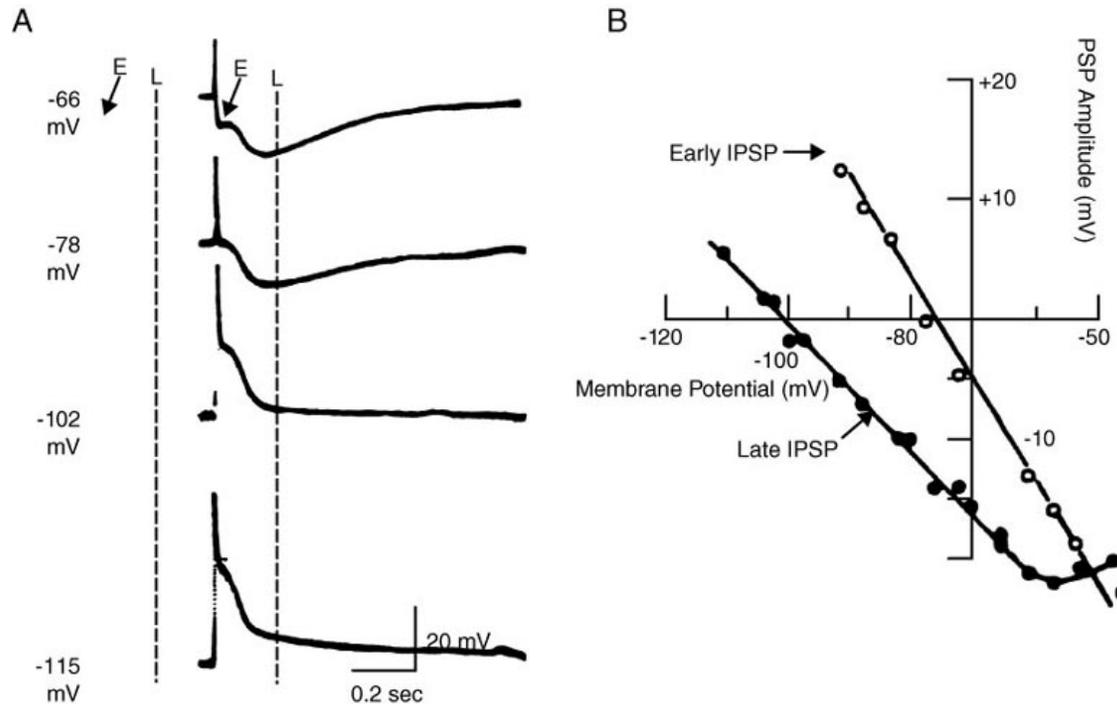
*Alle ZNS-Kerne enthalten inhibitorische (Inter)-Neurone*

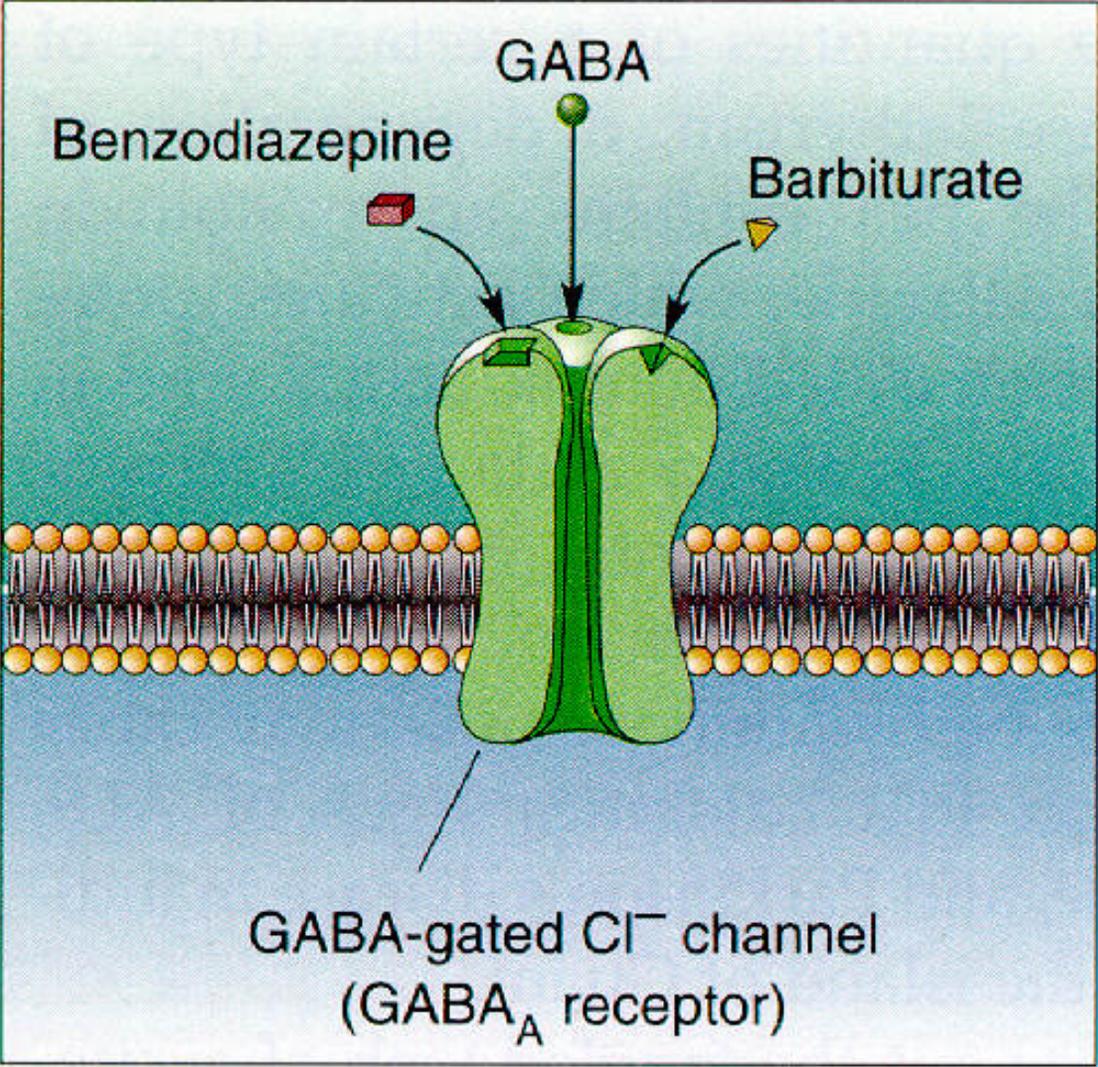


*Ohne Inhibition führt die positive Rückkopplung in hochvernetzten Kerngebieten zur Epilepsie*

