

Synaptic Plasticity

突触可塑性

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Synaptic Plasticity

突触可塑性

I. Synaptic Plasticity (Excitatory spine synapses)

- A. Changes in synaptic strength are important for formation of memory.
- B. Short Term Plasticity (paired-pulse facilitation, short-term potentiation, synaptic depression)
- C. Long-term potentiation (LTP) and long-term depression (LTD) at cortical and hippocampal excitatory synapses
 - 1. Frequency-dependent synaptic plasticity
 - 2. Spike-timing dependent synaptic plasticity (STDP)

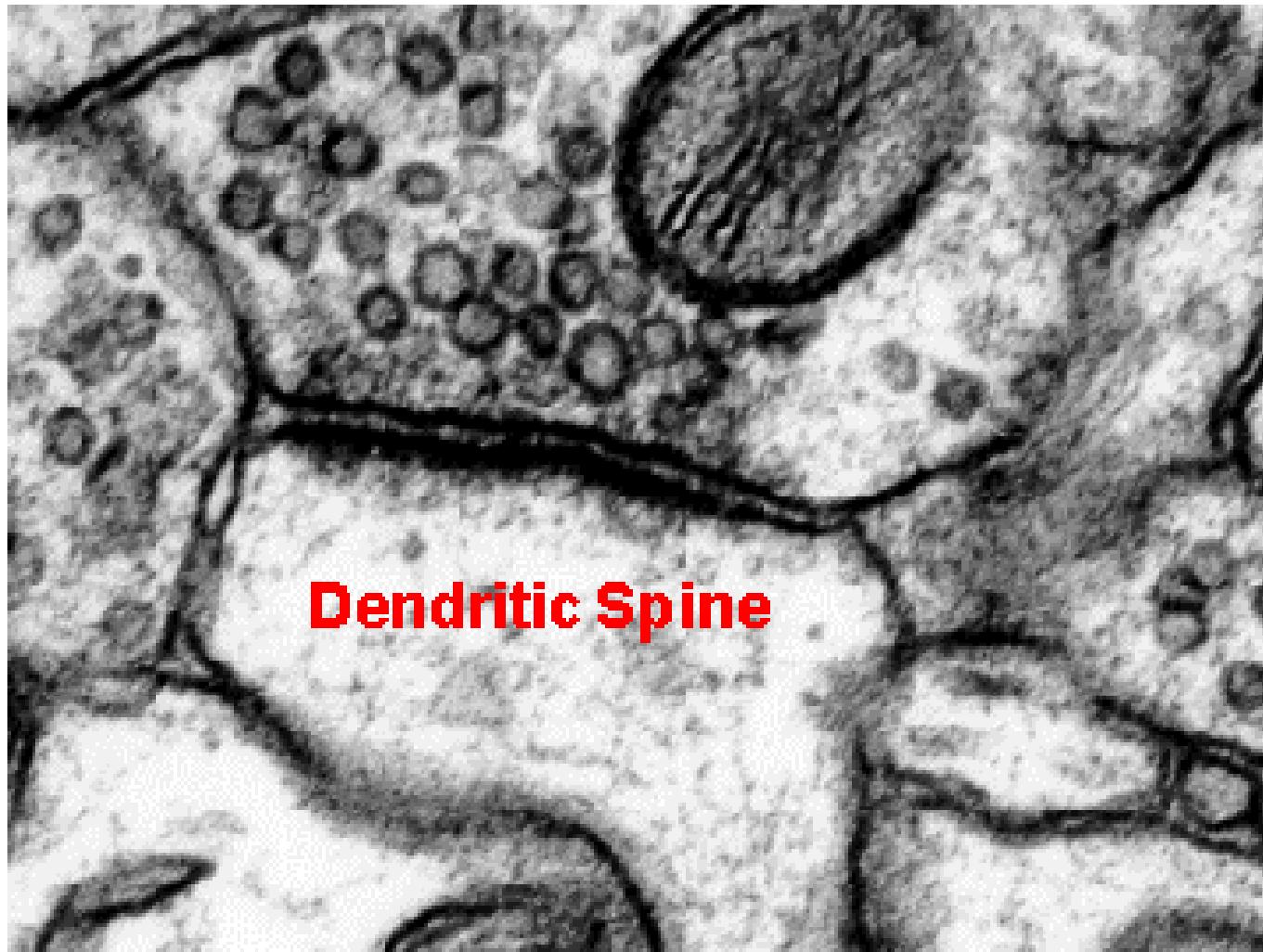
I. 突触可塑性（兴奋性突触棘）

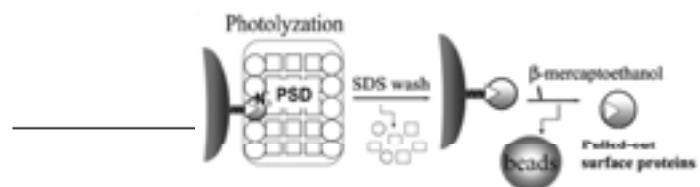
- A. 突触强度的改变对于记忆的形成至关重要
- B. 短时程可塑性（成对脉冲易化，短时程增强，突触压抑）
- C. 皮层和海马区域兴奋性突触的长时程增强（LTP）和长时程压抑（LTD）
 - 1. 频率依赖性突触可塑性
 - 2. 依赖于神经元动作电位时程的突触可塑性（STDP）

- II. The central role of Ca^{2+} in initiation of long-term plastic changes**
 - A. The “ Ca^{2+} hypothesis” for control of synaptic plasticity
 - B. Measurement of cytosolic Ca^{2+} with fluorescent dyes.
 - C. Control of postsynaptic Ca^{2+} by the NMDA receptor and “spike timing”
 - D. LTP and LTD are triggered by Ca^{2+} -sensitive signaling machinery located in the postsynaptic density.
 - III. Modulation of firing rate - an example: Accommodation in Hippocampal pyramidal neurons is regulated via Norepinephrine through a G-protein coupled adrenergic receptor linked to cAMP.**
-
- II. 钙离子在起始长时程突触可塑性变化中的作用**
 - A. 钙假说—控制突触可塑性
 - B. 利用荧光染料测量胞质内钙离子
 - C. 利用NMDA受体和火花时间控制突触后钙离子
 - D. 长时程增强和长时程压抑由位于突触后致密区的钙离子敏感的信号转导机制激活
 - III. 发放频率的调节-例如：海马锥体神经元经由去甲肾上腺素通过与环化腺苷酸相关的G-蛋白偶联的肾上腺素能受体调控**

The Postsynaptic Density (PSD)

突触后致密区





Protein Organization of the Postsynaptic Density

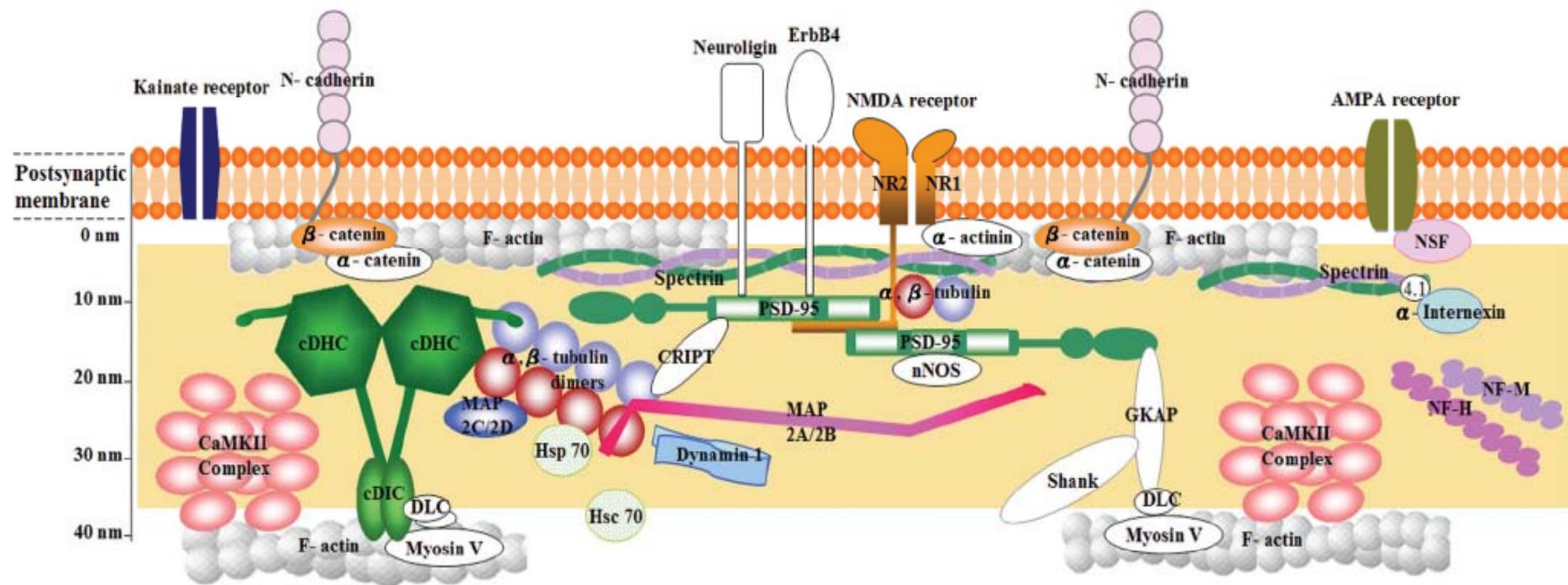


FIG. 8. A molecular model of the PSD. The PSD is assumed to be a disk-shaped protein complex of ~41 nm in thickness spanning from beneath the postsynaptic membrane to the cytoplasm of dendritic spines. A layer of phospholipid membrane is added to the PSD model to indicate the side of the PSD that faces the postsynaptic membrane. The cDIC, AMPA receptors, kainate receptors, N-cadherin, β -catenin, NSF, heat shock 70-kDa protein 8 (a member of hsc70), and actin reside primarily in the space within 3.5 nm from the surface, whereas the α, β -tubulin subunits, cDHC, MAP2A/2B, MAP2C/2D, spectrin, neurofilament heavy subunit (*NF-H*), neurofilament medium subunit (*NF-M*), heat shock 70-kDa protein 12A (a member of hsp70), α -internexin, dynamin-1, and PSD-95 reside primarily in a region deeper than 3.5 nm from the surface (yellow colored) of the PSD. α -CaMKII subunits form large complexes sitting at the edge of the cytoplasm-facing surface of the PSD. NMDA receptors reside on the postsynaptic membrane-facing surface of the PSD and are in close association with large proteins that also reside on the postsynaptic membrane. *DLC*, light chain of dynein; *nNOS*, neuronal nitric-oxide synthase; *GKAP*, guanylate kinase-associated protein.

Liu et al., 2006. Molecular & Cellular Proteomics 5:1019–1032.

Synaptic Plasticity in the Hippocampus and Cortex

海马和皮层区域神经元的突触可塑性

Synapses in the cortex and hippocampus are tightly regulated.

1. Regulation is used to maintain homeostatic balance
2. It is also used to process and store information in neural circuits.
3. Homeostasis and information storage must be coordinated to maintain proper function.

皮层和海马区域的突触紧密调节

1. 调节用于维持自我平衡
2. 处理和储存神经环路中的信息
3. 稳态和信息存储必须进行协调，以维持其正常功能

Presynaptic vs. Postsynaptic

突触前 vs 突触后

- I. The size of synaptic potentials can be modulated:
 - A. by regulating the amount of transmitter released at the synapse
 - B. by regulating the size of the current generated by postsynaptic receptors.

