Long-term potentiation (LTP)

- a candidate cellular mechanism of memory

Properties of learned behaviors:

- Experience-dependent
- Input specific
- Rapid induction
- Long-lasting
- Stimulus threshold required
- Associative or non-associative

Long-term Potentiation

- An enduring (>1 hour) increase in synaptic efficacy that results from high-frequency stimulation of an afferent (input) pathway

Hebbs Postulate:

- When an axon of cell A... excites[s] cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased."
- Bliss and Lomo discovered LTP in the hippocampus in 1973

Experimental design:

- Stimulate a bundle of presynaptic axons e.g. hippocampal perforant path
- Use extracellular recording electrode to measure monosynaptic EPSP e.g. dentate gyrus
  - Record population response before and after high frequency stimulation
  - Increase in population response indicates potentiation

Hippocampal slice preparations have supported and extended the findings of Bliss and Lomo

- Extracellular recordings
  - more cells fire after tetanus

- **Intracellular recordings**
  - **individual cells have increased EPSPs**
  - **more easily reach threshold for firing**

LTP is experience-dependent

- **Need stimulation to induce a large change in synaptic strength**

LTP is induced rapidly

- **Conditioning stimulation for only a few seconds can last hours**

LTP is induced cooperatively

- **There is a stimulus intensity threshold for the induction of LTP**

LTP can be induced in an associative manner

- **Co-activation of separate but converging input can induce LTP**
  - **Even when stimulation of either of these pathways alone is incapable of inducing LTP**
- **A weak input can sustain LTP if concurrently paired with a strong input**
- **Association must be in close temporal order**

LTP is input specific

- **Only the conditioned (tetanized) pathway is potentiated**

Events in LTP

- **Calcium entry into the postsynaptic cell**
- **Activation of the N-methyl-D-aspartate (NMDA) receptor**
- **A variety of second messenger cascades**
- **Enhanced presynaptic neurotransmitter release and/or increased receptor responses on the postsynaptic side**

LTP requires coincident presynaptic activity & postsynaptic depolarization

block postsynaptic inhibition with GABA antagonist

- **block postsynaptic depolarization with TTX**
- **pair weak presynaptic input with postsynaptic depolarization**

Activation of the NMDA receptor is necessary for LTP

- non-NMDA receptors dominate in normal synaptic transmission
- NMDA receptor is double-gated
  - Ligand-dependent (requires binding of glutamate)
  - Voltage-dependent (requires depolarization to remove magnesium from the channel pore)
- NMDA receptor gating provides associativity & cooperativity

Calcium entry into the postsynaptic cell is necessary for LTP

- NMDA receptor activation opens a calcium channel
- Calcium chelators block the induction of LTP
- Increasing calcium concentrations induces LTP-like phenomenon

LTP requires a variety of second-messengers

- Protein Kinase C (PKC)
  - PKC inhibitors block LTP
  - increase in PKC after LTP
- Ca2+/Calmodulin-dependent Protein Kinase II (CaM II)
  - inhibitors of CaM II block LTP
  - CaM II knockout mice express altered LTP
- persistent kinases- role of calpain

LTP is associated with increased presynaptic neurotransmitter release and enhanced postsynaptic receptor activity

- More glutamate released after LTP
- Enhanced postsynaptic calcium entry

Is LTP a biological correlate that can explain learning and memory?

LTP looks like learning & memory:

- Experience-dependent
- Induced rapidly and enduring consequences

- **Input specific**
- **Cooperative properties (to bring stimulus above threshold)**
- **Associative properties (with close temporal order b/n events)**

Ways to test LTP as a mechanism for learning and memory?

- **Correlate the ability to induce LTP with the ability to learn**
- **Test the effect of LTP induction on learning**
- **Test the effect of learning on LTP**
- **Test the effects of blocking LTP on learning and memory**
- **Test memory of knockout mice that are defective in LTP**

The ability to induce or sustain LTP is correlated with memory

- **Spatial memory in developing rats emerges at the same time that the hippocampus is functional & capable of LTP**
- **Old rats have poor LTP and poor spatial memory**

LTP induction affects subsequent learning

- **In old rats, memory is impaired after the induction of LTP**

Learning situations can induce LTP

- **Enhanced LTP in DG after trained to retrieve food**
- **LTP-like changes observed after placing rats in enriched environments**

Blockade of LTP can block memory

- **NMDA antagonists block spatial memory**
- **Many drugs impair both LTP and memory**

Gene knockout mice that have altered LTP have impaired memory abilities

- **PKC knockouts**
- **CaM II knockouts**

Amygdala & auditory fear conditioning

- **hypothesis: LTP strengthens input from auditory thalamus to amygdala; this is how fear gets attached to the tone**
- **tests: block LTP should block fear, sensory input path should be capable of LTP, auditory fear conditioning should increase postsynaptic responses to the tone, inducing LTP should attach fear to auditory stimuli**

How does LTP not look like learning and memory?

- **Duration**
- **Learning ability in the absence of LTP**
- **Learning prior to the expression of the NMDA receptor (but LTP is not always dependent on NMDA)**

Does LTP last long enough to act as a memory device?

- **LTP always decays**
- **There is no example of LTP lasting more than two months**
- **Memories can last forever**
- **But...The locus of memory may transfer after LTP induction**
- **And...LTP can cause long-lasting changes in dendritic morphology**

Can memories still be formed in the absence of LTP?

- **Yes. Rats can still eventually learn, even when NMDA receptors are blocked**

Can memories form before the NMDA receptor is expressed?

- **Yes. Memories can be formed embryonically before NMDA receptor expression**

LTP is not always dependent on the NMDA receptor.

- **LTP can be induced in CA3 of the hippocampus even with NMDA receptor blockade**