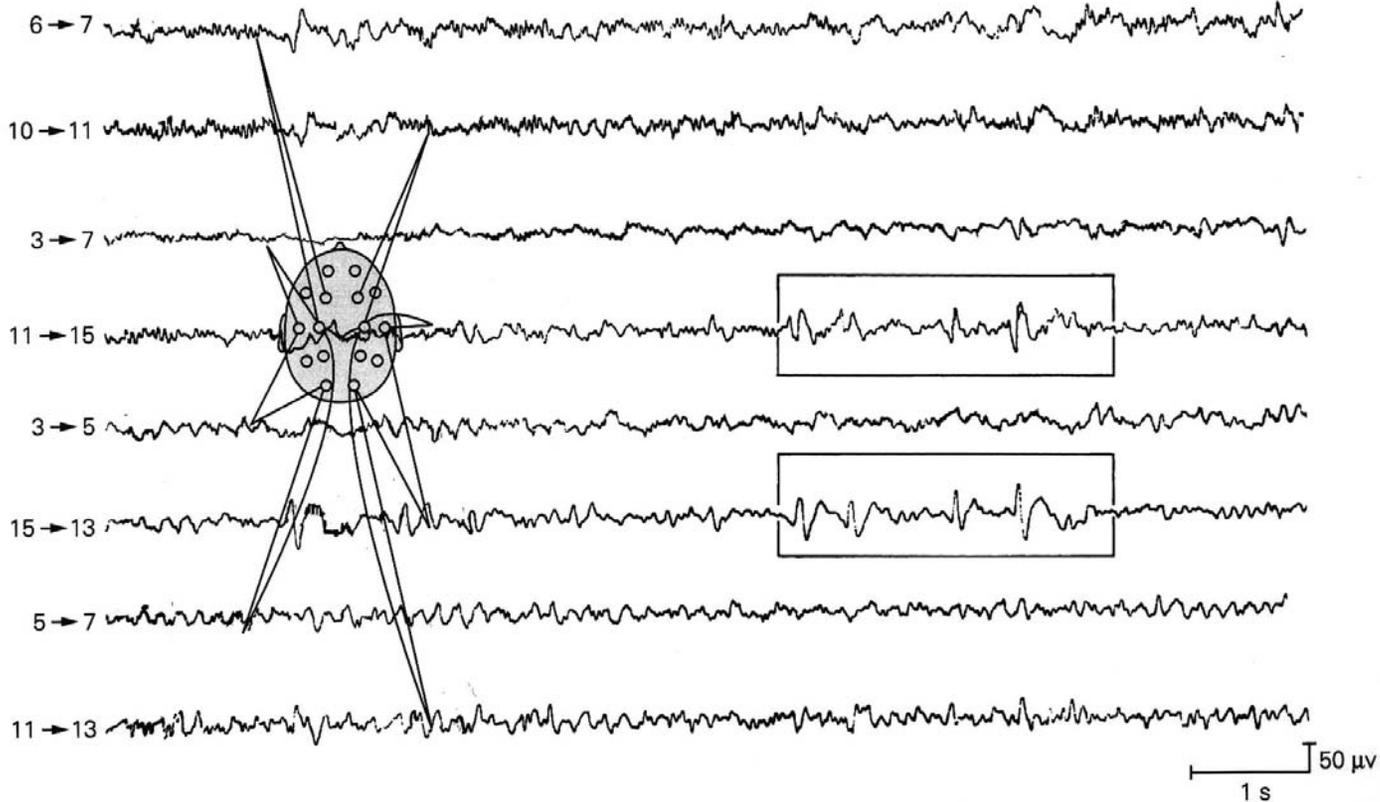


# GABA-A-Rezeptoren leiten selektiv $\text{Cl}^-$ GABA-B-Rezeptoren erhohen $g_{\text{K}^+}$

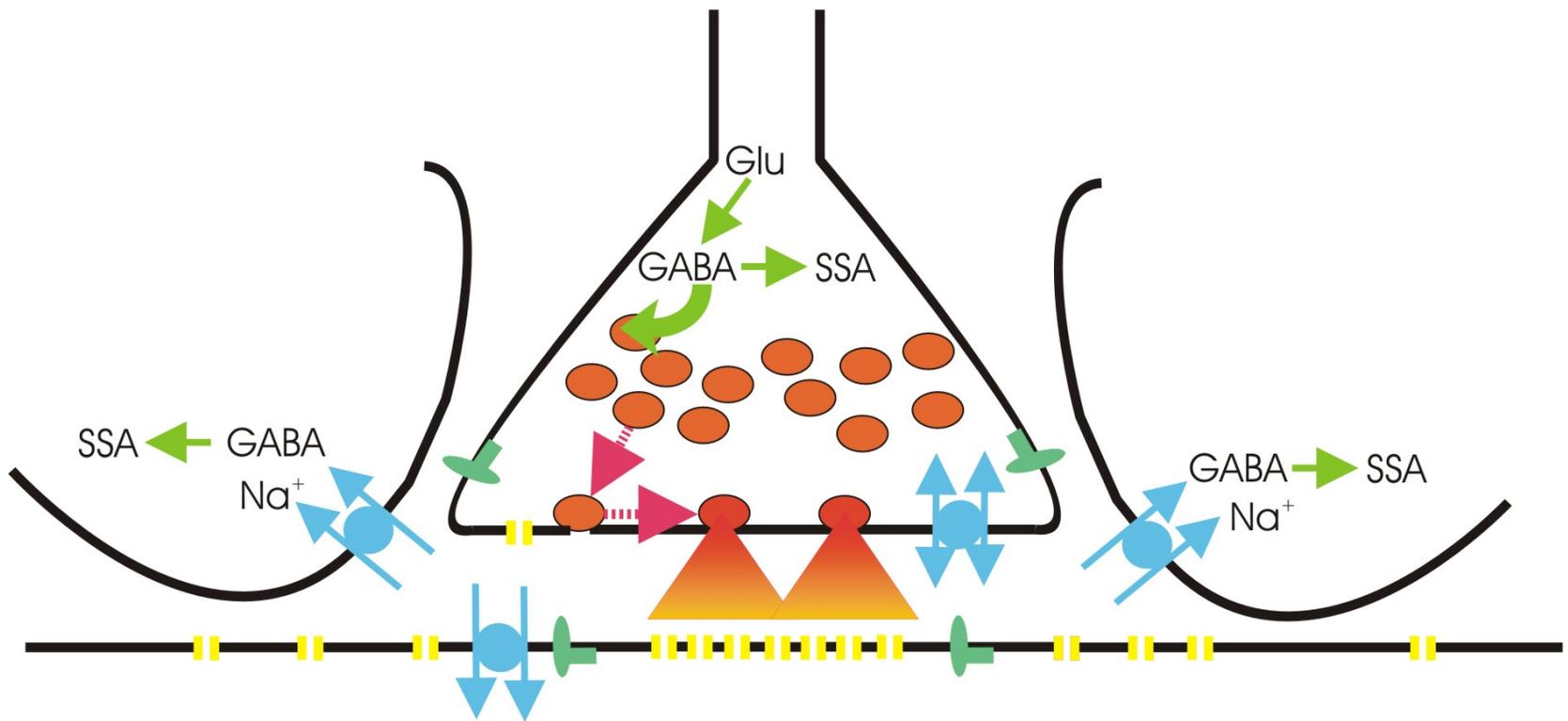




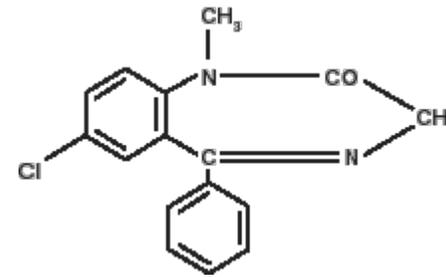
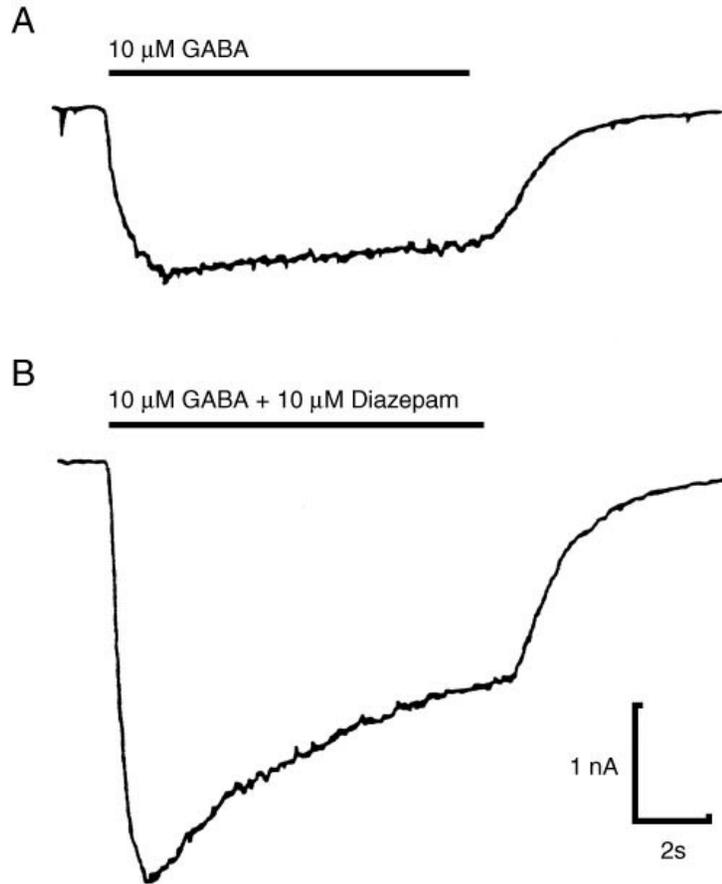
# Fokale Epilepsien