- I. 突触电位的大小可以通过以下几种方式调节

- A. 调节突触释放的神经递质含量
 - B. 调节突触后受体产生的电流大小

- II. Short term modulation (msecs - minutes)

- A. The mechanisms of these forms of modulation are almost always presynaptic.
 - B. Paired-pulse facilitation (~10 to 100 msecs)
 - C. Synaptic depression (50 msecs to mins)
 - D. Post-tetanic potentiation (mins)

- II. 短时程调节 (毫秒-分钟)

- A. 一般通过突触前调节
 - B. 双脉冲易化 (~10 to 100 毫秒)
 - C. 突触压抑(50毫秒-分钟)
 - D. 后强直电位 (分钟)

Presynaptic vs. Postsynaptic

突触前 vs 突触后

III. Long-term plasticity

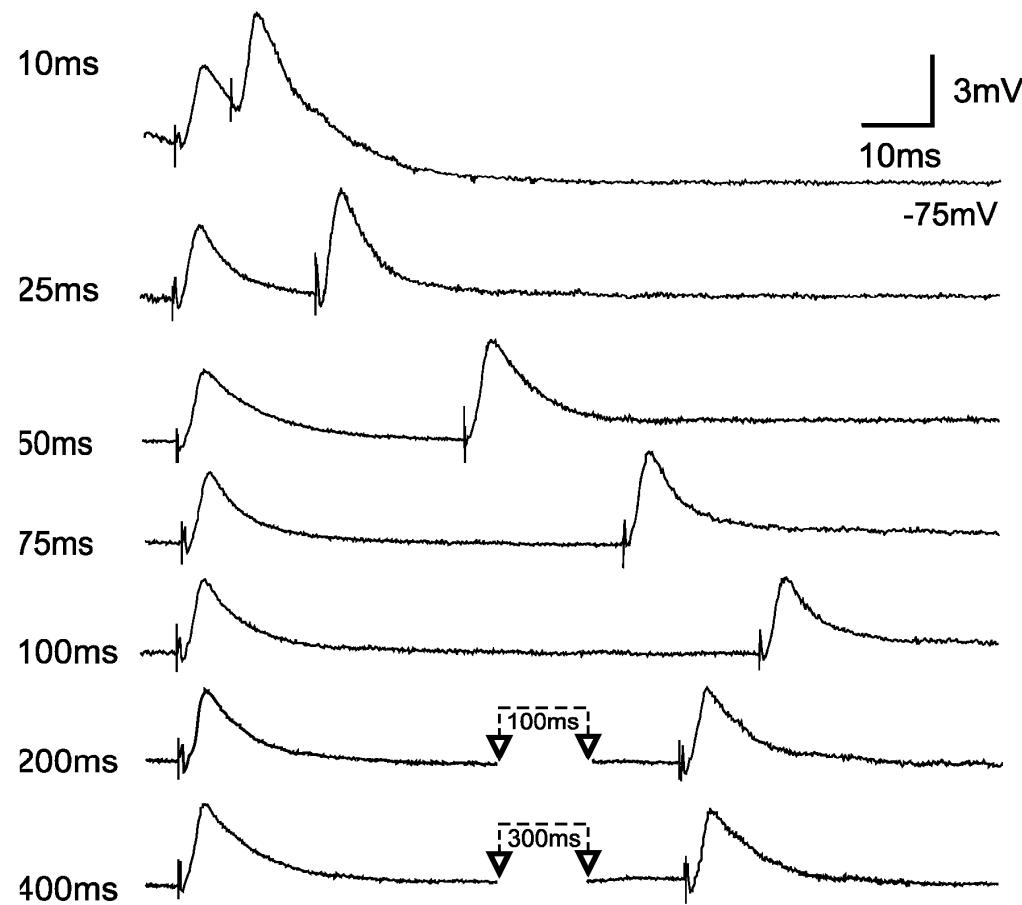
- A. The mechanisms of these forms of modulation are complex and usually both pre- and postsynaptic
- B. LTP (30 minutes to years)
- C. LTD (30 minutes to years)

III. 长时程可塑性

- A. 调节方式较为复杂，一般通过突触前，突触后两种方式调节
- B. 长时程增强 (30分钟-数年)
- C. 长时程压抑 (30 分钟-数年)

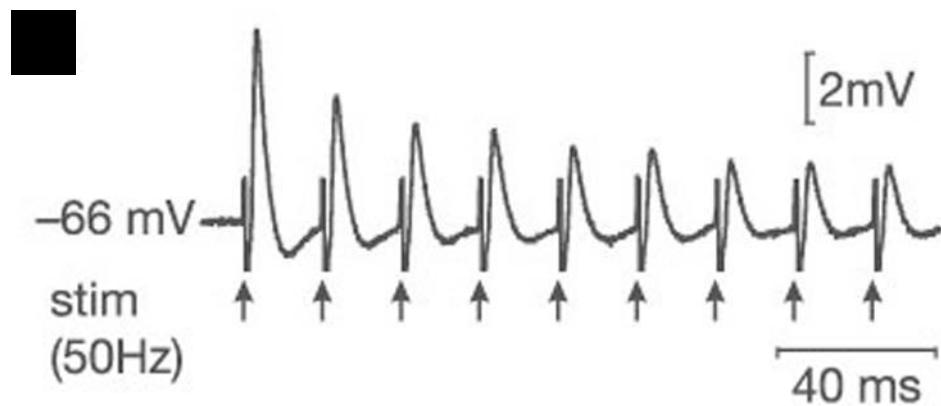
Paired Pulse Facilitation

成对脉冲易化



Synaptic Depression

突触压抑

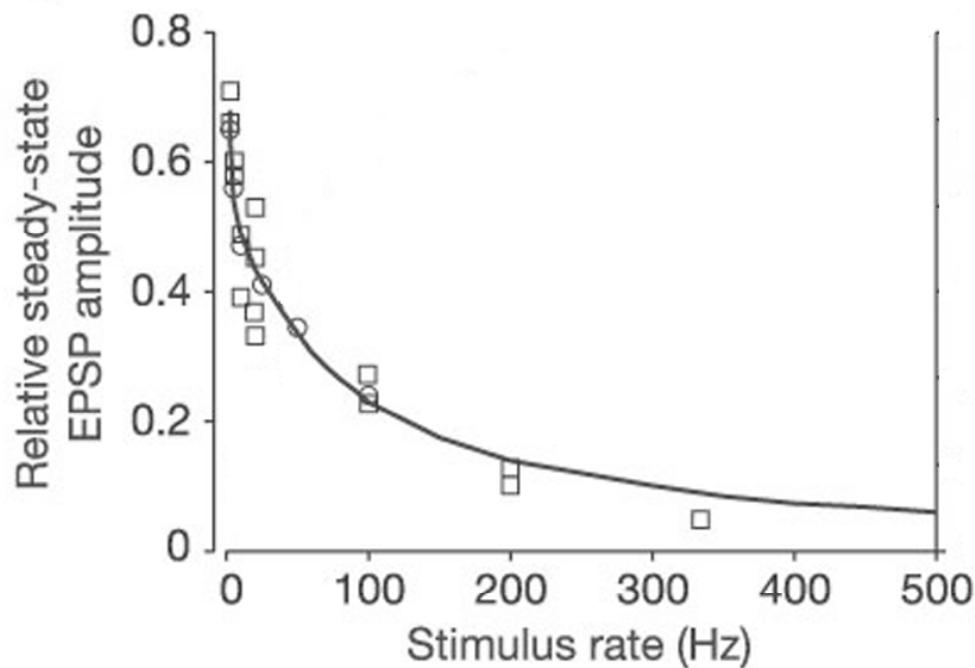


Successive stimuli at
50 Hz

50Hz的刺激频率

Both the rate and the
steady-state level of
depression depend on
the stimulus frequency.

压抑的速率和稳定水平
取决于刺激的频率



Long-term Synaptic Plasticity

长时程突触可塑性

I. Frequency-dependent Long-term Potentiation (LTP)

- A. This term actually represents many mechanisms, all of which result in strengthening of the synapse for varying periods of time following tetanic stimulation.
- B. The mechanisms for LTP lasting 30 minutes to a few hours do not require new protein synthesis
- C. The mechanisms for LTP lasting longer than a few hours do require protein synthesis.

I. 频率依赖性长时程增强

- A. 长时程增强的作用机制包括多种，每一种最终都会导致突触间的联系在强直刺激后变得更强
- B. 长时程增强可以持续30分钟-数小时，而不需要新蛋白的合成
- C. 超过数小时后的持续需要新蛋白的合成

Long-term Synaptic Plasticity

II. Frequency-dependent Long-term Depression (LTD)

- A. This term also represents many mechanisms
- B. LTD, like LTP is thought to be used for sculpting circuits to store information.

III. Spike-timing dependent synaptic plasticity (STDP) is thought to arise from the same set of mechanisms as LTP and LTD.

