The Time Machine: Transforming Molecular Signals into Long-Lasting Synaptic Change
Presynaptic Release

Long Term Potentiation

Difference in time scale > 6 orders of magnitude
Early
LTP Induction Protocols

tetanus

pre

post

pairing

pre

post

theta burst

pre

post

STDP

pre

post

LTP Induction Protocols
Blocking NMDA Receptors Blocks LTP
Uncaging Ca^{2+} Alone Can Induce LTP
Protein Kinases Catalyze the Phosphorylation of Proteins
Early
LTP Leads to an Increase in Surface AMPA Receptors
LTP Leads to an Increase in Spine Size
Early

Late
Depolarization leads to the release of glutamate, which activates AMPA and NMDA receptors. This results in the influx of sodium and calcium ions, leading to an increase in intracellular calcium. Calcium activates PKC, which in turn activates MAPK. This leads to the activation of CREB, which is involved in protein synthesis.
Blocking Protein Synthesis Blocks the Late Phase of LTP
Weak Stimulus Followed by a Strong Stimulus Produces LTP
Molecular Makeup of the PSD

- **6% scaffolds**
  - GKAP
  - Homer
  - Lin-7
  - PSD-95
  - Shank

- **6% receptors and channels**
  - AMPAR
  - NMDAR
  - mGlur1

- **6% translation**

- **7% cell adhesion**
  - α-Catenin
  - β-Catenin
  - δ-Catenin
  - N-Cadherin
  - Densin-180
  - NCAM-140
  - Neurofascin
  - Neuroligin

- **2% chaperones**
  - HSP40

- **12% cytoskeleton actin**
  - Actin
  - α-Actinin
  - α-Adducin
  - Ankyrins
  - Arp2/3 complex
  - Contactin
  - Drebrin
  - LIM
  - Neurabin
  - α/β-Spectrins

- **4% cytoskeleton others**
  - MAP1A
  - MAP1B
  - MAP2
  - Septin
  - Tubulin

- **6% mitochondria**

- **11% kinases/phosphatases and regulators**
  - CaMKIIα/β/δ/γ
  - Casein kinase 2
  - PKCy
  - Protein phosphatase PP1
  - Protein phosphatase PP2A

- **4% motor proteins**
  - Dynein
  - Myosin IIb
  - Myosin V
  - Myosin VI

- **8% GTPases and regulators**
  - ARF3
  - cAMP-GEFII (RapGEF)
  - GIT1 (ArfGAP)
  - Heterotrimeric G proteins
  - Kalirin (RhGEF)
  - PIKE-L (ArfGAP)
  - Ras
  - SPAR (RapGAP)
  - SynGAP (RasGAP)

- **7% metabolism**

- **5% membrane trafficking**
  - AP1
  - AP2
  - Clathrin
  - NSF
  - SNAP-25 IP
  - Synapsin
  - Syntaxin BP
Scaffolding Molecules
PSD Proteins Are In Flux
Actin Treadmilling, Capping, Cutting and Cross-Linking
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Single-Particle Tracking of AMPA Receptor Diffusion
Imaging of Isolated PSDs with Immunogold EM
EM Tomography of Molecular-Scale Structures in the PSD
Förster Resonance Energy Transfer (FRET)
Super-Resolution Imaging Using FPALM

488 nm  507 nm  405 nm  555 nm  572 nm

Bleached

Dendra2

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