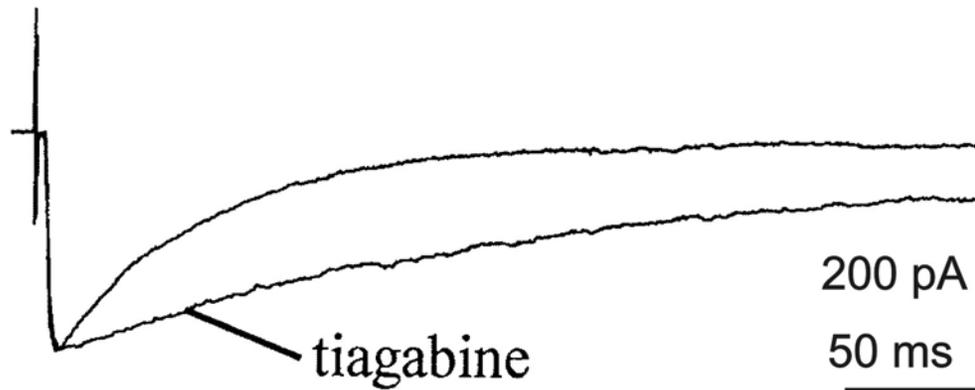
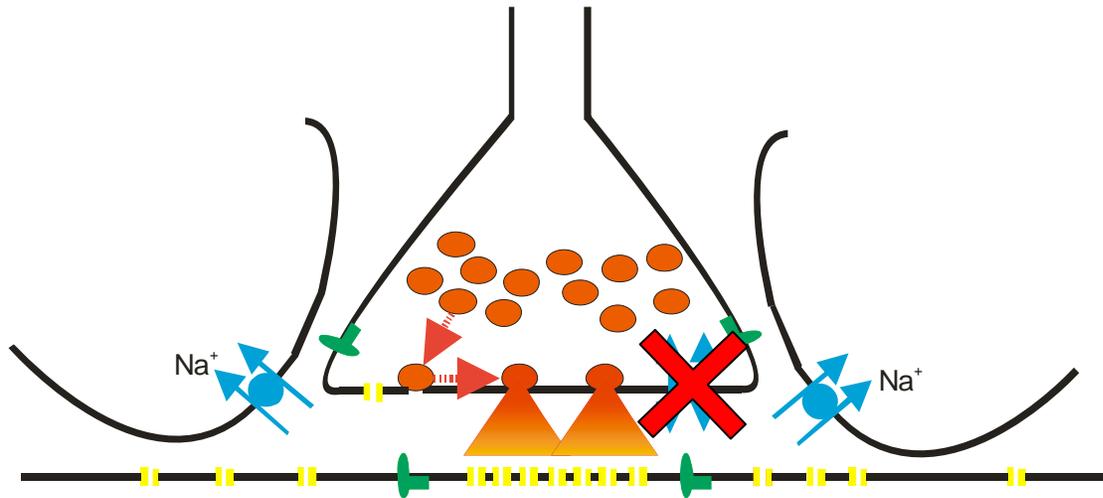
Kandel, Schwartz, Jessel – Principles of Neural Science  
McGraw-Hill, 42000



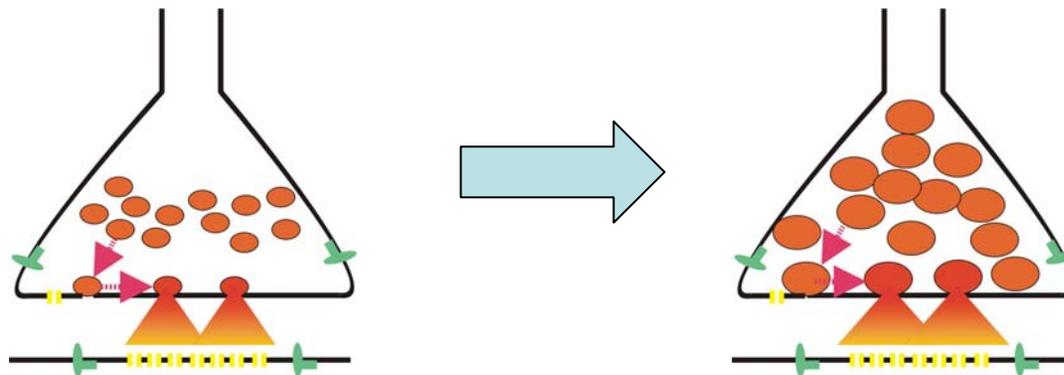
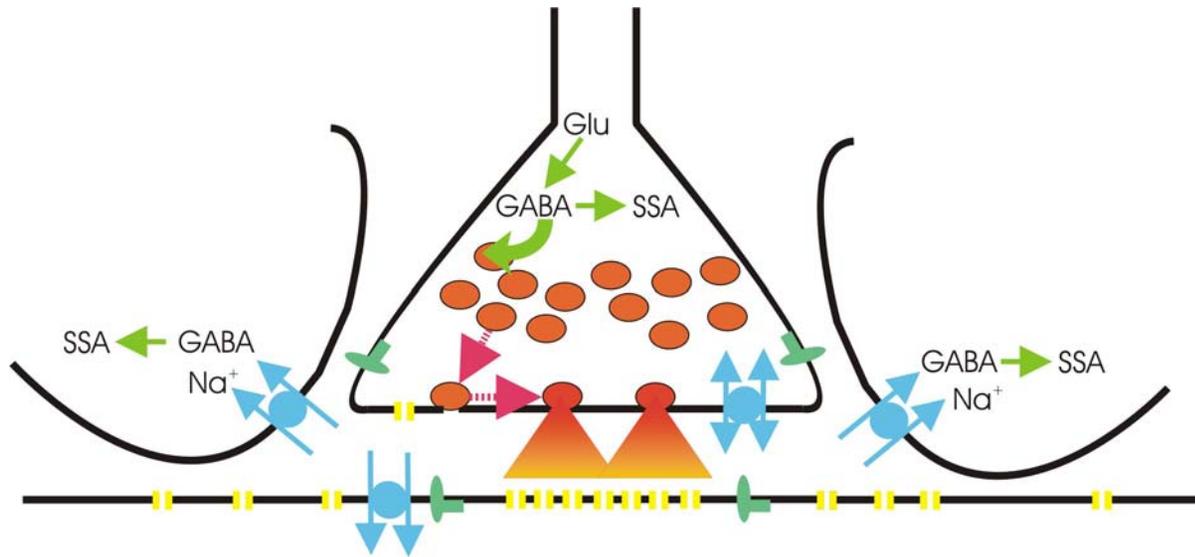
# Potenzierung von GABA<sub>A</sub>R



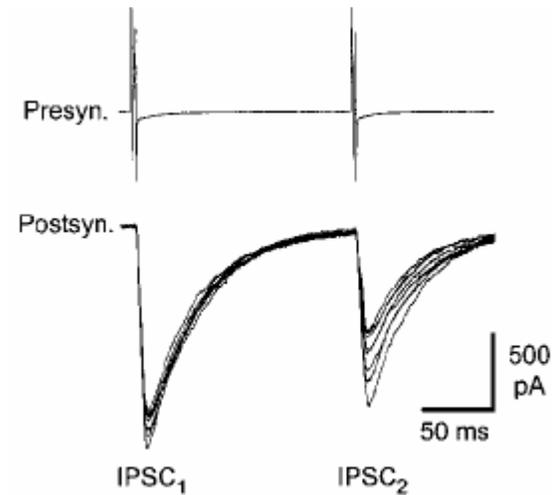
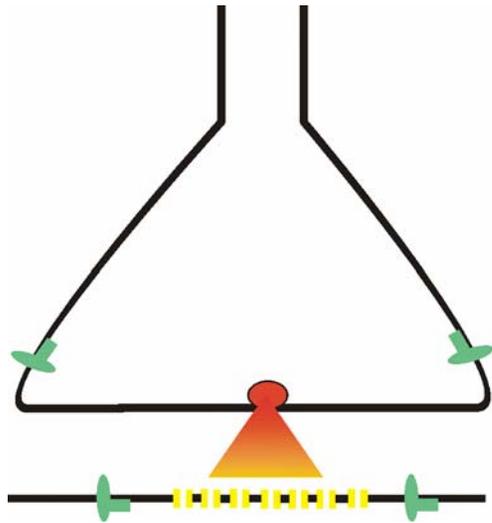
# Blockade des GABA-uptake



# Hemmung des GABA-Katabolismus



# Negatives feedback durch präsynaptische (Auto)-Rezeptoren



## Activity-Dependent Depression of GABAergic IPSCs in Cultured Hippocampal Neurons

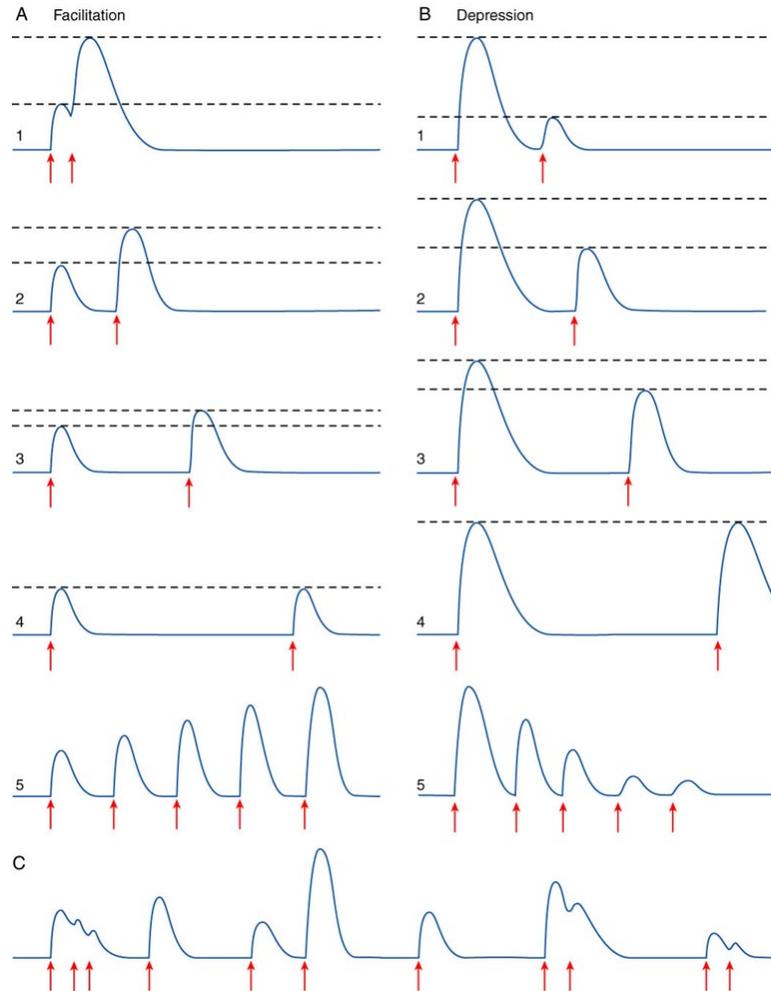
KIMMO JENSEN,<sup>1</sup> JOHN D. C. LAMBERT,<sup>1</sup> AND MORTEN SKOVGAARD JENSEN<sup>2</sup>