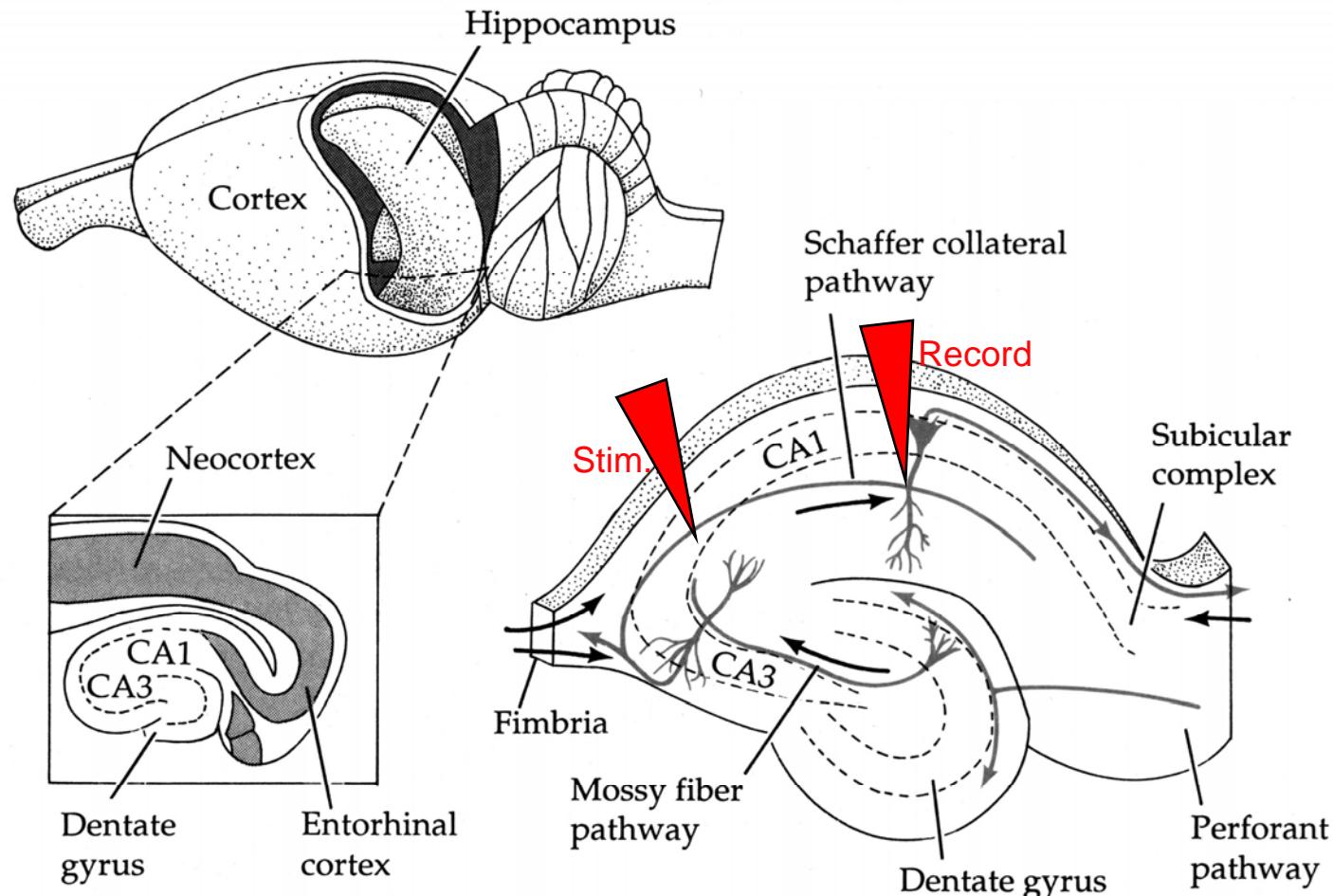
II. 频率依赖性长时程压抑

- A. 长时程压抑的作用机制包括多种
- B. 长时程压抑与长时程增强类似，被认为是用于构建神经环路用于储存信息

III. 人们普遍认为依赖于神经元动作电位时程的突触可塑性（STDP）机制与长时程增强，长时程压抑类似

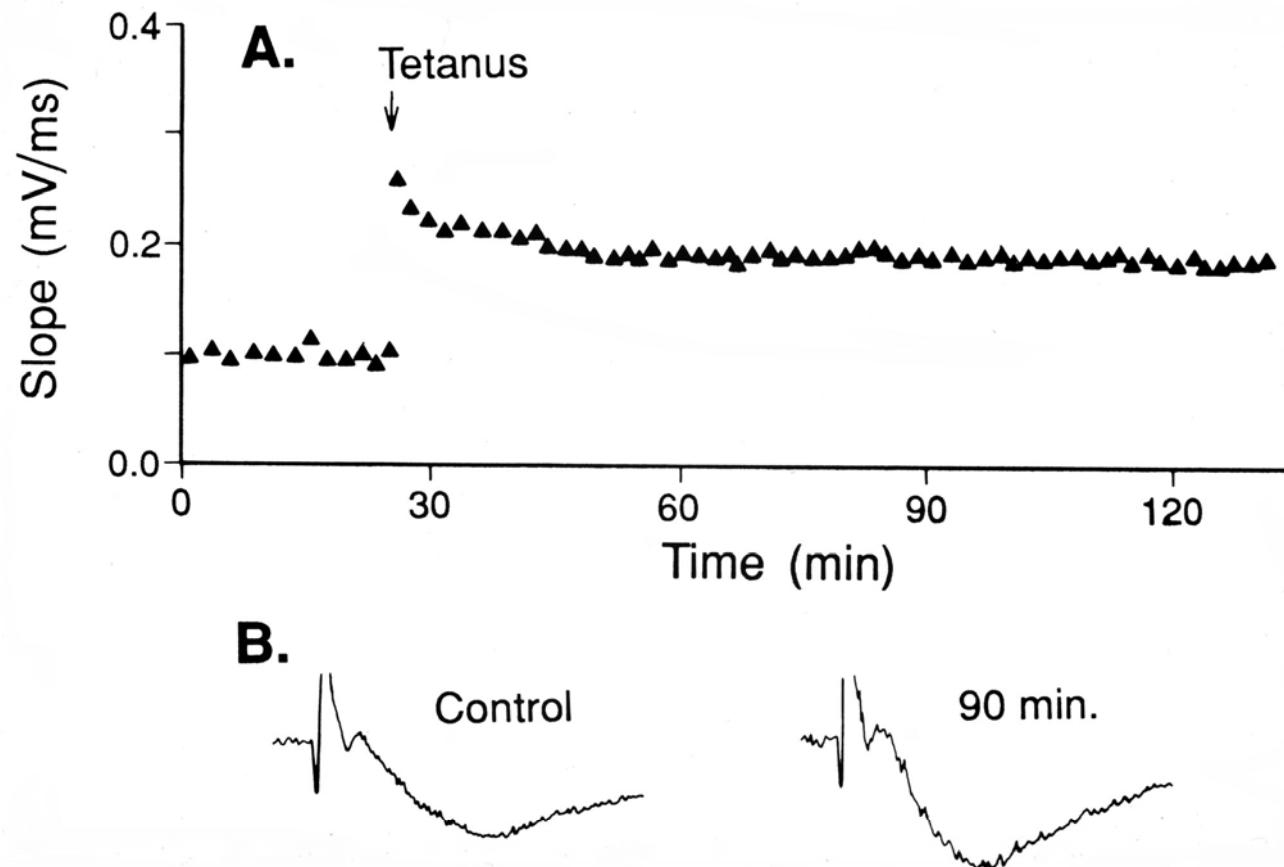
Long-Term Potentiation in the Hippocampus

海马区域长时程增强



Recording of LTP in a Hippocampal Slice

记录海马神经元的长时程增强

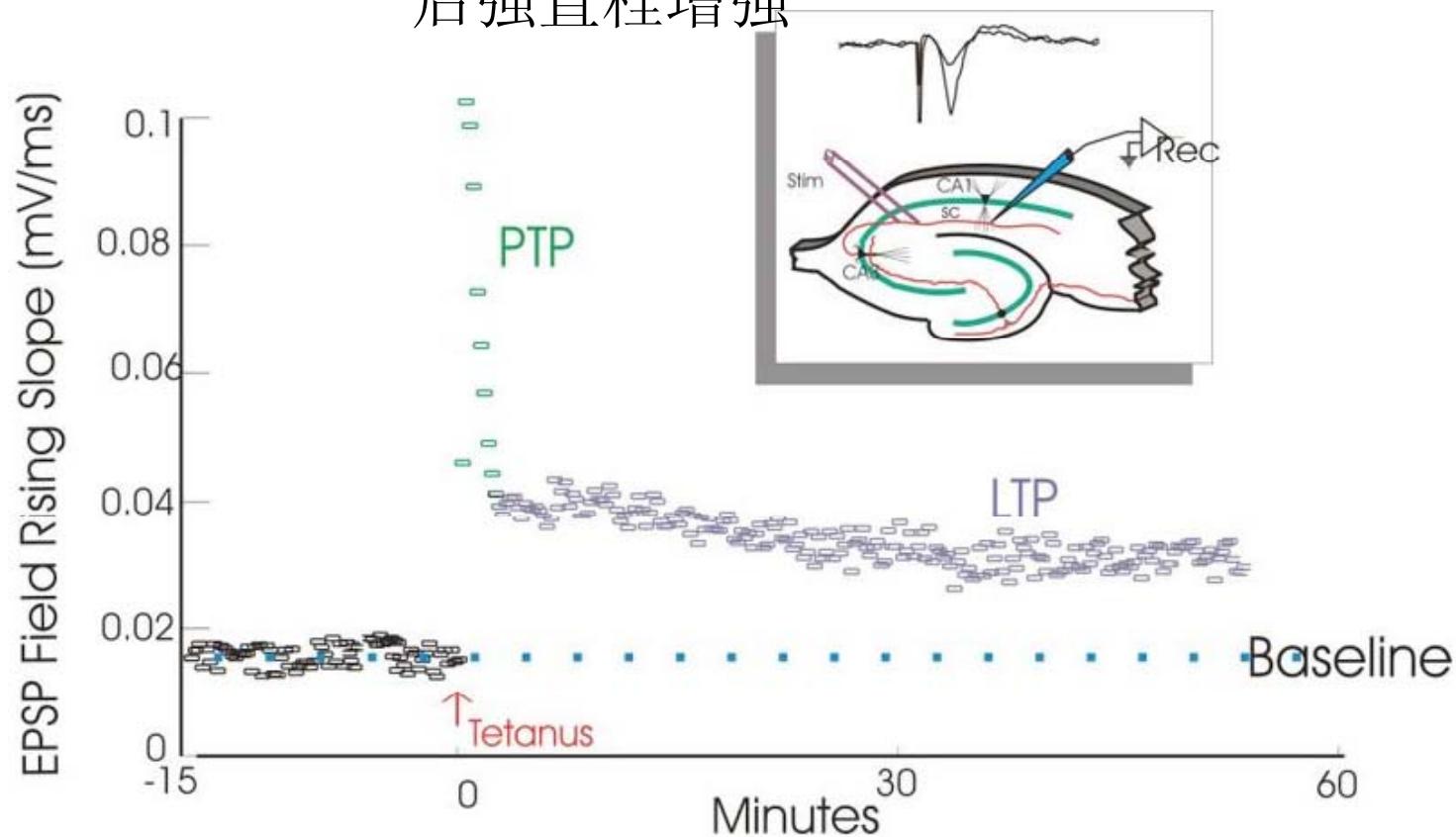


Stimulation frequencies that produce LTP usually range from ~50 to 200 Hz.

产生长时程增强的刺激频率一般在50–200Hz

Post-Tetanic Potentiation

后强直程增强

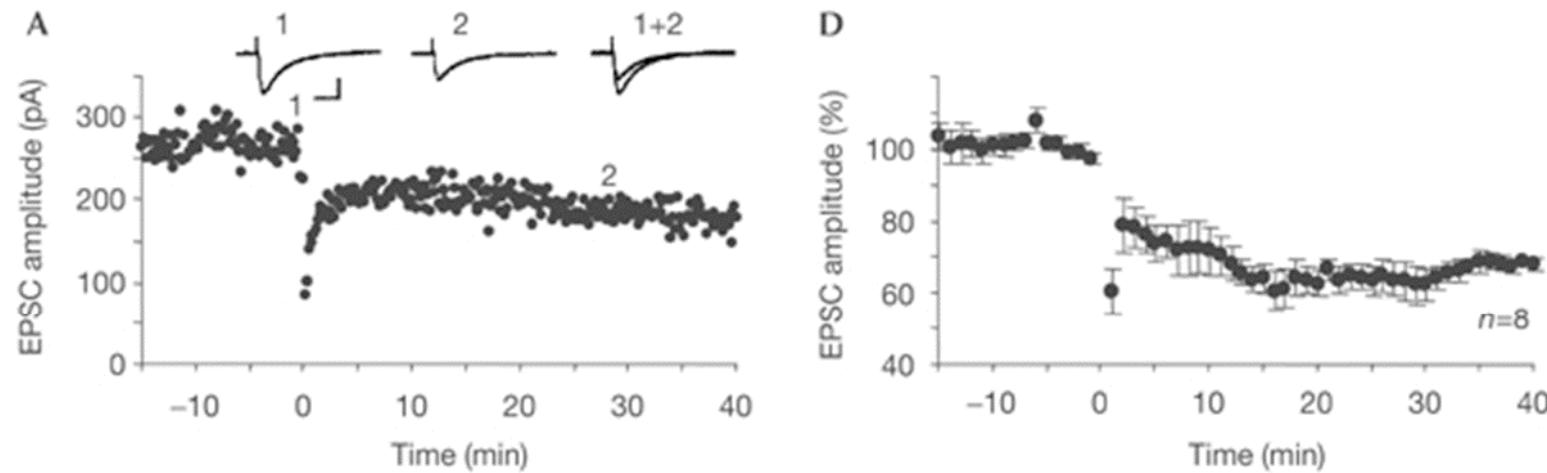


PTP believed to be caused by a large accumulation of Ca^{2+} in the terminal caused by a high frequency tetanic stimulation.

