Long Term Potentiation

by Richard H. Hall, 1998

Description

If we accept the assumption that all behavior is associated with some underlying physiological activity, then learning and memory must be represented by some type of relatively permanent change, so that, when we have "learned" something or "remembered" something, the nervous system has "learned" or "remembered" as well. Therefore, we will begin our exploration of the neurological basis of learning with an examination of learning at the basic level of the neuron. As we will see, there is a great deal of evidence that the nervous system, at the level of the neuron, does change as a result of prolonged experience. A phenomenon that is often used to explore such changes at the level of the neuron is termed long term potentiation.

Long term potentiation (Figure 1) is an experimental method in which axons coming from one part of a rat's **hippocampal formation**, the **entorhinal cortex**, are stimulated many times in rapid succession, which leads to an increase in activity in another part of the hippocampal formation, the **dentate gyrus**. More specifically, the procedure begins when a single pulse is sent via the axons of the entorhinal cells, and the **population EPSP** of the cells in the dentate gyrus is measured. EPSPs (excitatory post synaptic potentials) are depolarizations that make a neuron more likely to fire. This first measure is used as a base line. After this, the axons are stimulated with several pulses in quick succession. Following this, the effect of a single pulse is measured again, as representing long term potentiation. If the second single pulse results in a significantly higher population EPSP, than the base line pulse, then long term potentiation has occurred. This type of potentiation can be long lasting. Thus, in long term potentiation it appears that the nerves in the dentate gyrus "remembers" that they have fired before, and, as a result, are more sensitive to new input.

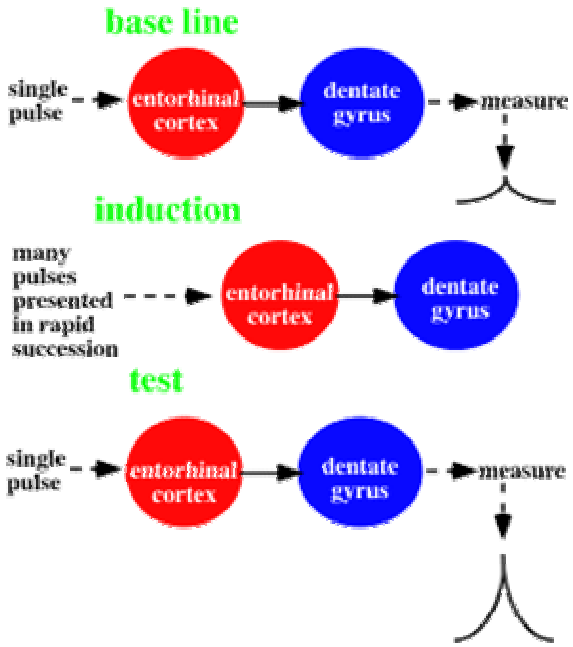

Figure 1. Long Term Potentiation Experimental Method

Formation

Now that a model (i.e., long term potentiation) had been delineated for representing learning at the neurological level, the next step is to explore the underlying processes that account for it. In this way we begin to get some idea as to how learning and memory are represented in the nervous system at the cellular level. One of the first things that neuroscientists found with respect to long term potentiation, was that **NMDA**, a type of glutamate receptor, was particularly important in the formation of long term potentiation. **Glutamate** (also called glutamic acid) is the most common excitatory neurotransmitter in the central nervous system. There are multiple types of glutamate receptors, and glutamate plays a particularly important role in learning and memory. NMDA glutamate receptors, in particular, are a necessary component in memory formation, as modeled by long term potentiation. The most direct evidence for this is that, when drugs that block NMDA receptors are administered to rats, long term potentiation does not occur. The mechanism by which NMDA has its effects, appears to be via calcium **(Ca^2+) ion channels**. Research indicates that Ca^2+ channels, which are normally blocked by magnesium (Mg^2+), open when glutamate activates NMDA receptors, with one important qualifier. The membrane must already be partly depolarized - an EPSP must be in progress. Research indicates that, even if Ca^2+ channels are activated, long term potentiation will not occur, if the post synaptic membrane is not partly depolarized. This explains why, in long term potentiation, many pulses in quick succession are necessary. Thus, two important criteria must be met for long term potentiation to occur. NMDA receptors must be activated, and the membrane of the post synaptic neuron must be partially depolarized. The Ca^2+ channels are, therefore, neurotransmitter and voltage dependent.

