Chapter 9: Biochemical Mechanisms for Information Storage at the Cellular Level

From *Mechanisms of Memory*, second edition
By J. David Sweatt, Ph.D.
Chapter 9: Dendritic Spine
Summary: Three Primary Issues Related to Mechanisms for E-LTP
Structures of Calcium-Binding Proteins
Structure of CAMKII

A

<table>
<thead>
<tr>
<th>Catalytic</th>
<th>Autoinhibitory</th>
<th>Self-association</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inhibitory</td>
<td>Calmodulin Binding</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>TT</td>
</tr>
</tbody>
</table>

286 Autonomous Activity

305/306 Inhibitory

B

C

Figure 3
Three Different Effects of Ca/CaM on CaMKII

- Transient CaMKII Activation
- CaMKII
- Ca++/CaM
- Thr 286 Autophosphorylation (persistently active)
- CaMKII
- NMDAR Association (persistently active)
- NMDA Receptor
Catalysis of cAMP by Adenylyl Cyclases
LTP in Adenylyl Cyclase-Deficient Mice
Domain Structures of Isoforms of PKC

Classical
- α: alpha
- βI/βII: Beta
- γ: Gamma

- PS: Phospholipid
- Calcium
- ATP
- Substrate

Novel
- δ: Delta
- ε: Epsilon
- η: Eta
- θ: Theta
- μ: Mu

Atypical
- λ/ι: Lambda/Iota
- ζ: Zeta

Auto-phosphorylation sites

Hinge Region
Hippocampal LTP in PKC Isoform-Specific Knockout Mice

Figure 8

A. PKC Beta Knockout

B. PKC Gamma Knockout

C. PKC Alpha Knockout
PKM$\zeta$ mRNA Formation from Internal Promoter within PKC$\zeta$ Gene
PKMζ and LTP Maintenance

Figure 10
**TABLE I: PROPOSED MECHANISMS FOR GENERATING PERSISTING SIGNALS IN E-LTP**

<table>
<thead>
<tr>
<th>MOLECULE</th>
<th>MECHANISM</th>
<th>ROLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaMKII</td>
<td>Self-perpetuating autophosphorylation, coupled with low phosphatase activity</td>
<td>Effector phosphorylation, Structural changes</td>
</tr>
<tr>
<td>Various PKCs</td>
<td>Direct, irreversible covalent modification by reactive oxygen species</td>
<td>Effector phosphorylation</td>
</tr>
<tr>
<td>PKMζ</td>
<td>De novo synthesis of a constitutively active kinase</td>
<td>Effector phosphorylation</td>
</tr>
</tbody>
</table>
**TABLE II: PROPOSED MECHANISMS FOR AUGMENTING AMPA RECEPTOR FUNCTION IN E-LTP**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Likely molecular basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased single-channel conductance</td>
<td>Direct phosphorylation of AMPA receptor alpha subunits by CaMKII or PKC</td>
</tr>
<tr>
<td>Increased steady-state levels of AMPAR</td>
<td>CaMKII (+ PKC?) phosphorylation of AMPAR-associated trafficking and scaffolding proteins</td>
</tr>
<tr>
<td>Insertion of AMPAR into silent synapses</td>
<td>CaMKII phosphorylation of GluR1-associated trafficking proteins</td>
</tr>
</tbody>
</table>
AMPA Receptor Regulation During LTP

1. Extrasynaptic insertion

2. LTP induction

3. Synaptic incorporation

4. Activation of GluR1 homomers

5. Exchange by GluR2 containing receptors

6. Ca^{2+}
Glutamate Receptor Insertion and Stabilization in E-LTP

* = Autophosphorylated CaMKII, Autonomous PKC
Retrograde Signaling in E-LTP

Figure 13

NMDA Receptor

GAP43

↑CaM

↑release

*PKC

PKC oxidation

NOS

NO^-

ONOO^{-}

O_2^{-}

Ca^{++}

O_2^{-}
Activity-Dependent Regulation of Local Protein Synthesis and Spine Morphological Changes in LTP

Figure 14
Altered Protein Synthesis as Trigger for Memory

Memory-Causing Event

- NMDA Receptor
- Altered Synthesis of Specific Proteins = The Trigger
- Effector Protein Complex = The Readout *
- Positive Feedback to Synthesis or Recruitment = The Maintenance Mechanism

Dendritic Spine
- "Housekeeping Proteins"

Constitutive Effector Protein

Signal to Specific Proteins

 mRNA

Constitutive Protein Synthesis

Induced Protein Synthesis

Perpetuated Structural/Functional Change

MEMORY STORAGE

*New Spine Structure, Potentiated Synapse, etc.
CAMKII as a Temporal Integrator

![3D Graph showing the relationship between calmodulin concentration, Ca²⁺ spike frequency, and autonomous activity. The graph has color-coded regions indicating different activity levels.](image)
Oxidative Activation of PKC in LTP

- NMDA Receptor
- Presynaptic? - PKC
- Release Process
- Presynaptic?
- Ca^{++}
- Oxidative Activation of PKC in LTP
  - Ca^{++}/CaM
  - NOS
  - NO
  - O_2^-
  - Superoxide
  - ONOO^- peroxynitrite
  - Zn^{++} release
  - cys
  - Persistently Active PKC
**Sites of Cleavage of Phospholipids by Phospholipases**

- **FA1** = Any of a number of 16-20 carbon fatty acids
- **FA2** = Typically Arachidonic Acid in plasma membrane

**Diagram:**
- PLA1
- PLA2
- PLC
- PLD

**Chemical Structures:**
- Inositol (Inositol Phosphates)
- Serine
- Ethanolamine
- Choline

**R =** OH OH

**FA1** =

- OH (PO₄)
- OH (PO₄)
- OH

**FA2** =

- COOH
- OH
- NH₂

**R =** O C O

- C = O C = O

**R =** O C O

- N(CH₃)₃
- +

**R =** OH OH

- Inositol (Inositol Phosphates)

**Arachidonic Acid**
Synaptic Tagging and the E-LTP/ L-LTP Transition

New gene products or proteins

Signal to nucleus

Locally generated tag captures new gene product

NMDAR

Synaptic Potentiation

New gene products or proteins

Synaptic tag