通常认为，后强直程增强是由高频强直刺激产生的突触末梢钙离子大量聚集引起的

Recording of LTD in the Hippocampus

海马神经元的长时程压抑

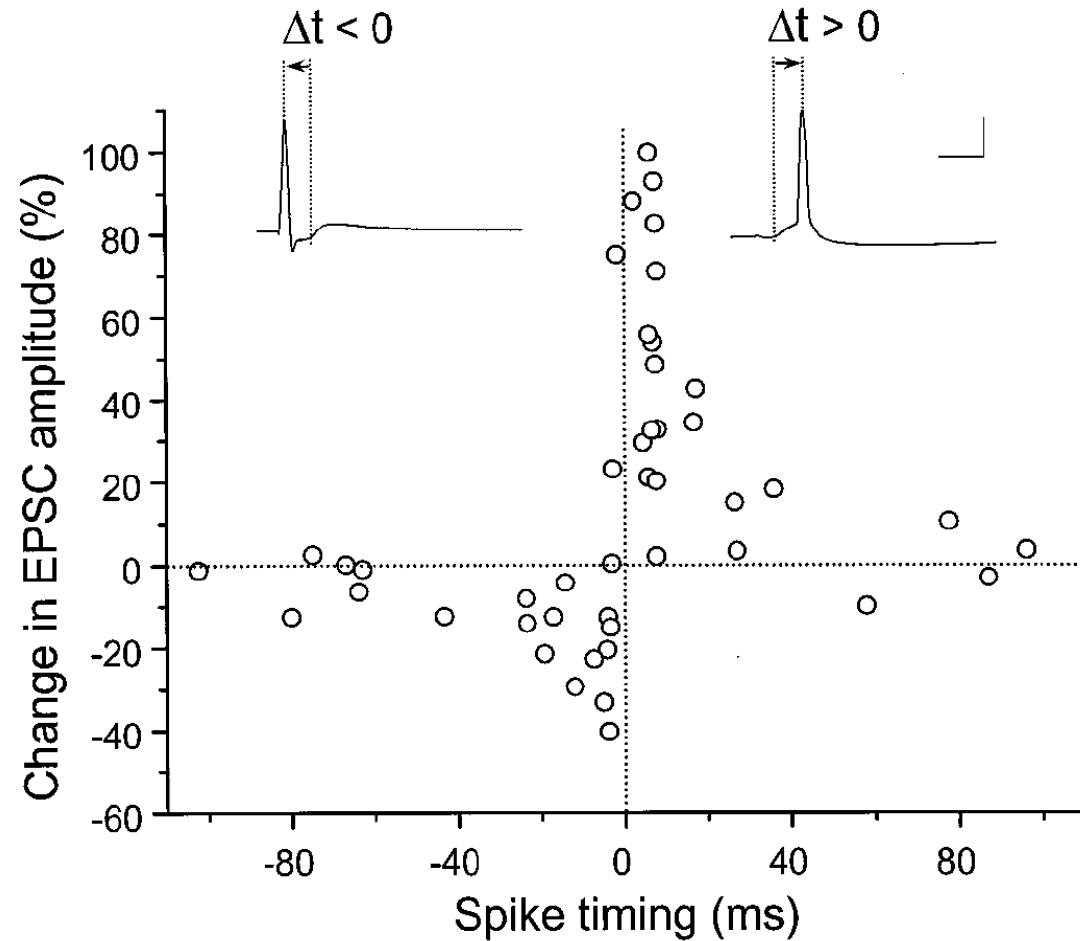


Stimulation frequencies usually range from 1 to 10 Hz.

刺激频率一般在1-10Hz

Spike-timing Dependent Synaptic Plasticity

动作电位-时间 依赖性突触可塑性



From Bi and Poo J. Neurosci. 18, 10464 (1998)

These recordings were made on cultured neurons recorded from with a “whole-cell patch”.

利用全细胞膜片钳记录培养的神经元

More recently, similar time dependencies have been observed in slices.

记录脑片神经元细胞也得到类似的时间依赖性结果

Spike-timing Dependent Synaptic Plasticity

动作电位-时间 依赖性突触可塑性

Pre- fires 5-30 msec before post - LTP

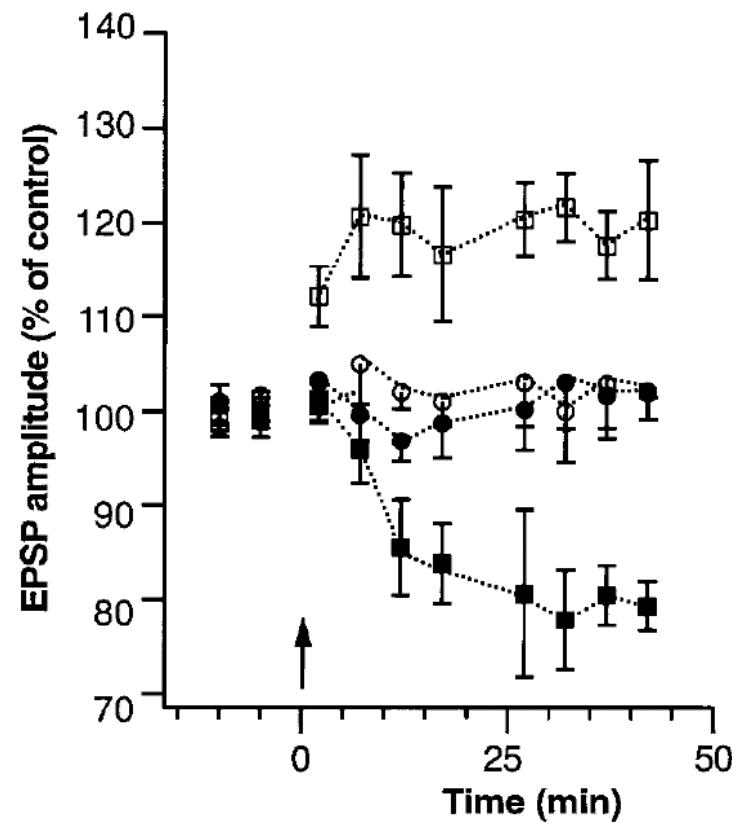
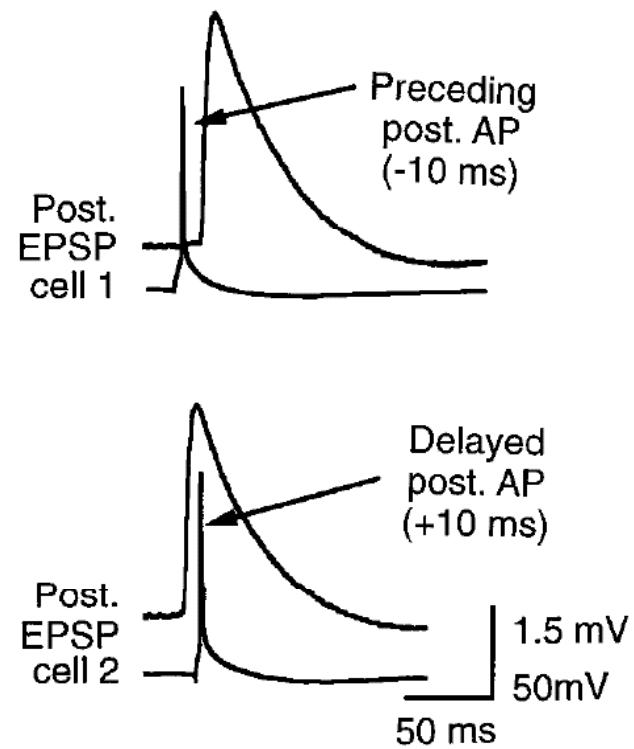
突触后长时程增强前，突触前发放5-30毫秒

Pre- fires 5-30 msec after post – LTD

突触后长时程强压抑后，突触前发放5-30毫秒

Spike-timing Dependent Plasticity in Cortical Neurons

皮层神经元 动作电位-时间 依赖性突触可塑性



Dual whole-cell patch recordings from neurons in cortical slices from 14-16 day old rats

14-16天大鼠皮层脑片两个全细胞膜片钳记录

The Hebbian Synapse

Hebbian 突触

From *The Organization of Behavior* by Donald Hebb, 1949:

“When an axon of cell A is near enough to excite 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.”

Hebb postulated that this behavior of synapses in neuronal networks would permit the networks to store memories.

NMDA receptors, back-propagating action potentials, and summation of epsp's appear to be the components that confer “Hebbian” behavior on the synapse.

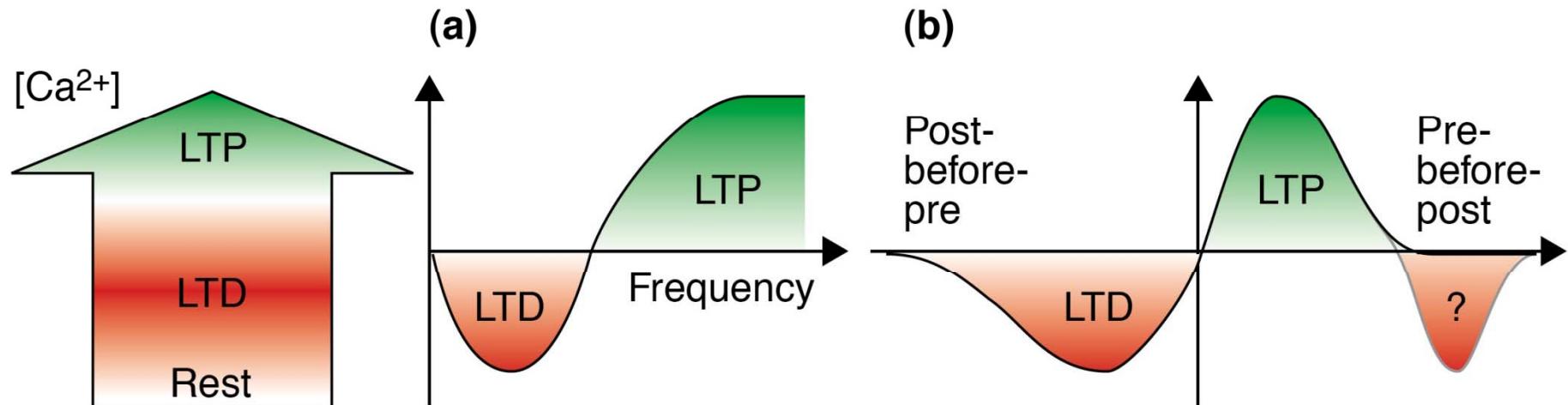
当A细胞轴突和B细胞足够近并且能够使B细胞兴奋时，重复或持续的使B细胞发放会让A/B细胞生长过程或代谢发生改变，A细胞使B细胞兴奋的效率增大。

Hebb假定神经网络中突触的这种行为有利于储存记忆。

NMDA受体，反向传播的动作电位以及EPSP共同作用于突触的Hebbian行为。

Postsynaptic Calcium Levels and Synaptic Plasticity

突触后钙离子水平 和突触可塑性



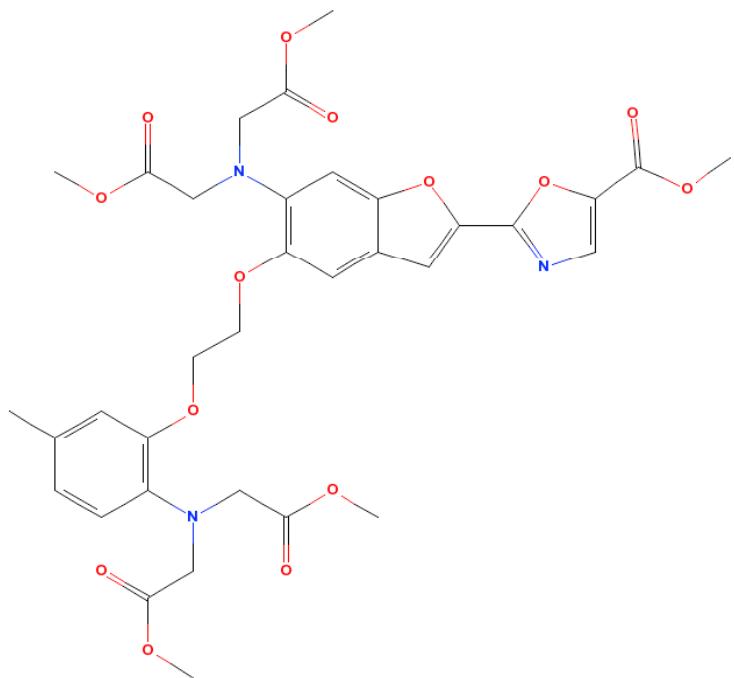
Current Opinion in Neurobiology

1. Level and timing of Ca²⁺ rise in spine determines LTD or LTP.
突触棘钙离子增长的水平和时间决定LTD 和LTP
2. Low frequency synaptic firing (~5 Hz) produces LTD; high frequency synaptic firing (~50 to 100 Hz) produces LTP.
低频突触发放(~5Hz)产生LTD;高频突触发放(~50-100Hz产生LTP)
3. The same Ca²⁺ rules are believed to underlie “spike-timing-dependent synaptic plasticity (STDP).”
同样的Ca²⁺的规则被认为也存在于STDP中

