back to Lectures page

Neurotransmitter Systems IV

LTP, LTD & the Hebbian synapse

Review: The NMDA receptor

The NMDA receptor

- is activated by glutamate
- The receptor is linked to a Ca^{++} channel
  - some intracellular effects of Ca^{++}
    - activation of kinases leading to
      - phosphorylation of receptors
      - phosphorylation of proteins regulating gene expression
      - structural changes
    - at lower concentrations, Ca^{++} may activate protein phosphatases, thus counteracting the effects of kinases
      - kinases add phosphate groups to proteins; phosphatases remove them
- The NMDA receptor is both ligand (transmitter) gated *and* voltage sensitive
  - the channel is blocked by magnesium ions (Mg^{++}) at membrane potentials near resting value
  - depolarization displaces magnesium ions that block the channel at resting potential
  - if glutamate is applied ***and*** the magnesium block has been removed due to depolarization, then the NMDA-related channel opens, allowing Ca^{++} to enter the neuron
- the dual sensitivity of the NMDA-gated channel allows this channel to detect correlated activity in presynaptic and postsynaptic neurons
  - such detection of correlated activity has been implicated in learning and memory

The Hebbian synapse

- The Canadian psychologist, D. O. Hebb proposed a very influence principle concerning the modification of synpatic connections:

Hebb's postulate

"*When an axon of cell A is near enough to excite a 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.*"

D. O. Hebb, 1949

"*Inputs that fire together, wire together.*"

Mark Bear, 1996

- The properties of the NMDA-gated channel are consistent with Hebb's postulate
- in order for the post-synaptic cell to be depolarized sufficiently to remove the Mg^{++} block from the Ca^{++} channel, presynaptic neurons must be active
  - glutamate released from the presynpatic neurons could depolarize the post-synaptic cell by acting at AMPA receptors
  - once the Mg^{++} block is removed by the depolarization, action of glutamate at the NMDA receptor would cause Ca^{++} influx
  - intracellular effects of increasing the concentration of Ca^{++} would then lead to the change in synaptic efficiency

Long-term potentiation

Long-term potentiation (LTP) is a strengthening of synaptic transmission

- LTP can induced by conditions that produce prolonged depolatization of post-synpatic neurons, such as temporal and spatial summation of EPSPs
- LTP is often studied in the hippocampus, a structure that lends itself well to neurophysiological analysis
  - the hippocampus is also of interest because of abundant evidence of its importance in learning and memory
  - one region of the hippocampus that is used frequently for such studies is the CA1 area (CA = "cornu ammonis" (Ammon's horm))
  - CA1 neurons receive an excitatory input from axons called "Schaffer collaterals"
  - these axons release glutamate onto CA1 neurons, evoking an EPSP
  - following a brief period of high-frequency ("tetanizing") stimulation, the size of the evoked EPSP is increased
    - thus, synpatic transmission has been potentiated
    - this potentiation may last for many weeks ("long-term")
  - LTP is input-specific
    - the size of the EPSPs evoked by stimulating excitatory inputs other that those that were

subjected to the high-frequency stimulation remains the same
- what is critical about the conditions for evoking LTP is that the post-synpatic cell must be depolarized at the time that the pre-synaptic fibers are firing
  - high-frequency stimulation is effective in depolarizing the post-synaptic cells, due to temporal summation
  - spatial summation also contributes
    - EPSPs evoked at multiple synpases on a given neuron add up over space
    - Thus, multiple terminals must be active to produce sufficient depolarization of the post-synaptic neuron

The NMDA-gated channel is involved in LTP at the synapses between Schaffer collaterals and CA1 neurons

- LTP can be prevented by administering drugs that block NMDA receptors
- LTP can also be blocked by preventing the rise in intracellular Ca^{++} that normally results from opening the NMDA-gated channel

Ca^{++} influx is critical to the induction of LTP at the synapses between Schaffer collaterals and CA1 neurons

- two kinases have been implicated in LTP at the synapses between Schaffer collaterals and CA1 neurons
  - protein kinase C (PKC)
  - Calcium-calmodulin dependent protein kinase II (CaMKII)
- It is suspect that these kinases produce several different changes that contribute to LTP. These may include
  - phosphorylation of AMPA receptors, which increases the ionic conductance of the AMPA-gated channel
  - insertion of additional AMPA receptors into the post-synaptic membrane
    - a store of AMPA receptors is thought to be held in reserve near the membrane
  - structural changes such as the "budding" of new dendritic spines and the formation of new synpases on them

Long-term depression

Long-term depression (LTD) is a weakening of synaptic transmission

- one can think of LTD as the complement to the Hebbian strengthening of synpases that underlies LTP
  - in the case of LTP, strengthening occurs following the co-activation of the pre- and post-synpatic neurons
  - in the case of LTD, weakening of synpatic connections occurs following the activation of the pre-synaptic neuron in the absence of strong activation of the post-synpatic neuron
- Ca^{++} appears to play a role in LTD
  - if the Ca^{++} concentration in the post-synpatic neuron is only slightly elevated when the pre-synaptic neuron is activated, then the enzymes that are stimulated are protein phosphatases rather than protein kinases
    - protein phosphatases remove phosphate groups from proteins
  - during LTD, it is suspected that AMPA receptors are de-phosphorylated
  - In addition, AMPA receptors may be removed from the membrane and placed in the reserve pool
- In short, LTD appears to involve mechanisms that reverse the changes underlying LTP

LTP, LTD and memory

- a commonly used experimental paradigm for studying memory in lab animals is the "Morris water maze"
  - a rat or mouse (both good swimmers) is placed in a large pool of opaque fluid (e.g., milk)
  - at a hidden location in the pool is a platform submerged at a depth that allows the rodent to stand with its head comfortably above the waterline. This is a safe haven for the rodent.
    - initially, the animal finds the platform by trial and error
    - over repeated trials, the animal learns the location of the platform and swims directly toward it after being placed in the pool
  - learning the location of the submerged platform is disrupted by drugs that block the NMDA receptor
  - blocking the expression of the gene for CaMKII disrupts learning in this test and interferes with LTP as well
  - blocking the expression of the gene for NMDA receptors in the CA1 region of the hippocampus disrupts learning in the water maze, LTP & LTD
  - Overexpression of NMDA receptors seems to enhance learning in some tasks
- many of the molecular changes implicated in LTP and LTD are relatively long-lasting
  - nonetheless, their time-courses are not sufficiently long to account for long-term memory storage
- according to a hypothesis proposed by John Lisman, auto-phosphorylation of CaMKII, a very long-lasting protein, contributes to long-term storage of information by maintaining the phosphorylated state of other proteins

Previous Next

back to Lectures page