Dynamics of Synapses

- Transmission, Modulation and Plasticity at the Hippocampal Mossy Fiber Synapse -

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Outline

Background

- History of Neurons and Synapses
- Technical Developments for Studying Synaptic Transmission
- Diversity of Synapses

MF Synapse I

- Hippocampal Mossy Fiber Synapse as Experimental System
- Synaptic Transmission and Short-Term Plasticity (STP)
- Contribution of Adenosine to STP Characteristics

MF Synapse II

- Experimental and Theoretical Investigation of Mossy Fiber STP
- Interplay between Long-Term and Short-Term Plasticity
History of Synapses: Staining Technique

- Layering of the neocortex
- Diversity of cell types

- "Golgi stain" of neurons
- relatively sparse staining, therefore better identifiability of individual structures
History of Synapses: Neuron Doctrine

- sketch of mammalian hippocampus after Golgi’s technique with silver nitrate

- Ramon y Cajal: used also Methylene blue staining, got same results…
- Cajal put forward the „neuron doctrine“ with nerve cells as individual structures
The term ‘synapse’ was introduced by Charles Sherrington (1897) to describe these zones of contact between neurons, specialized in the transmission of information.
Types of Synapses

Anatomy and constituents of synapses differ depending on the brain region, developmental stage etc.
Principles of Synaptic Transmission

1. Action Potential Invasion into Presynaptic Terminal
2. Calcium Influx through Voltage-Dependent Calcium Channels
3. Triggering of Vesicle Docking
4. Release of Transmitter into Synaptic Cleft
5. Transmitter Binding at Postsynaptic Receptors
6. Postsynaptic Current
Diversity of Chemical Synaptic Transmission

Synapse-Specific Parameters
1. Action Potential Waveform
2. Calcium Influx
3. Intraterminal Ca\(^{2+}\) Concentration
4. Calcium Buffering
5. Readily Releasable Vesicle Pool
6. Docking of Vesicles
7. Presynaptic Receptors
8. Postsynaptic Receptors
Dynamics of Synapses – Plasticity on Different Timescales

Short-Term Plasticity
Dynamical, instantaneous regulation of synaptic strength in response to varying presynaptic input

Long-Term Plasticity
Constant, longer-lasting change in synaptic strength in response high presynaptic activity
Investigating Synapses

Recording Techniques
• Whole-cell
• Field-potentials
• Sharp electrodes
Investigating Synapses

Recording Techniques
- Whole-cell
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Rat brain with brainstem, cerebellum, neocortex and hippocampal formation
Example System: Hippocampal Mossy Fiber Synapse
Characteristics of Mossy Fiber Synaptic Physiology

A

1/10 Hz

200 pA
10 ms

B

1 Hz

overlay

200 pA
10 ms

recording electrode

stimulation electrode

EPSC amplitude (pA)

EPSC amplitude (pA)

Stimulus number

Stimulus number

1/10 Hz

1 Hz

1/10 Hz

10 30 50 70 90 110 130

250 260 270 280 290 300 310 320

Characteristics of Mossy Fiber Synaptic Physiology

„Paired-Pulse Facilitation“
Characteristics of Mossy Fiber Synaptic Physiology

Stimulation Frequency

Response Amplitude

"Frequency Facilitation"
Regulation and Modulation of Synaptic Transmission

Neuromodulation of Transmission

- Modulatory substances can bind pre- or postsynaptically
- Influence on e.g. calcium or potassium conductances
- Physiologically: behaviorally coupled regulation of neuromodulators. Tuning of synaptic weight to needs
- Mechanisms of action are very diverse
Mossy Fiber Synapse is Regulated by
1. mGluR
2. Kainate Autoreceptors
3. Several Neuromodulatory Systems (incl. GABA, opioid, adenosine)

What is the Cellular Mechanism of Adenosine-Mediated Inhibition of Transmission?
Adenosine Inhibits MF Synaptic Transmission

Gundlfinger et al.
JPhysiol. (2007a)
Microfluorometry of Calcium Transients
Calcium Current Recordings in Single Boutons

Gundlfinger et al.
JPhysiol. (2007a)
Adenosine (AD) tonically inhibits mossy fiber synaptic transmission. AD binds to presynaptic A₁ receptors coupled to Gᵢ protein. βγ subunit directly inhibits presynaptic calcium influx. P/Q- and N-type calcium channels affected.
Physiological Consequence of Adenosine Action

Adenosine Tonically Acts on the Presynapse

Low Release Probability

Large Short-Term Plasticity of Synaptic Strength

100s of milliseconds

10s of seconds
Physiologically Motivated Irregular Stimulus Trains

A

B

cumulative probability

inter-stimulus interval (s)
Physiological Stimulus Trains Modulate MF Transmission

A

presynaptic input

B

200 pA

20 ms

C

D

Gundlfinger et al.
JPhysiol. (2007b)
Model of Mossy Fiber Short-Term Plasticity

Descriptive Model of STP – combining facilitatory processes

\[ x(t+0) = x(t-0) + 1 \]

at each time \( t \) of synaptic activation

followed by exponential decay

Parameters of Model Description

- \( A_0 \) basal response amplitude
- \( a_{\text{slow}} / a_{\text{fast}} \) amplitudes of facilitation
- \( \tau_{\text{slow}} / \tau_{\text{fast}} \) time constants of facilitation
- \( g \) saturation of facilitation
Goodness of Model Description of STP

Best Model Description of Mossy Fiber STP

\[ A = A_c \left[ 1 + a_{\text{slow}} (y_{\text{slow}})^d + a_{\text{fast}} (x_{\text{fast}})^e \right] \]

\[ r = 0.988 \]
Expression of MF Long-Term Potentiation

Short-Term Plasticity

Long-Term Plasticity
STP before and after Long-Term Potentiation
Modulation of Synaptic Gains by LTP

Change in Range of Synaptic Gain

Amplitude-Dependence of Change in Gain
Mossy Fiber Synaptic Responses are Highly Dynamic
Reliable Model Description of MF Short-Term Plasticity
LTP Differentially Affects Different Temporal Components of STP
LTP as an Adaptive Process

Gundlfinger et al.
JPhysiol. (2007b)
Outlook - Physiological Stimuli Induce LTP?
Conclusion

• Synaptic transmission is a highly dynamic process
• Synaptic strength can be regulated by a variety of mechanisms
• Short-term and long-term plasticity modulates response amplitudes on different timescales
• There is not one fixed value $w$ of synaptic strength