Detection of intracellular Ca^{2+} transients with the fluorescent dye, FURA-2

荧光染料检测细胞内钙离子瞬时浓度，FURA-2

FURA-2 am



“Ratio Imaging”

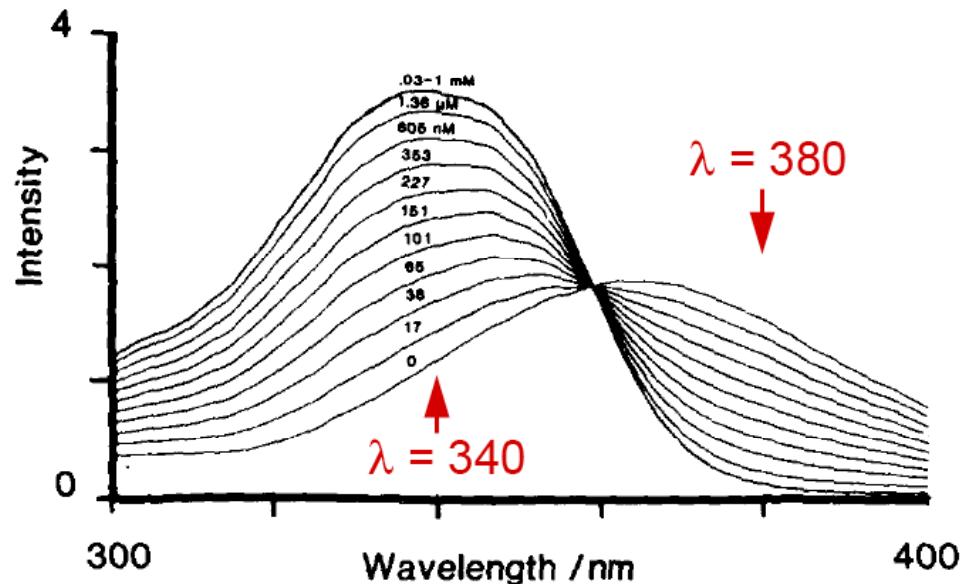
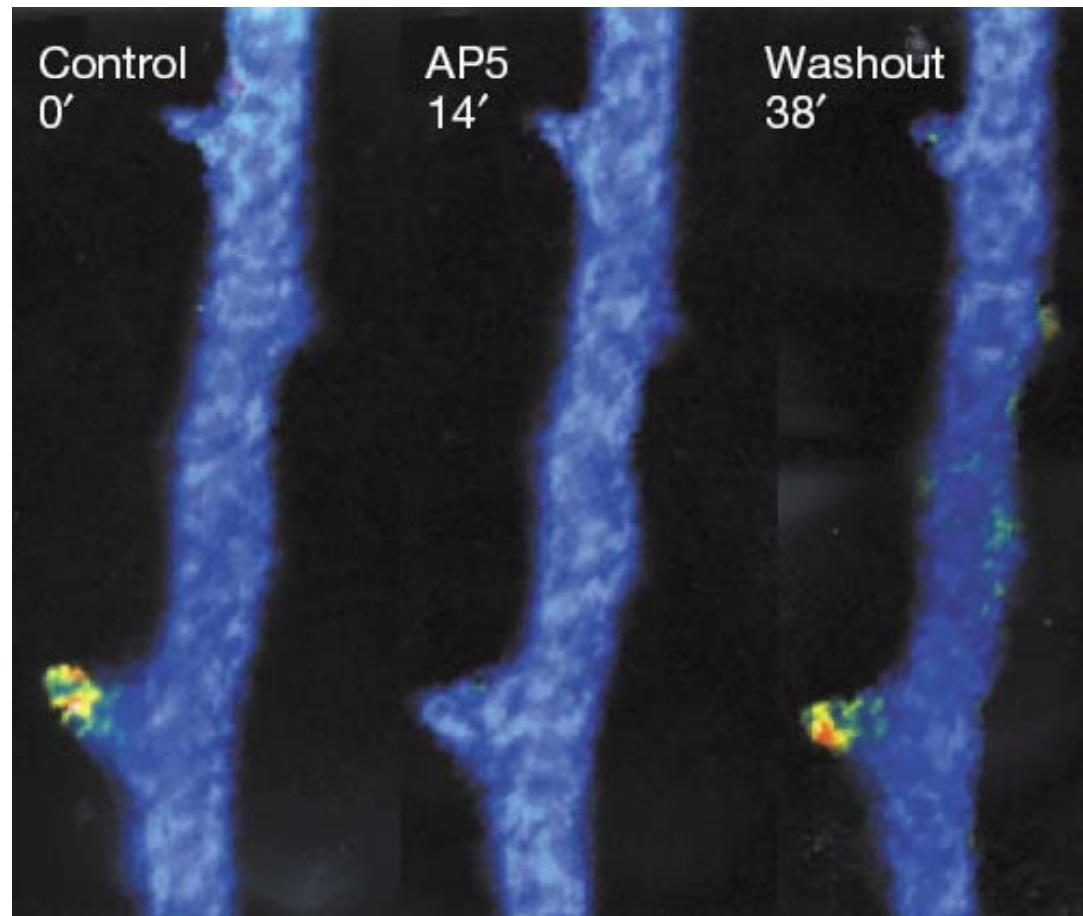


FIG. 3. Excitation spectra for $1 \mu\text{M}$ fura-2 at 20°C in buffers with free Ca^{2+} values ranging from $<1 \text{nM}$ to $>10 \mu\text{M}$. The

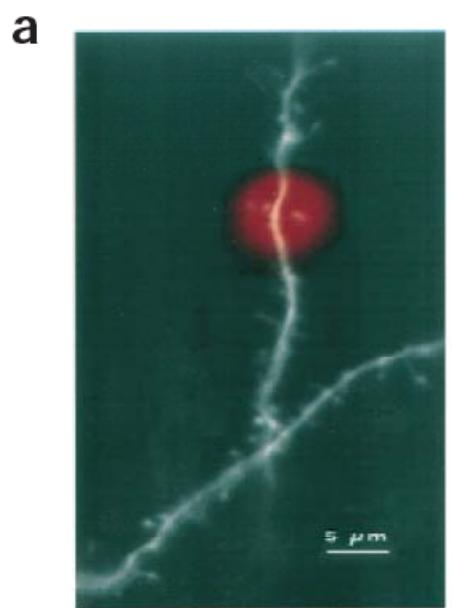
From Grynkiewicz, Poenie, and Tsien (1985) J. Biol. Chem. 260, 3440.

NMDA Receptors Mediate Synaptic Ca^{2+} Entry

NMDA受体调节突触钙离子的流入



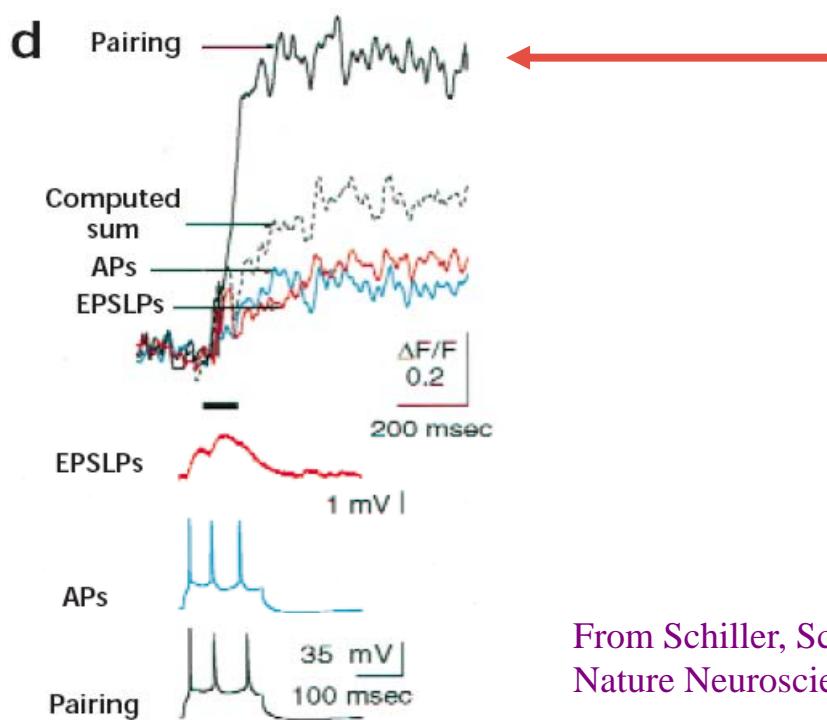
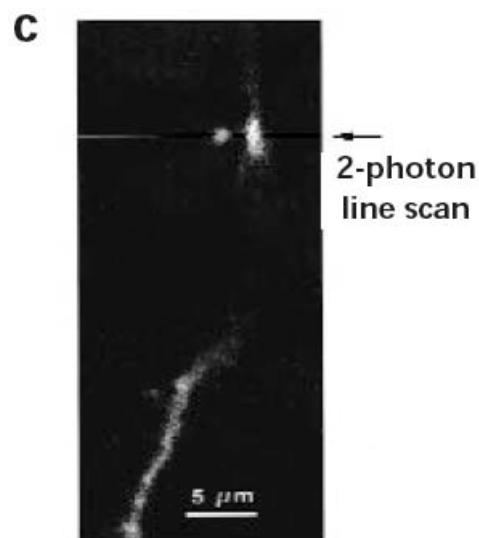
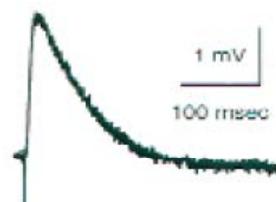
Lisman et al. *Nature Rev. Neurosci.* 3: 175 (2002)



b Glutamate uncaging



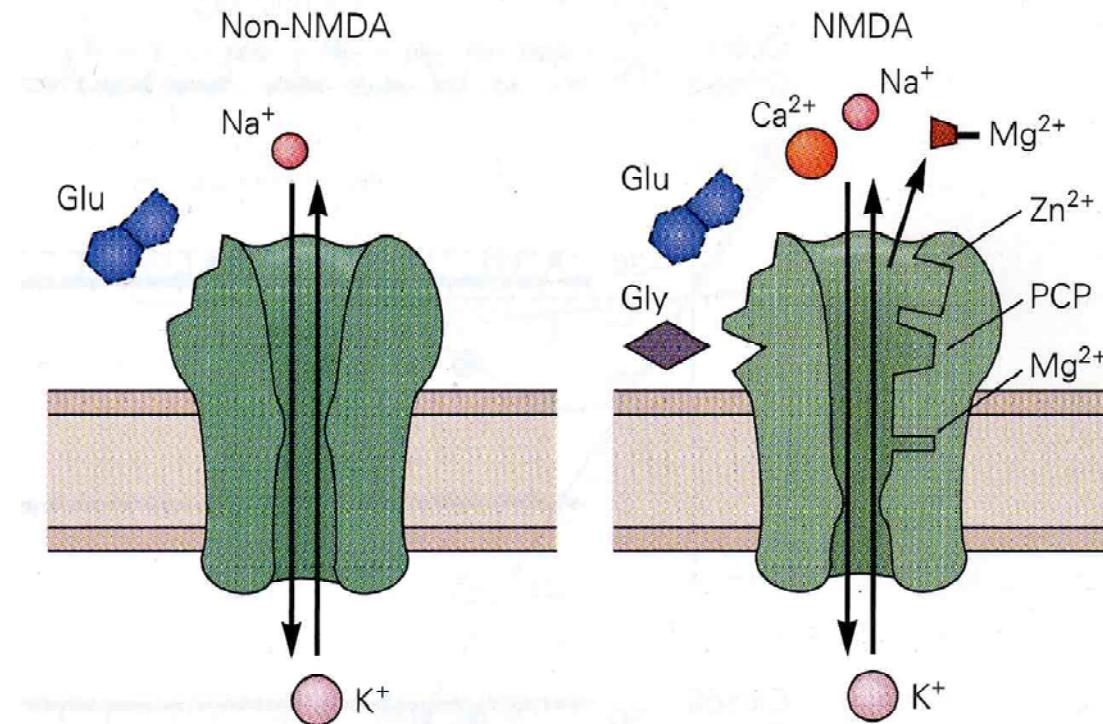
Synaptic stimulation



From Schiller, Schiller and Clapham,
Nature Neuroscience 1, 114 (1998)