<sup>1</sup>Department of Physiology and <sup>2</sup>Department of Neurobiology, Institute of Anatomy, University of Aarhus, DK-8000 Aarhus C, Denmark

- Aufbau
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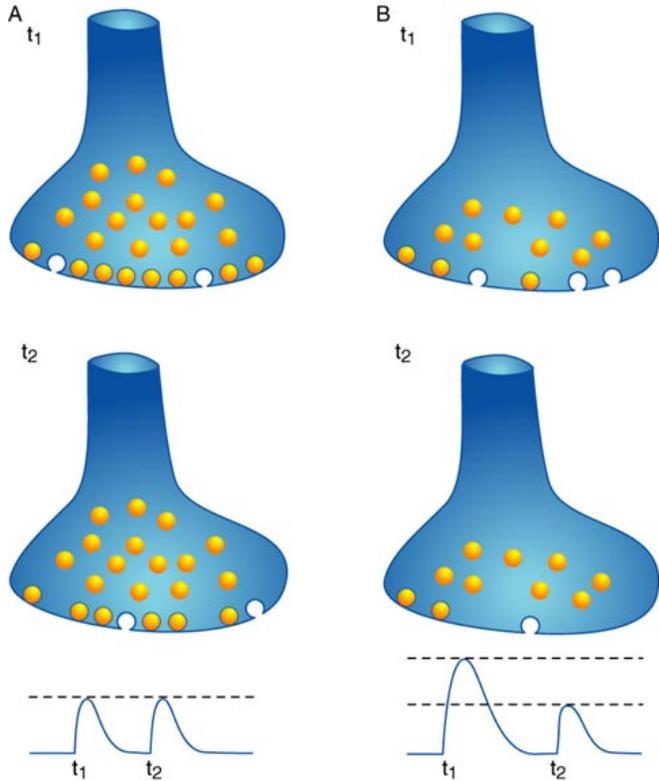
# Zeitabhängiges Verhalten von Synapsen

Bahnung  
(Facilitation)

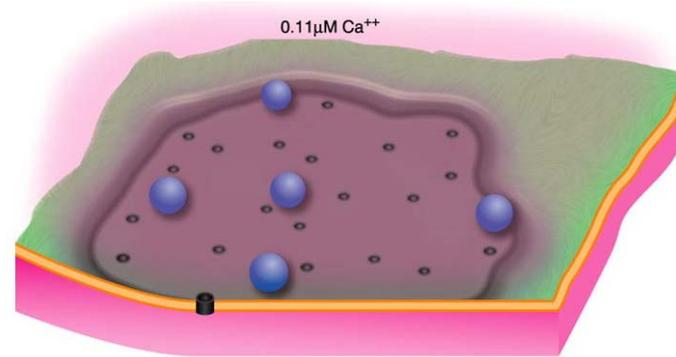


Depression

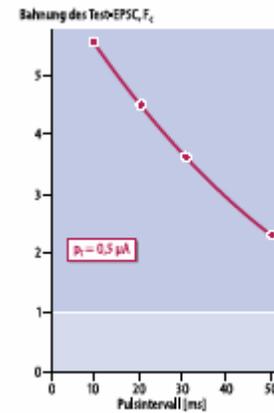
# Mechanismen



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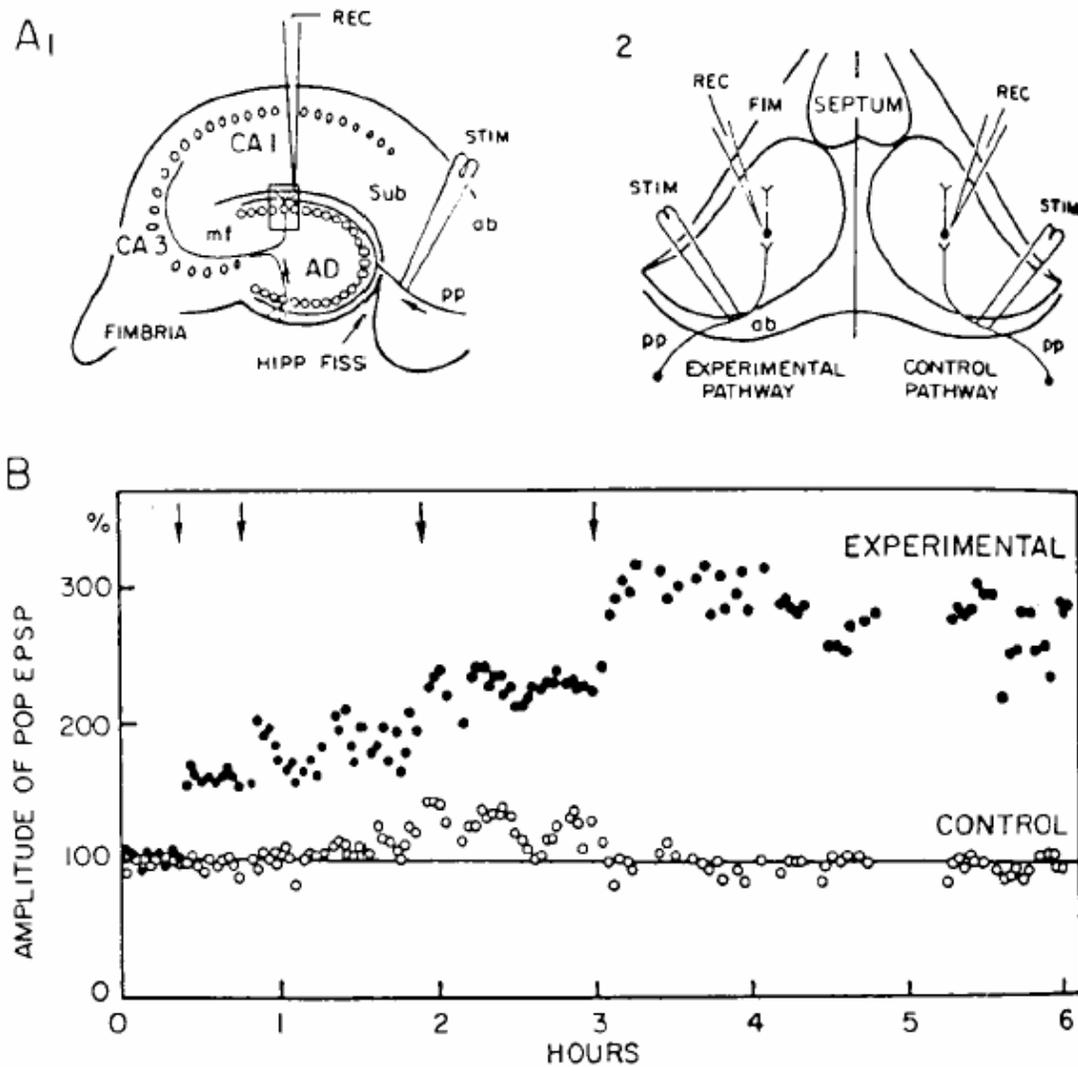
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1. Grösse des Vesikel-Pools und Freisetzungswahrscheinlichkeit