Sustained Structural Change

The previous section explains the mechanism for the formation of long term potentiation, but it does not explain how long term potentiation is sustained. Long term potentiation, once established (i.e. learned or remembered), may last for a very long time, so, based on our assumptions of a neurological-behavior relationship, there should be some sort of semi-permanent changes at the level of the nervous system. In fact, researchers know that, while NMDA receptors are very important in establishing long term potentiation, they are not a part of the maintenance process. When the same NMDA blocking drugs that inhibit long term potentiation from being established are administered after the long term potentiation has been formed, they have no effect on the phenomenon. On the other hand, research indicates that another type of glutamate receptor, AMPA, does play an important role in sustained long term potentiation.

When a neuron in the dentate gyrus is examined, after long term potentiation, there is a significant change in the number of receptor sites present on the post synaptic membranes. More **AMPA** glutamate receptors are present. Presumably, this is one mechanism that accounts for the increased level of excitability in these neurons. Researchers now know that a very interesting change occurs in the AMPA receptor sites. The sites double their contact surface by splitting in two. These new synapses are referred to as "perforated synapses". We can then imagine that a very similar process is occurring in the millions of neurons with their billions of connections in our own brains every time we learn something new.

The next question to be addressed, with respect to sustained structural changes, has to do with the internal cellular mechanism that directs these permanent structural changes (e.g., the doubling of receptor surfaces). One proposed mechanism is depicted in Figure 2. In order for the structure of the cell to change, new proteins must be synthesized, just as new materials must be created if we wanted to change the structure of, say, a house. In the case of nerve cells, this material building process takes the form of **protein synthesis**. The evidence indicates that the process of protein synthesis in the post synaptic cells responsible for long term potentiation occurs inside the dendrite themselves. (This is unusual, since protein synthesis normally occurs in the cell body.) All the necessary components for protein synthesis are present in the dendrites of these cells (e.g., ribosomes and transfer RNAs). So, it is quite possible, as depicted in figure 2, that $Ca^{2}+$ channels act to initiate protein synthesis.

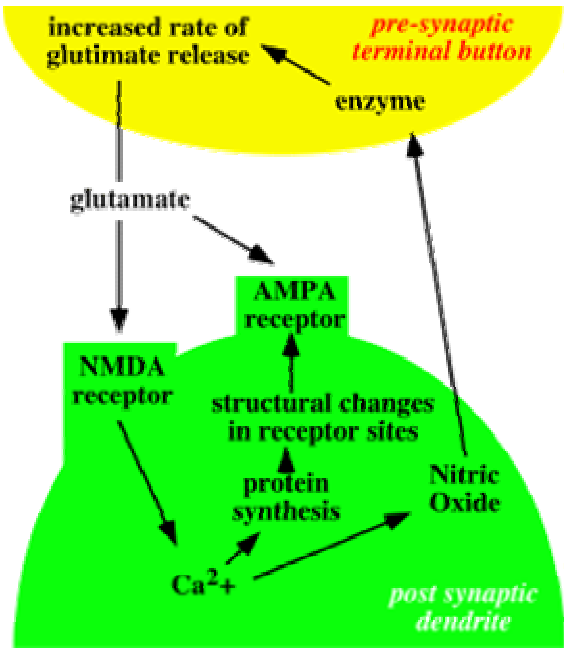

Figure 2. Proposed Mechanism for LTP Sustained Structural Change

When long term potentiation occurs, in addition to an increase in AMPA receptor sites, there also appear to be permanent changes in the presynaptic neuron. The terminal buttons of the neurons involved in long term potentiation release more neurotransmitter after the potentiation has been created. The soluble gas, **nitric oxide**, most likely accounts for this phenomenon, as evidenced by the fact that, when the synthesis of nitric oxide is inhibited, long term potentiation is inhibited. It is also known that nitric oxide, since it is a soluble gas, could diffuse out of the postsynaptic membrane, and nitric oxide can interact with an enzyme which is involved in the production of glutamate. So, as indicated by the model in figure 2, Ca^2+ could act to initiate protein synthesis in the post synaptic membrane, and to simulate the diffusion of nitric oxide out of the post synaptic membrane and into the pre synaptic terminal button, where it would stimulate the production of glutamate, resulting in an increase in the rate of glutamate release.