NMDA AND NON-NMDA RECEPTORS FUNCTION DIFFERENTLY

NMDA受体和非NMDA受体不同的功能
A Ionotropic glutamate receptor



NMDA receptors open only when depolarization precedes glutamate binding.

Depolarization releases Mg^{2+} blocking particle from ligand-binding site.

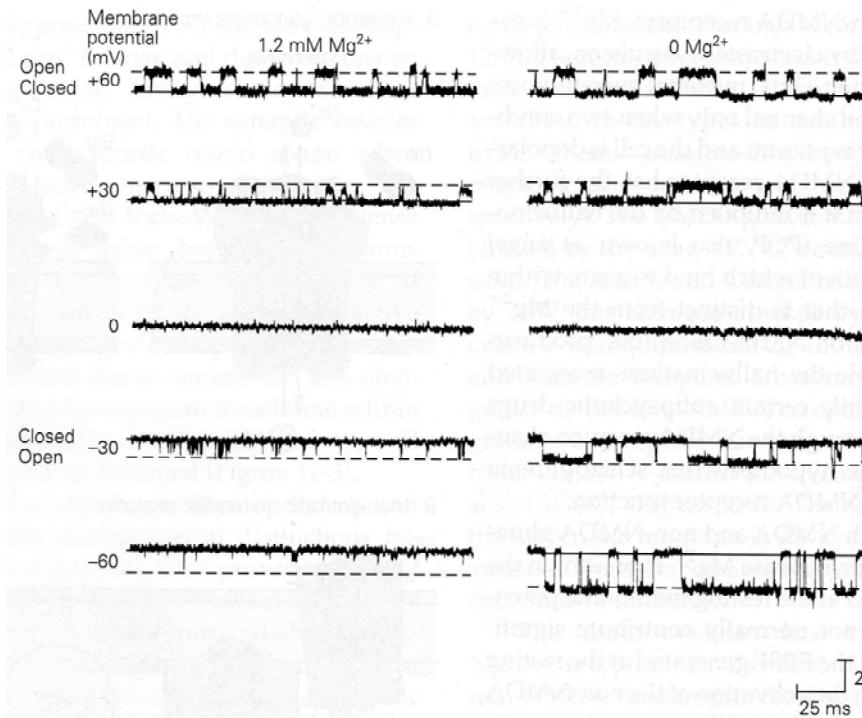
NMDA受体只有当突触后膜去极化后，镁离子从通道内结合位点解离，再被谷氨酸激活后才会打开

NMDA receptors only open with prolonged presynaptic activity.

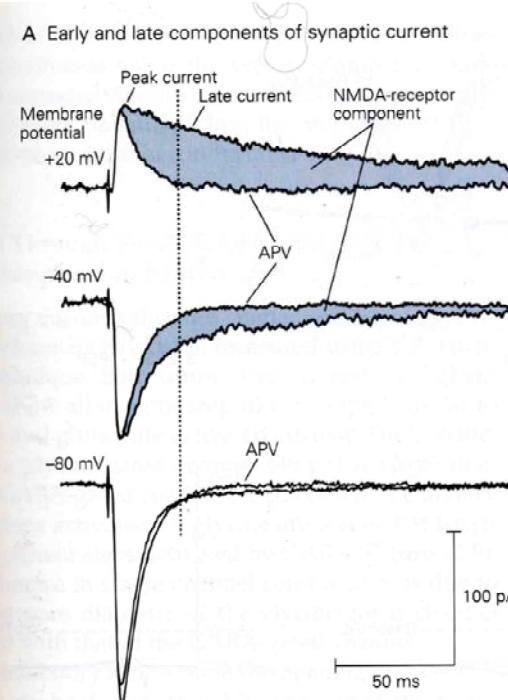
长时间的突触前活动的同时，NMDA受体才打开

NMDA RECEPTORS CONDUCT LATE CURRENT AFTER DEPOLARIZATION

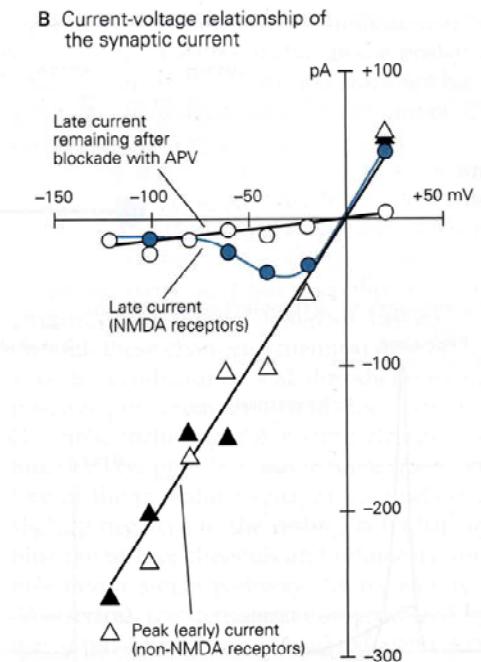
突触后膜去极化后NMDA受体传导电流



Single Channel Recordings in V-Clamp



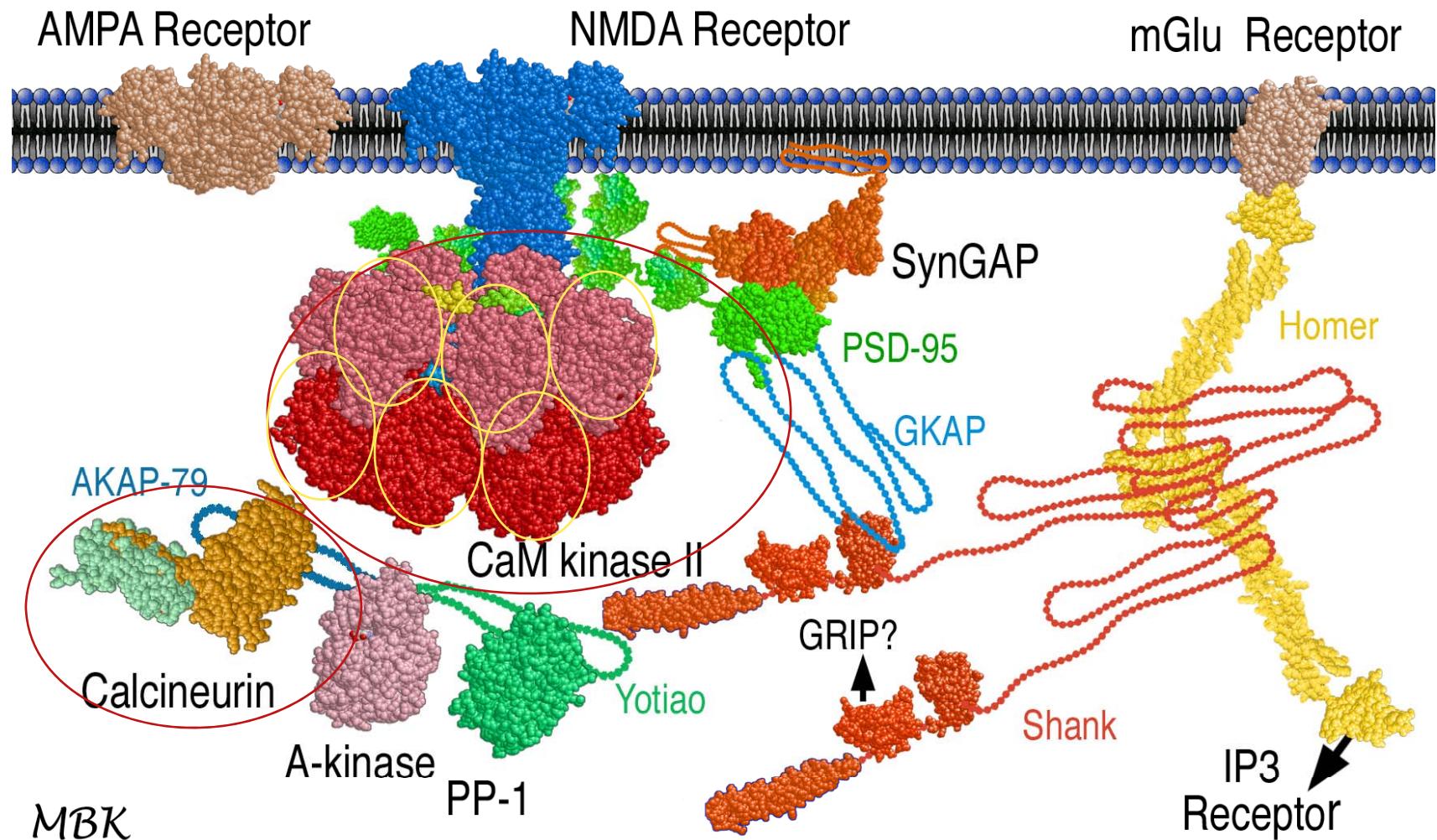
Whole Cell Recordings in V-Clamp



Calcium entry through NMDARs induces signaling processes that can modify synaptic behavior both short- and long-term