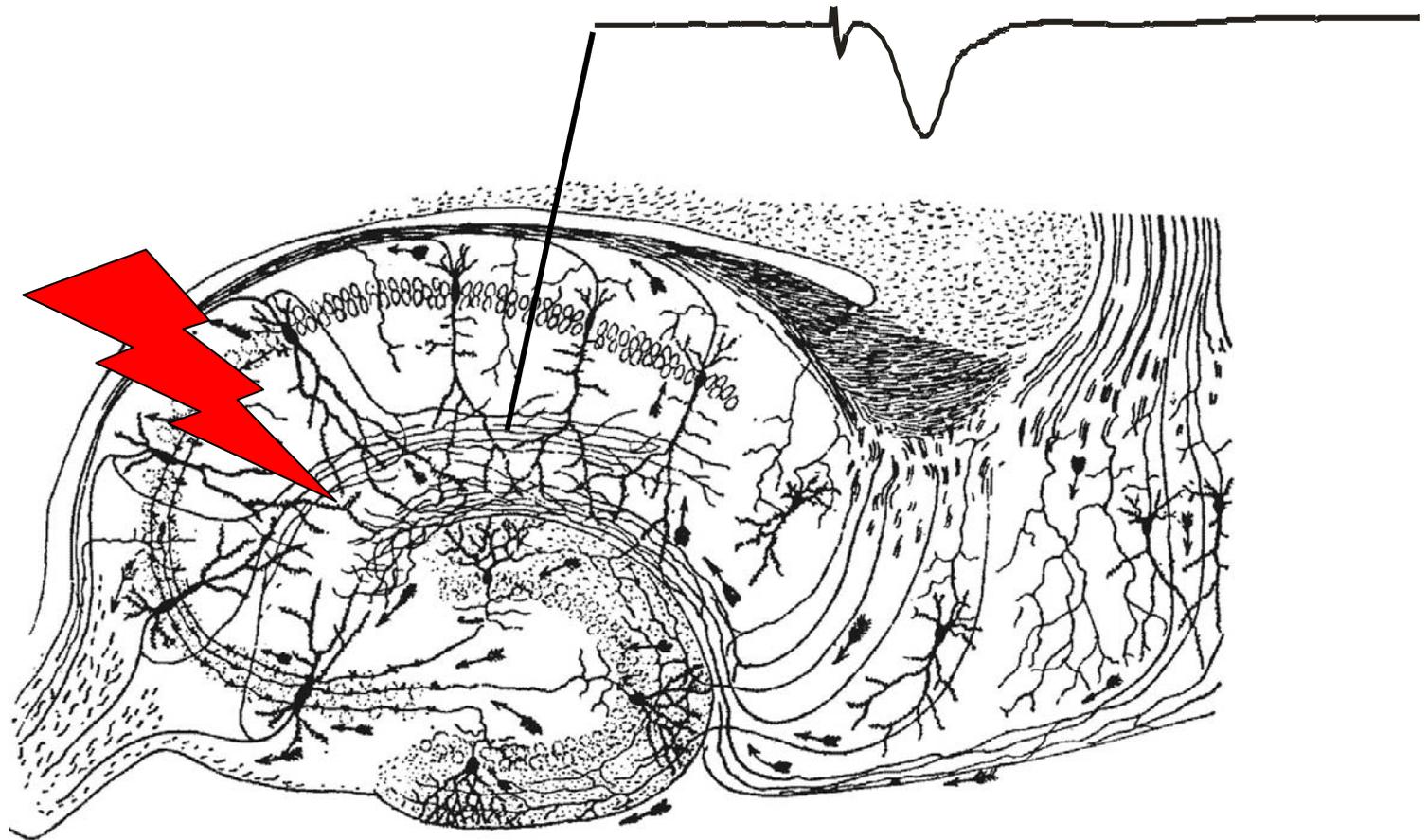
2. Rest-Kalzium (besonders nach Tetani = posttetanische Potenzierung)

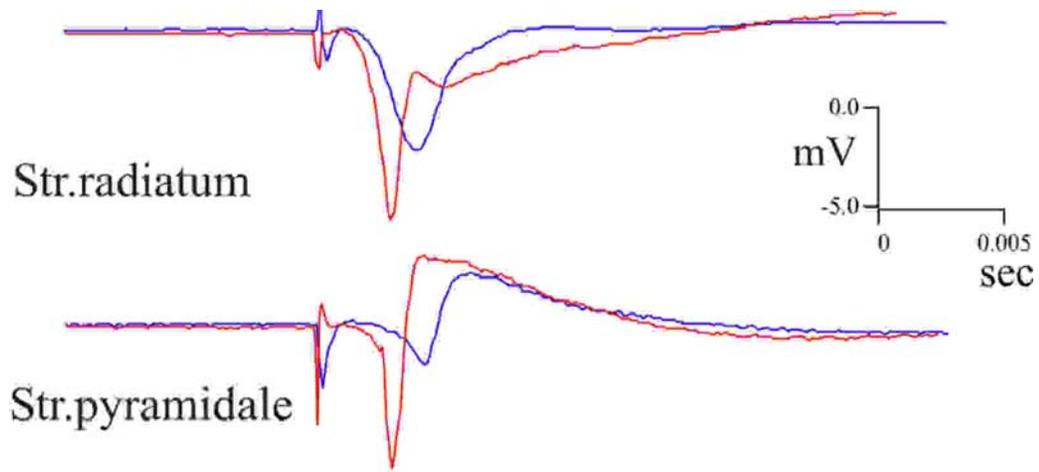
# Langzeitpotenzierung (LTP)



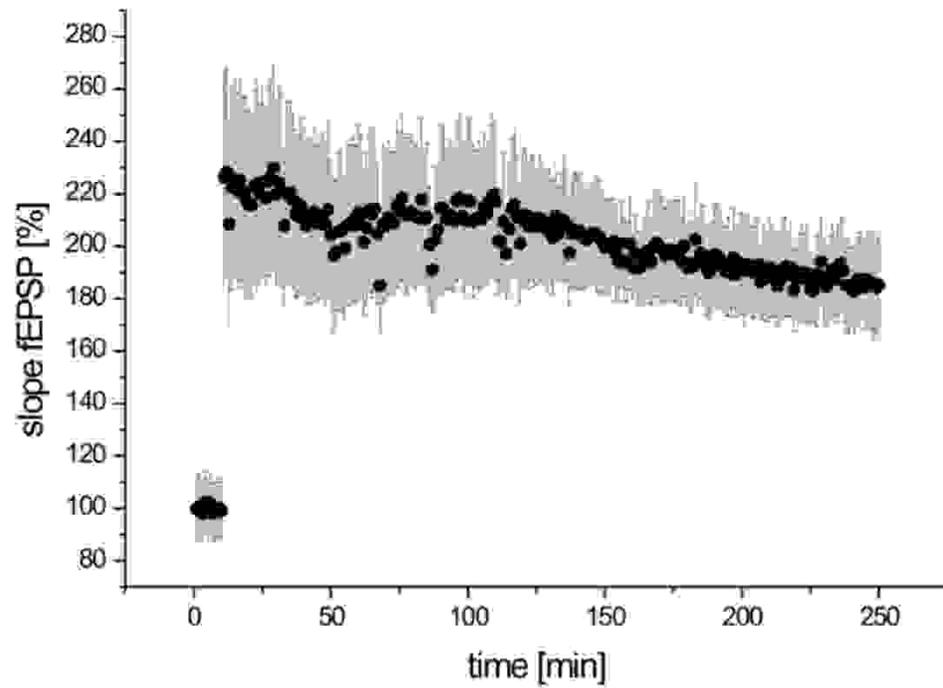
Bliss, T.V.P., and Lømo, T. (1973). Long lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.* 232, 331–356.