钙离子通过NMDA受体进入突触后，引起一系列信号转导过程，调节长时程，短时程突触行为

Signaling Complexes in the Postsynaptic Density

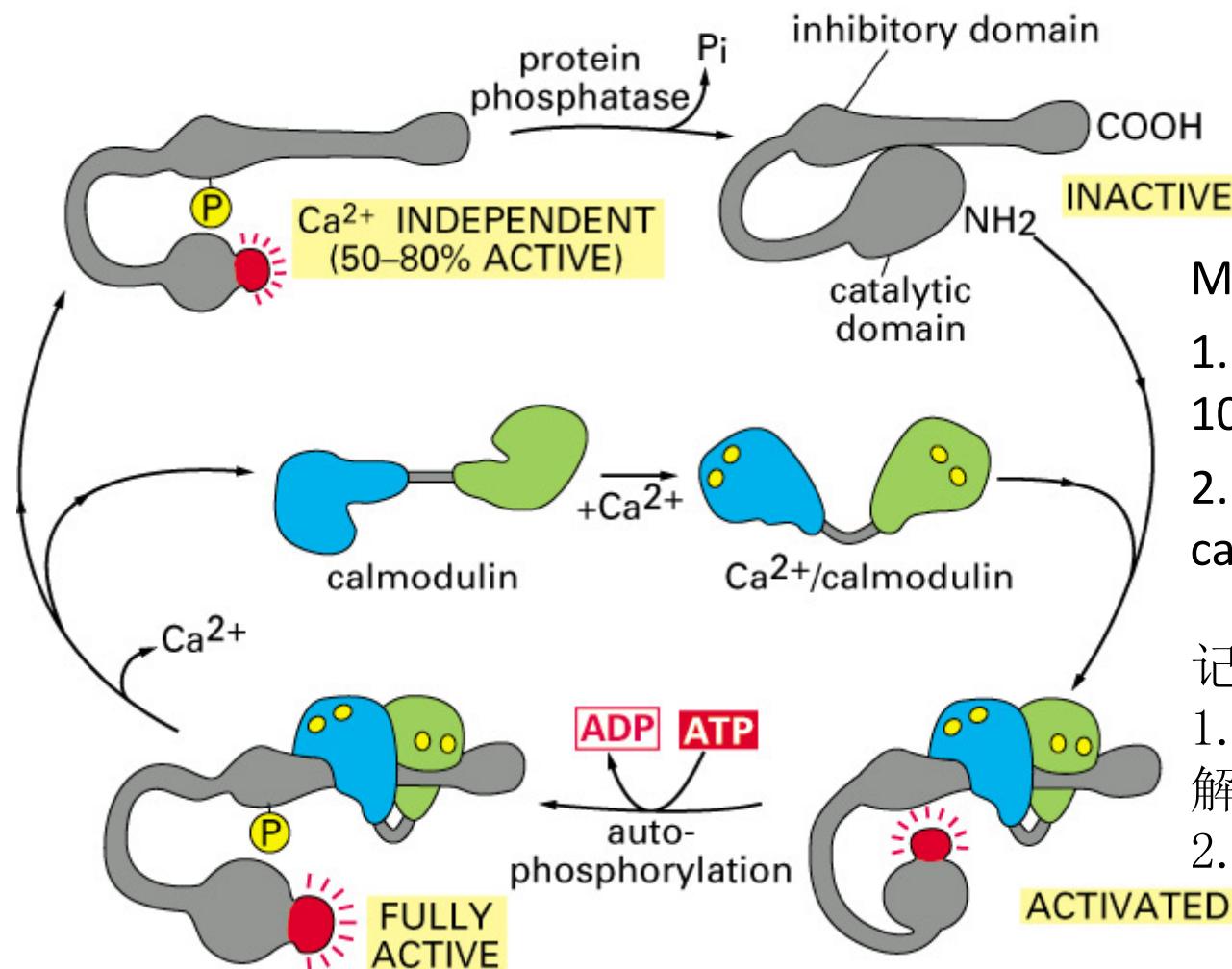


Recall the CaMKII Molecular Mechanism of Memory?

CaMKII 参与记忆的分子机制

Ca^{2+} /calmodulin dependent protein kinase (CaM-kinase)

钙离子/钙调蛋白依赖型蛋白激酶



Memory function:

1. calmodulin dissociate after 10 sec of low calcium level;
2. remain active after calmodulin dissociation

记忆的功能

1. 10秒中低钙后钙调蛋白解离
2. 仍然保持活性

Ca^{2+} /calmodulin dependent protein kinase (CaM-kinase)

钙离子/钙调蛋白依赖型蛋白激酶

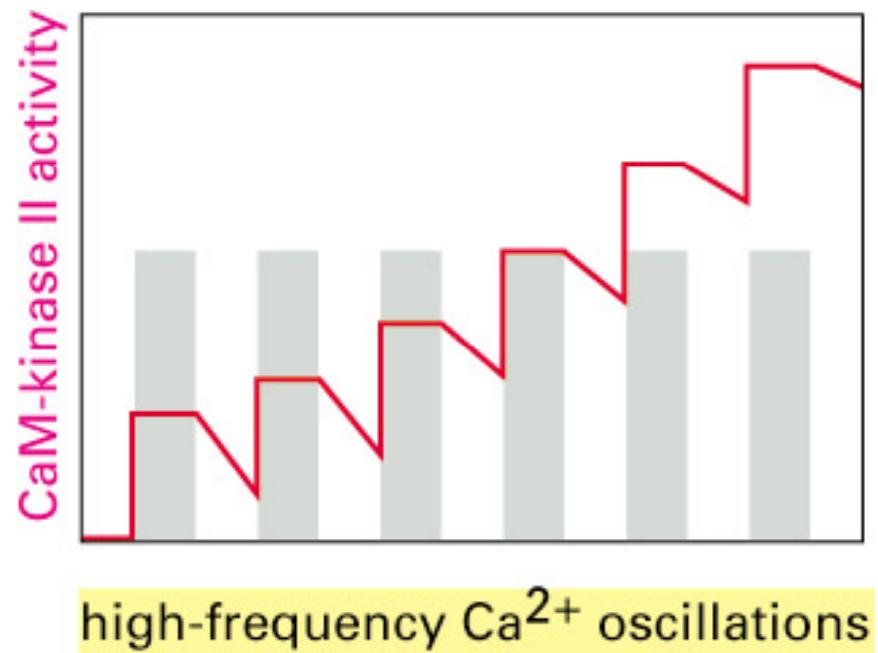
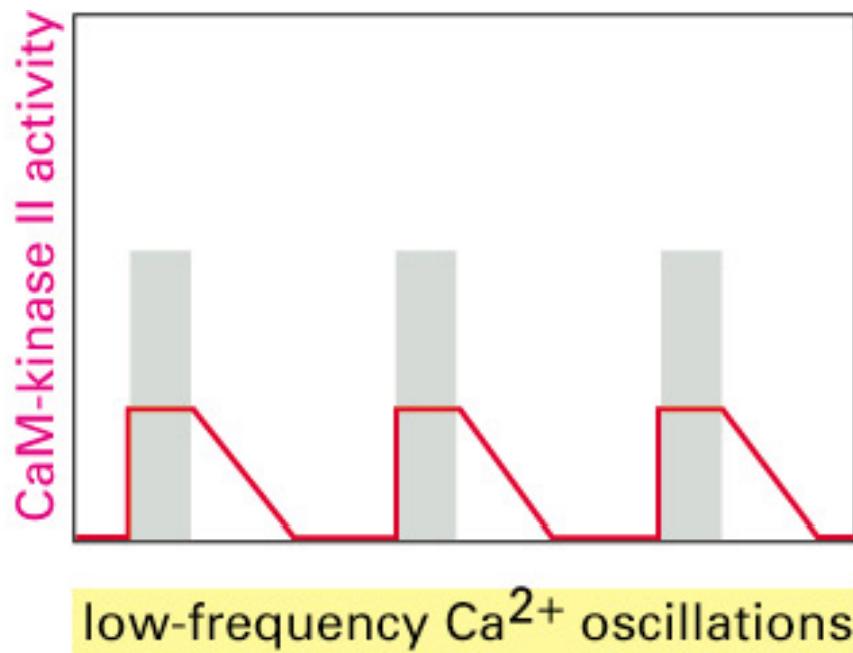
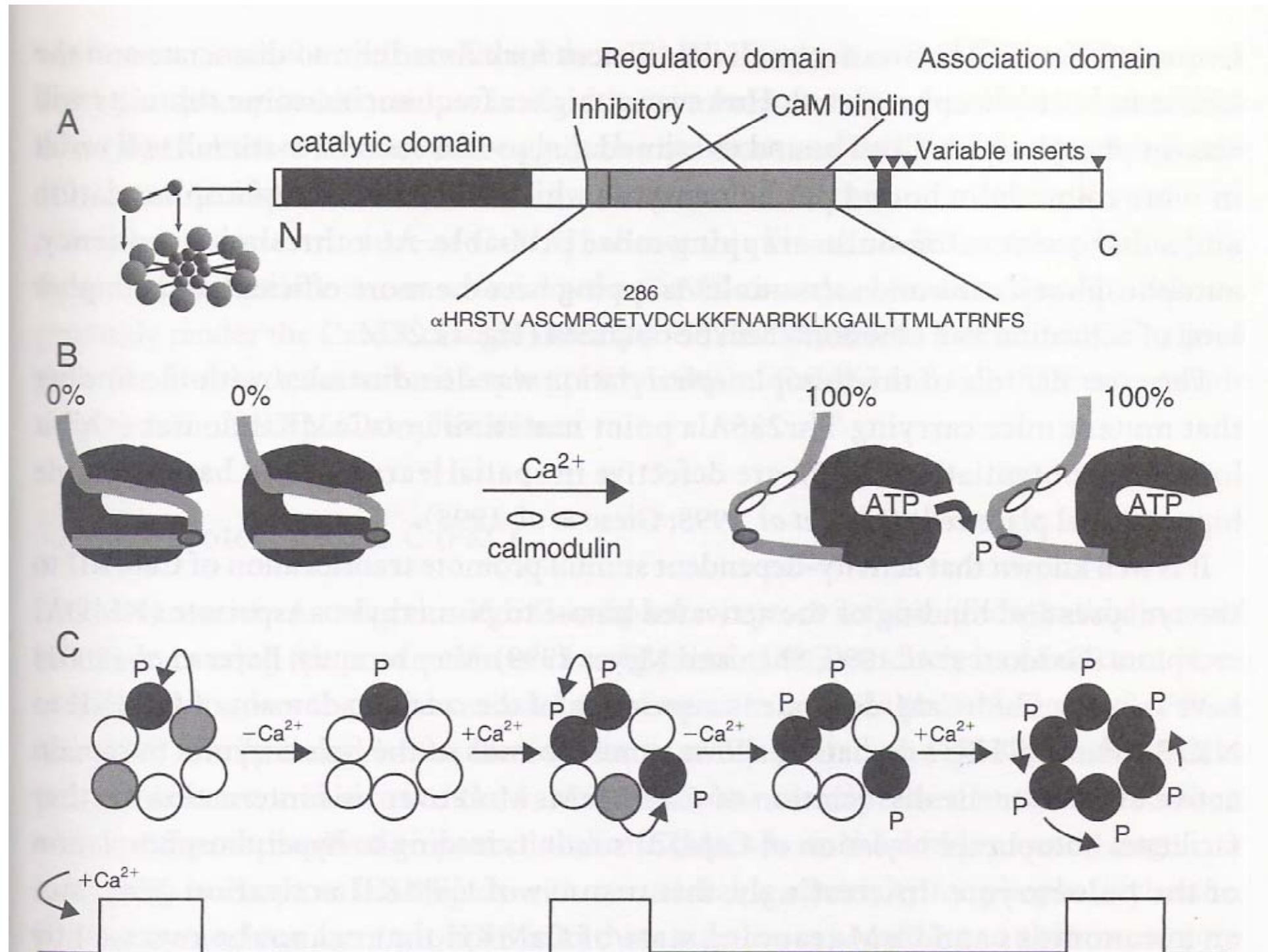
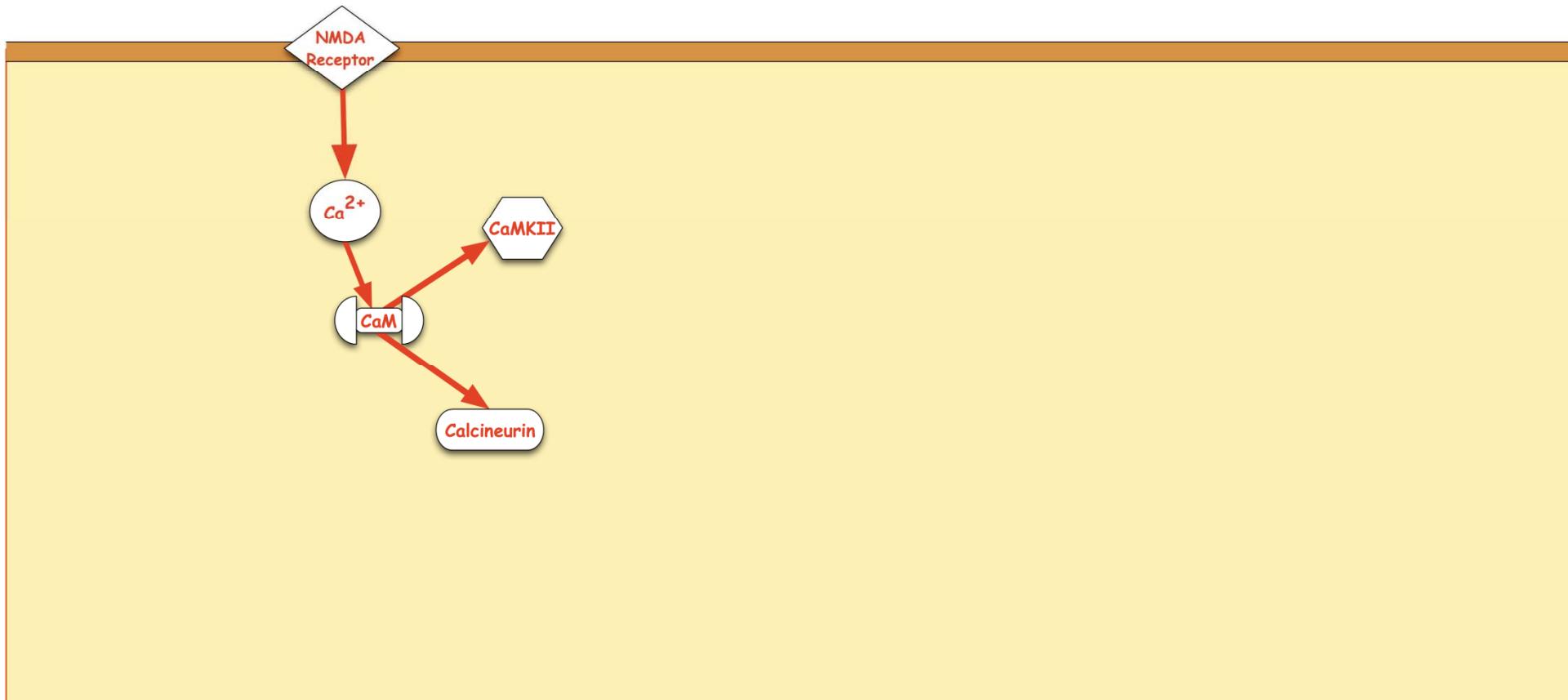