# Langzeitpotenzierung (LTP)



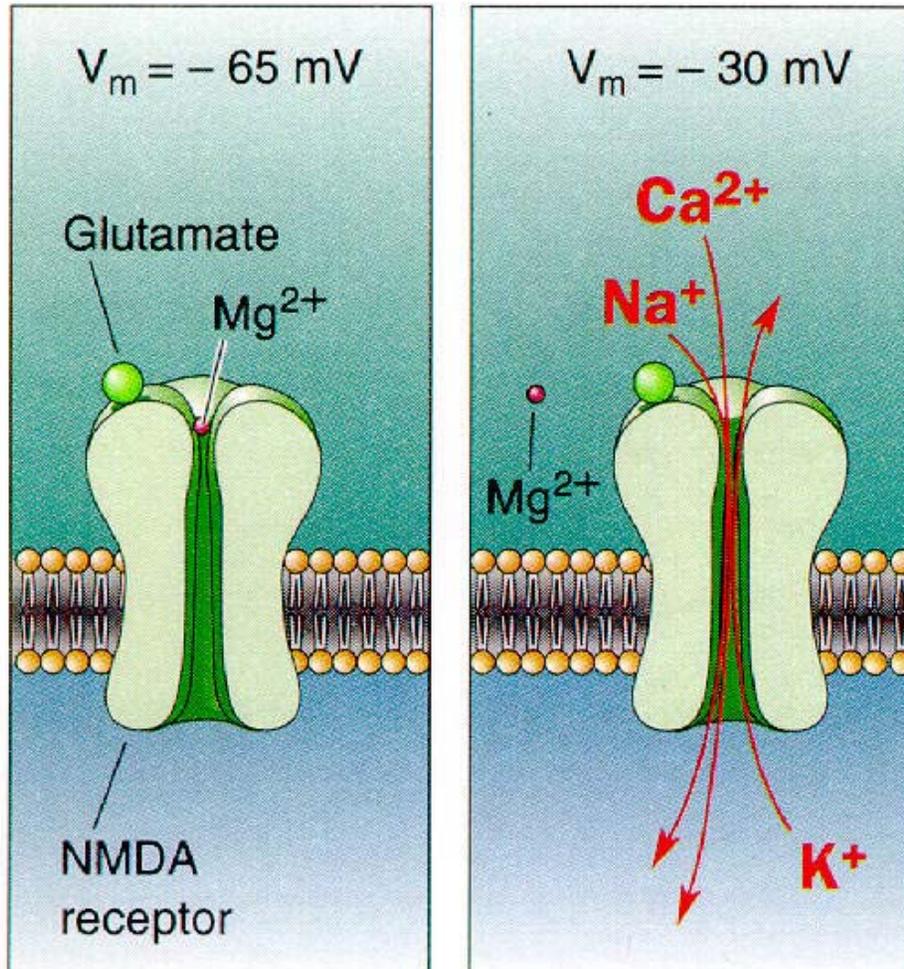


n = 10



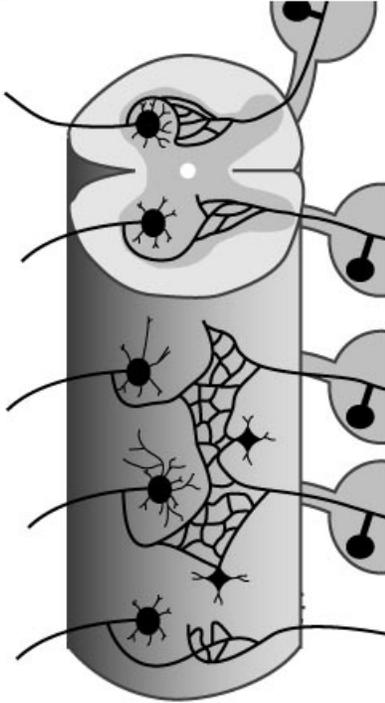
# Der NMDA-Rezeptor: ein molekularer Koinzidenz-Detektor

- Öffnen nur bei Vor-Depolarisierung
- $\text{Ca}^{2+}$ -permeabel

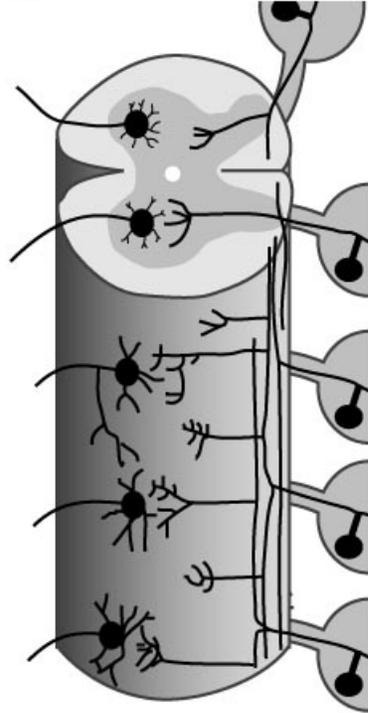


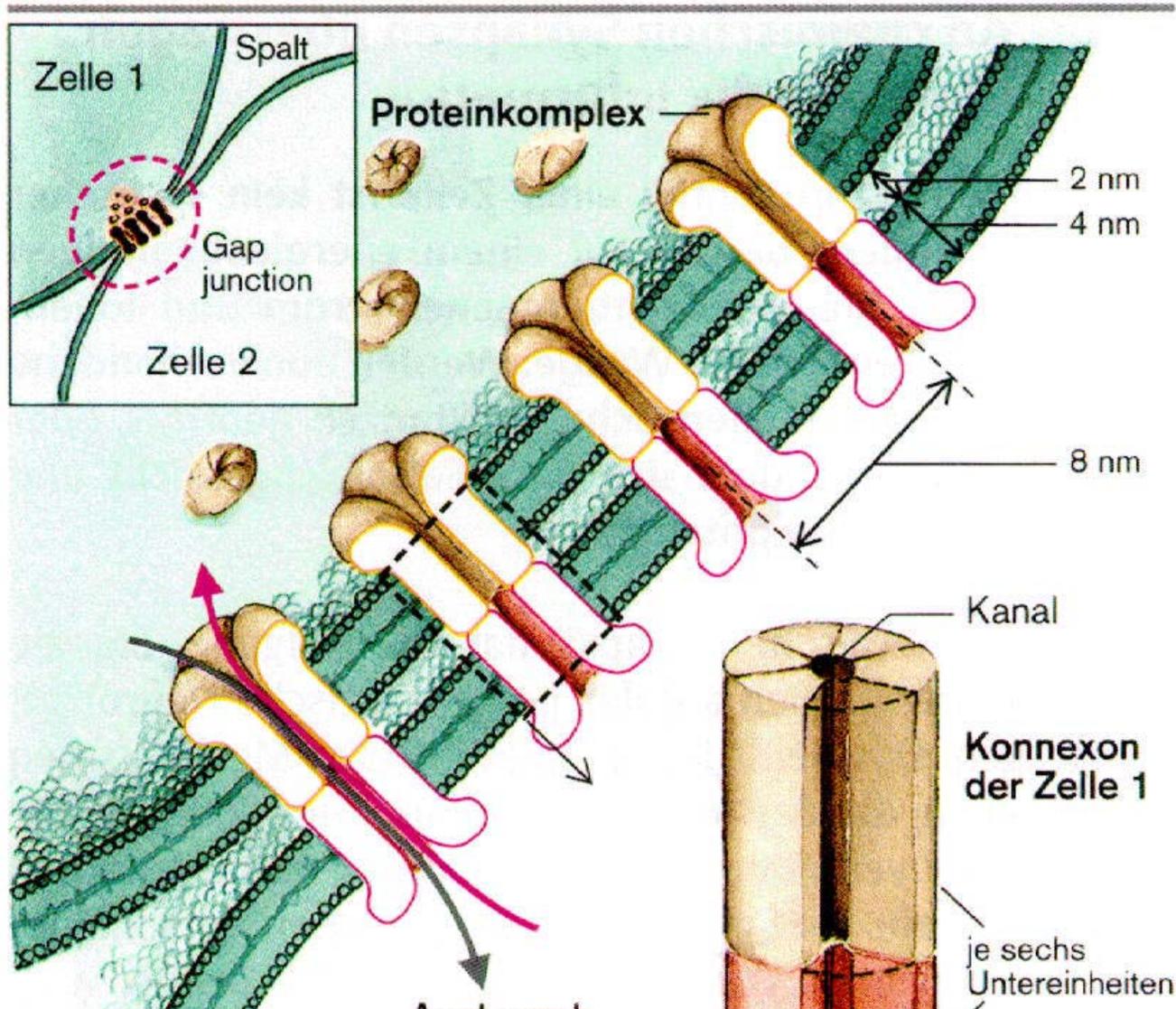


A

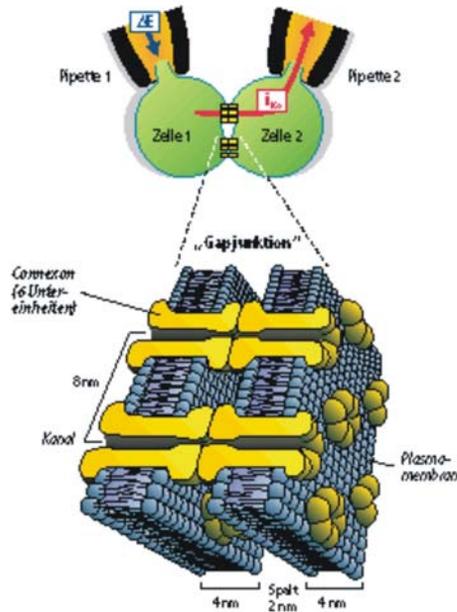


B

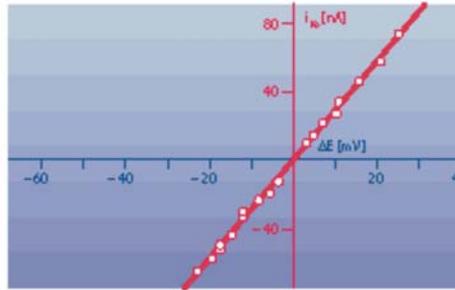




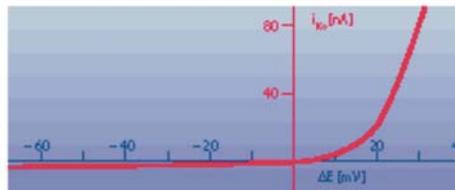
**A Messung der elektotonischen Kopplung**