Figure 15–42. Molecular Biology of the Cell, 4th Edition.



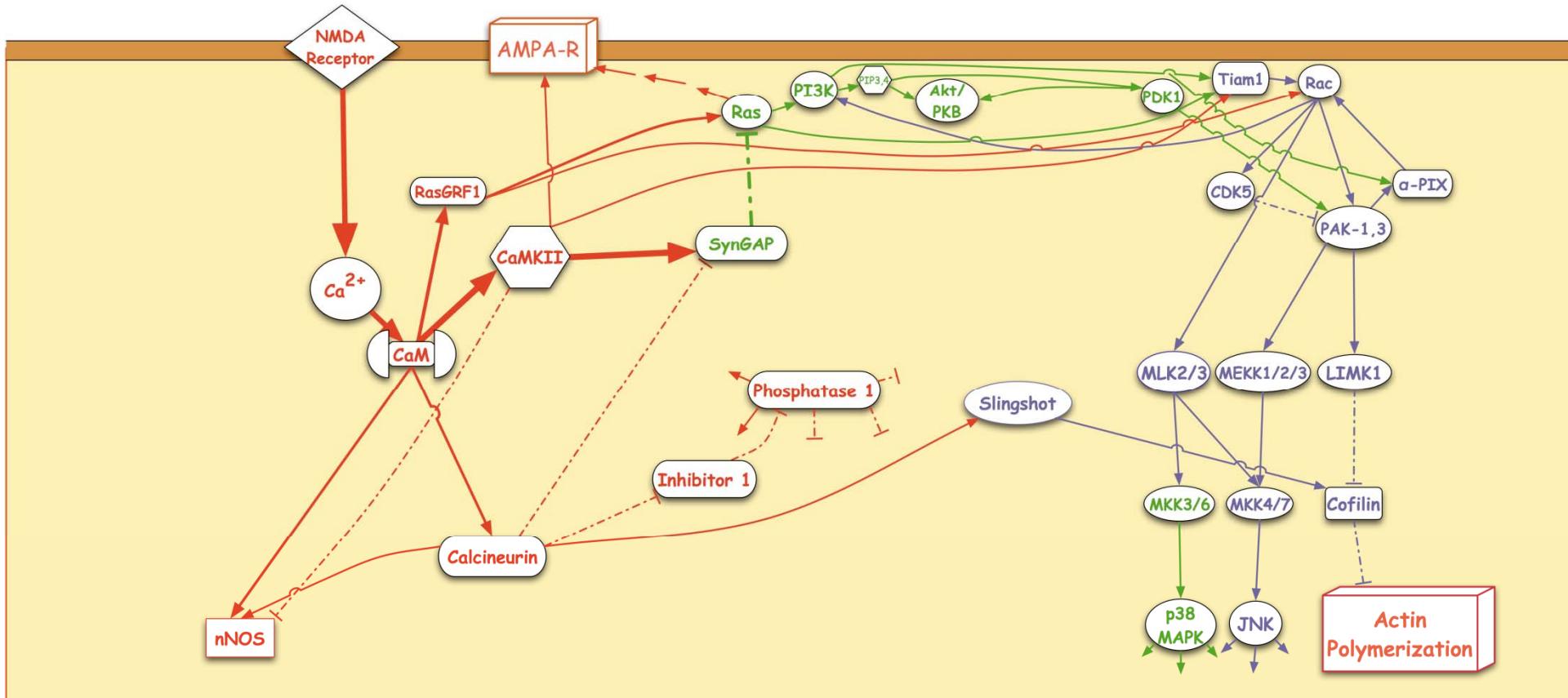
Targets of calcium coming through the NMDA receptor

钙离子进入NMDA受体的位点



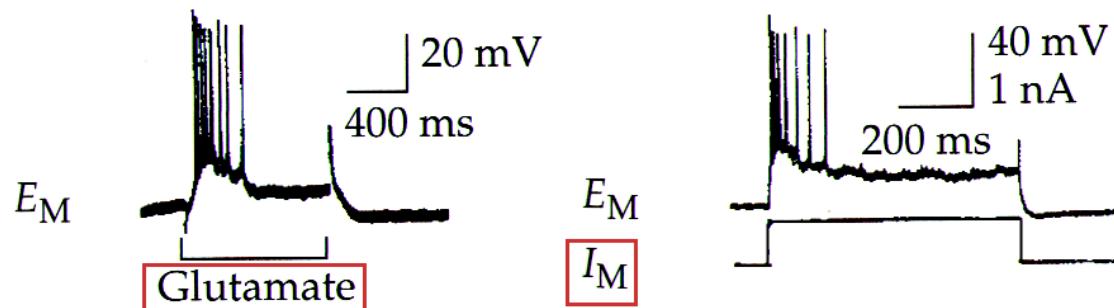
Targets of calcium coming through the NMDA receptor

钙离子进入NMDA受体的位点



Modulation of “Intrinsic Properties” Accommodation in Hippocampal Neurons

海马神经元适应性调节—内在性质



Prolonged stimulation of a neuron produces a burst of action potentials of limited length. Ca^{2+} influx during AP's activates dendritic SK channels that cause accommodation, and, when short stimuli are applied, produce a large after-hyperpolarization (ahp).

对神经元进行延长刺激可以产生动作电位。动作电位发生过程中钙离子内流激活树突SK通道，引起适应性调节。当给与短时间刺激，产生一个大的后-去极化

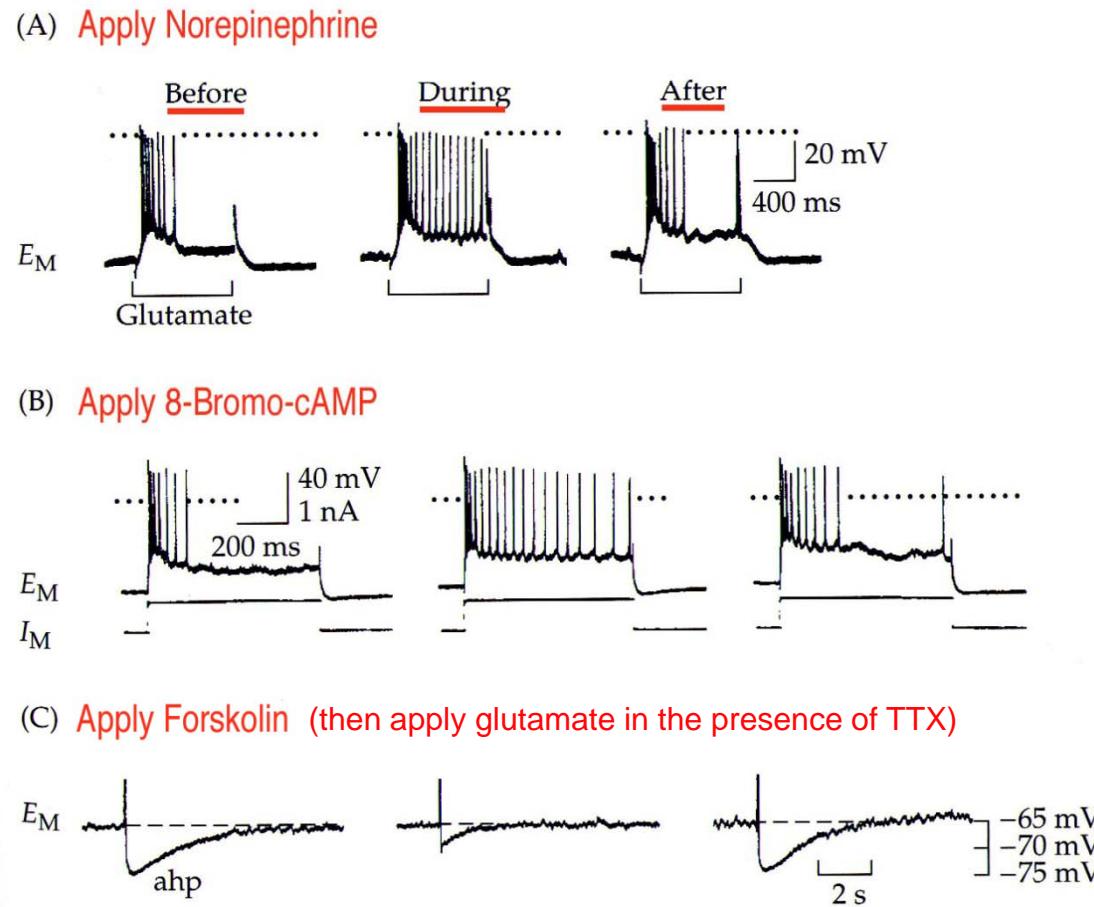
Regulation of Accommodation in Hippocampal Neurons

After application of norepinephrine, the SK channel is inhibited, so that the ahp is smaller and spike trains are longer.

加入去甲肾上腺素之后，SK通道被抑制，因此ahp变小，spike trans延长。

The effect of Norepinephrine is mimicked by agents that increase the level of cAMP.

去甲肾上腺素产生的效应可以由能提高环化腺苷酸的药物模拟



The Genome Contains a Large Number of K⁺ Channels

基因组中包含大量的钾离子通道