**B nicht gleichrichtende Kopplung**



**C gleichrichtende Kopplung**

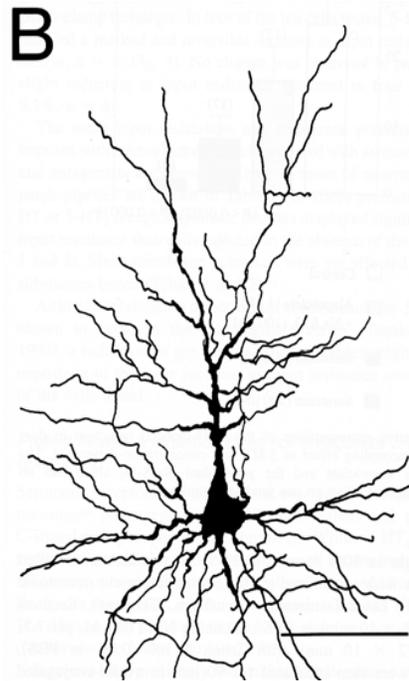
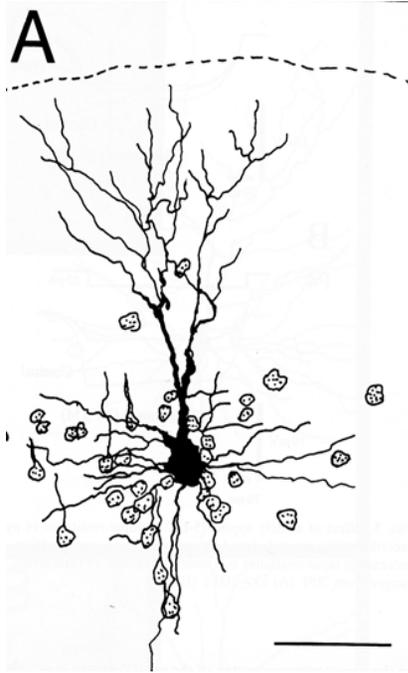


“gating“

Gap junctions werden geöffnet durch

- i)  $\text{Ca}^{2+}$
- ii) pH
- iii) verschiedene Transmitter / Hormone

Abb. 3-23 aus Schmidt/Thews: Physiologie des Menschen 27. Auflage 1997  
 Kapitel 3: J. Dudek: Erregungsübertragung von Zelle zu Zelle  
 © Georg Thieme Verlag Stuttgart 2004, 2007



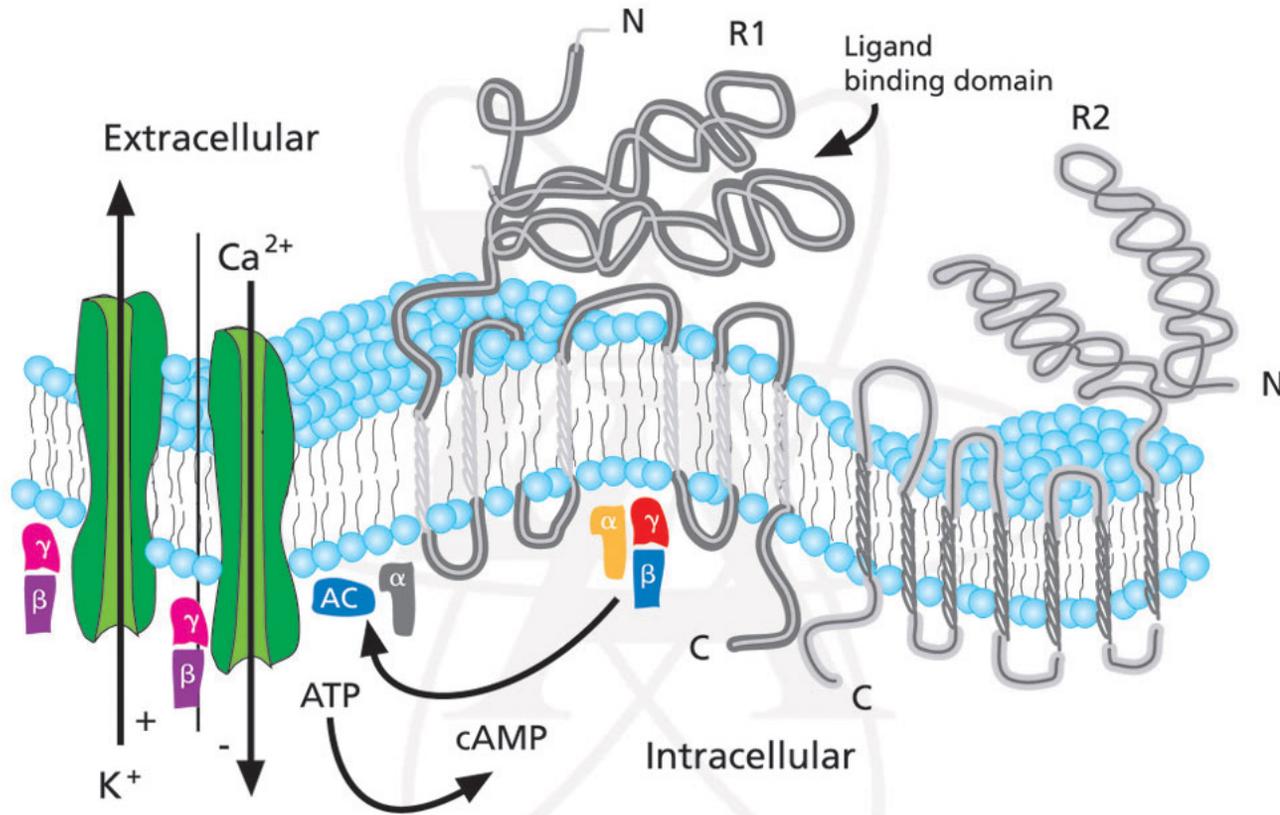
Beispiele für elektrische Kopplung:  
Rörig and Sutor, 1996

- i) glatte Muskulatur (single unit-Typ)
- ii) Herzmuskulatur
- iii) Gliazellen
- iv) Neurone, besonders im unreifen NS



# Schematic Representation of the GABA<sub>B</sub> Receptor

SIGMA-ALDRICH

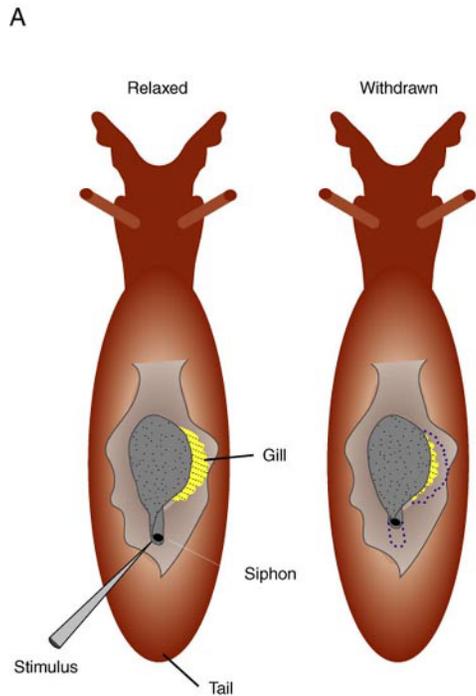


# Mechanismen synaptischer Plastizität:

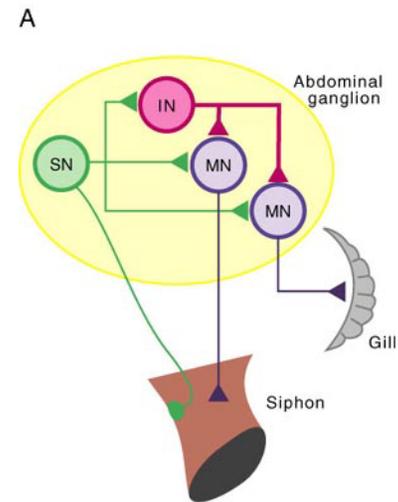
- Einfache nicht-assoziative „Gedächtnisprozesse“
  - i- Bahnung, Depression und posttetanische Potentizierung
  - ii- Habituation und Sensibilisierung
- **Assoziative Mechanismen**
  - i- Die Hebb-Regel
  - ii- klassische Konditionierung in Aplysia
  - iii- LTP und LTD
- Langfristige Engramme:
  - i- Entwicklung und Lernen
  - ii- Kortikale Plastizität

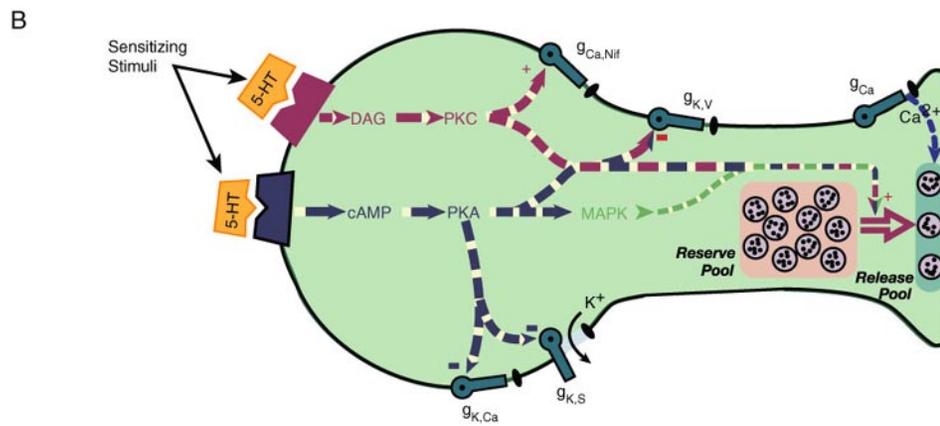
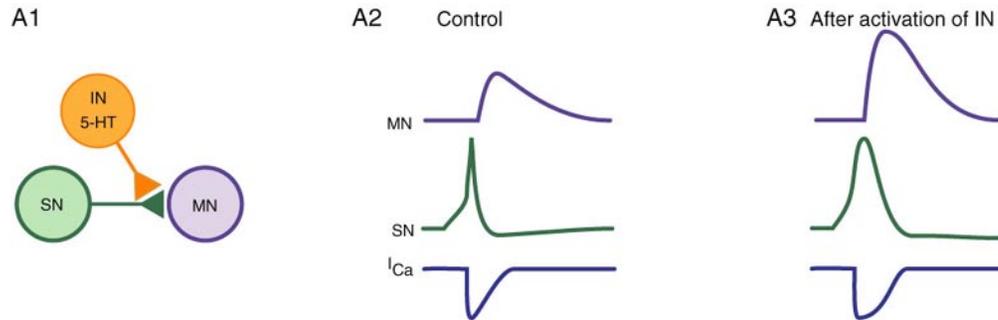
# Markram Faczili versus Depress

# Einfache nicht-assoziative Mechanismen: Habituation und Sensitisierung



I





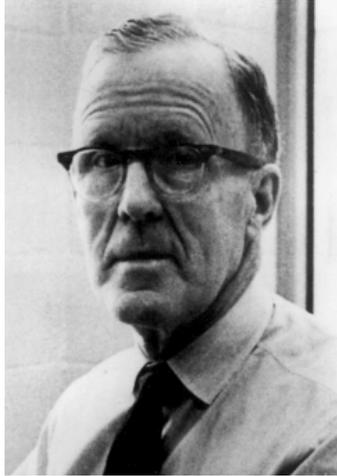
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## Effekte von 5-HT:

- $K^+$ -Leitfähigkeit ↓ (PKA)
- $Ca^{2+}$ -Leitfähigkeit ↑ (PKC, PKA)
- Vesikel-Exocytose ↑ (MAPK)

# Mechanismen synaptischer Plastizität:

- Einfache nicht-assoziative „Gedächtnisprozesse“
  - i- Bahnung, Depression und posttetanische Potentizierung
  - ii- Habituation und Sensibilisierung
  
- Assoziative Mechanismen
  - i- Die Hebb-Regel
  - ii- LTP und LTD
  
- Langfristige Engramme:
  - i- Entwicklung und Lernen
  - ii- Kortikale Plastizität

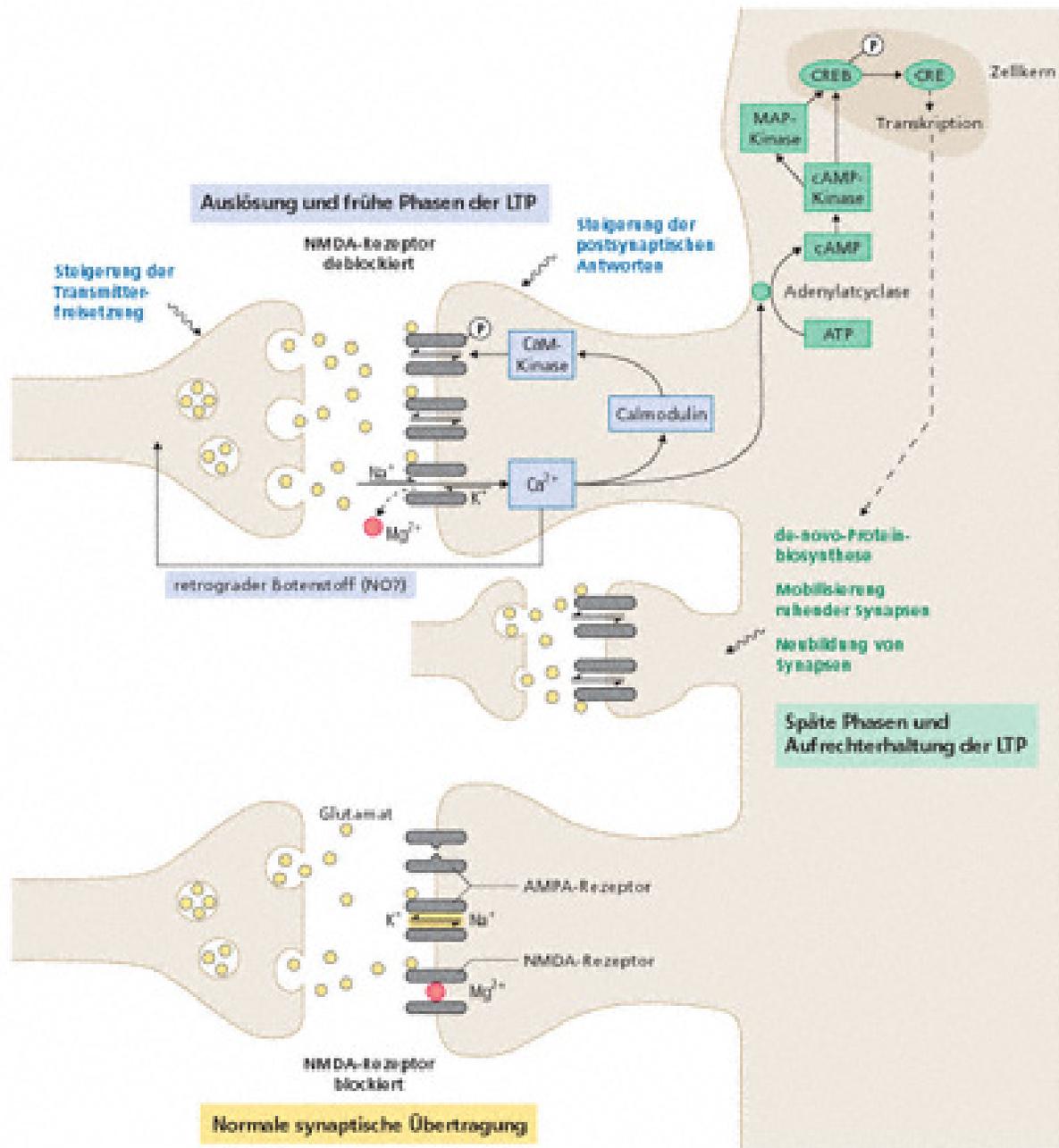


Donald O. Hebb  
1904 - 1985

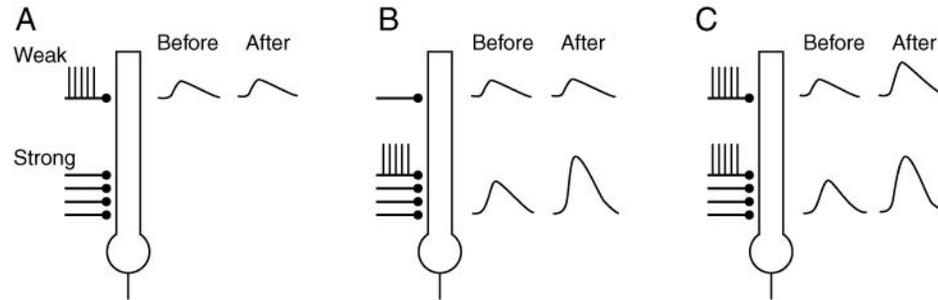
When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

**Koinzidenz!**





# Eigenschaften von LTP



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Kooperativ

→ grosser Effekt bei gleichzeitiger Aktivierung vieler Synapsen

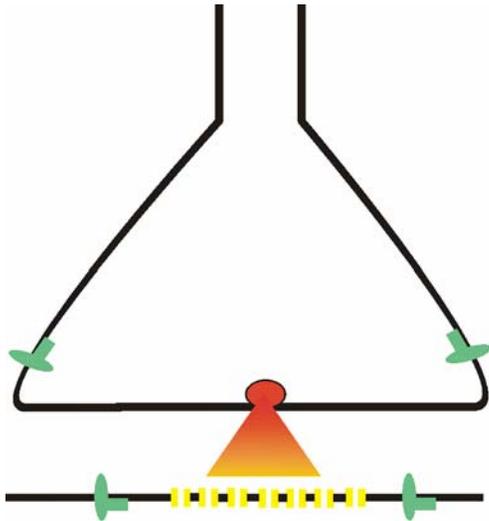
Assoziativ

→ Gleichzeitige aktivierte Pfade werden gleich verändert

Spezifisch

→ nur die Synapsen werden stimuliert, die während der Induktion von LTP aktiv waren

## Effekte von LTP



Erhöhung der Wahrscheinlichkeit von Exozytose (prä)

Erhöhung der postsynaptischen Rezeptoraktivität (post)

Einbau von Rezeptoren (post)

**Extremfall: silent synapses**

Neubildung / Stabilisierung von Synapsen

Veränderungen in „Schaltkreisen“ (Netzwerken)







