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Synaptic Plasticity In Vitro and In Silico: Insights into an Intracellular Signaling Maze

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Synaptic plasticity provides a record of neuronal activity and is a likely basis for memory. The early apparent simplicity of the process of synaptic plasticity has been lost in a flood of experimental data that now implicates some 200 signaling molecules in cellular memory. It is now clear that these signaling networks perform surprisingly sophisticated cellular decisions that weigh factors such as input patterns, location of stimulus, history of activity, and context. Computer models have followed experiments into this maze of molecular detail, often matching closely with their experimental counterparts, but perhaps losing simplicity in the process. Here, we suggest that the merger of models and experiment have begun to restore the earlier simplicity by outlining a few key functional roles for signaling networks in synaptic plasticity. In this review, we discuss the current state of understanding of synaptic plasticity in terms of models and experiments.

Many synapses in the central nervous systems are plastic; that is, they exhibit the ability to change their biophysical properties. As a result of such biophysical changes, the synaptic transmission efficacy changes such that incoming action potentials from presynaptic neurons elicit altered responses from postsynaptic neurons. The response efficacy of postsynaptic neurons can be modulated by either changing the properties of action potentials or by changes at the synapse resulting in alteration of synaptic strength.

Changes in synaptic strength are the substrate for most theoretical analyses of memory in neuronal networks. This phenomenon has therefore been the focus of a particularly fertile interdisciplinary effort involving modelers, physiologists, and molecular biologists. This interplay is the theme of this review.

Brief Historical Review

In the early 1950s, Donald O.Hebb made the insightful prediction of a specific form of synaptic plasticity that could form the basis for memory (34). This consisted of an association between pre- and postsynaptic activity, resulting in an enhancement of synaptic transmission. Such an enhancement was first observed in the early 1970s, when it was discovered that brief but intense synaptic activity can change the properties of synaptic transmission by stably potentiating transmission for periods of hours to days (14). This was termed long-term potentiation or LTP. There were strong theoretical reasons to expect a mirroring process of weakening synaptic transmission (13), but this turned out to be difficult to confirm. Long-term depression (LTD) was first observed at the mossy fiber/Purkinje neuron synapse (40), but this appeared to be unidirectional. There were some indications of synaptic depression between distinct synapses (17), but single-synapse depression remained elusive. About 20 years after the discovery of LTP, another long-duration form of plasticity (LTD) was discovered at CA3-CA1 synapses in the hippocampus (26), thus finally demonstrating bi-directional synaptic plasticity at single synapses. LTD, as the term suggests, is the stable depotentiation or weakening of synaptic transmission. These two broad categories of synaptic plasticity (LTP and LTD) have been the focus of intense research for the past three decades.

LTP and LTD are thought to accompany learning events and are considered as cellular mechanisms that may store information at synapses for long durations. When subsequent neural activity traverses the same synapses, the altered levels of responsiveness are believed to form the basis for memory (58). Research dating from the late 1980s has uncovered many of the molecular details related to LTP and LTD. In vitro experiments using hippocampal slices and pharmacological agents have implicated nearly all major signaling pathways and more than a hundred different molecules in plasticity (42, 53, 77). In recent years, another form of plasticity induction has been found, that of spike timing-dependent plasticity or STDP. Here, in accordance with the Hebb's original proposal, LTP is induced when the presynaptic neuron fires an action potential in a narrow time window before the postsynaptic neuron. Furthermore, reversal of this timing, that is, postsynaptic firing before presynaptic neuron or outside the narrow time window, results in LTD (11).

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The broad picture that emerges from these and many other studies is that suitable patterns of activity can induce stable strengthening or weakening of synaptic efficacy. As a consequence of the detailed molecular and biochemical analysis of synaptic plasticity, there has been an explosion of information on its molecular nature, which has also been the subject of many debates and controversies in the field (70). Above all, it has highlighted that the mechanisms are far more complex than ever anticipated.

Functional Modules in Plasticity

Despite the complexity and debates in the field, there are a few general functional steps in synaptic plasticity that encapsulate many of the key events. These steps include *1*) induction, *2*) input selectivity in space and time, *3*) expression and modulation of plasticity, and *4*) maintenance of synaptic changes. We have chosen to partition synaptic plasticity into these four steps partly from a functional viewpoint and partly because these also seem to describe the main categories of simulation studies in the system (FIGURE 1). Such modularization is also instructive from the viewpoint of understanding the role of the many biochemical players. At many synapses, the initial steps in synaptic plasticity resulting in the induction of LTP and LTD are thought to be largely postsynaptic, whereas both presynaptic and postsynaptic processes contribute to the subsequent steps in synpatic plasticity. Several excellent reviews have summarized the combined role of these processes (76). In this review, we have restricted our discussion to postsynaptic processes.

Induction

This is the process of conversion of incoming action potentials into cellular signals that trigger plasticity. It is now quite well established that Ca^{2+} entry into the postsynaptic terminal after either a burst of synaptic activity or after coincident pre- and postsynaptic activity is an essential primary step in the induction of synaptic plasticity (58). The association resulting from coincident activity in pre- and postsynaptic neurons was originally a theoretical proposition (34, 75). The first candidate molecular substrate for associativity was the NMDA receptor at the hippocampal Schaffer collateral-CA1 synapses. NMDA receptors detect the coincident activity of pre- and postsynaptic neurons because presynaptic glutamate release must be coupled to postsynaptic depolarization that releases an Mg^{2+}-dependent block (36). The NMDA receptors were further demonstrated to be the main source of Ca^{2+} in the postsynaptic terminal of this synapse (54). It was soon realized that many aspects of Ca^{2+} dynamics affect synaptic plasticity. A number of simulation studies have addressed Ca^{2+} dynamics (31, 41, 61, 68, 87). These studies have provided several insights.

First, very high local concentrations of calcium (~100 μM) build up near the open receptor channels. This may cause interesting local signaling effects, particularly in the postsynaptic density (PSD) that acts as a scaffold for many receptors and signaling proteins.

Second, calcium concentrations decline rapidly with distance, partly due to diffusive effects but in large part due to extremely high levels of calcium buffering. This results in a tight regulation of intracellular Ca^{2+} levels ($[Ca^{2+}]_i$) both in space and time. Alteration in the concentration of these buffers can change $[Ca^{2+}]_i$ significantly, such that its downstream activities, including synaptic plasticity, are effected.

Third, the dendritic spine plays a major role in localizing calcium spread, since the neck size can act as a physical constraint for free Ca^{2+} diffusion.

Fourth, there is a lower $[Ca^{2+}]_i$ increase in dendrites distal to the soma. Calcium channel distribution and attenuation of action potentials or synaptic depotentiation are responsible for such differences.

Fifth, calcium buildup is a nonlinear function of input frequency (61). Simulations as well as fluorescence imaging experiments suggest that, for different stimuli, Ca^{2+} amplitudes are not only different but that Ca^{2+} buildup is nonlinear. As a result, $[Ca^{2+}]_i$ resulting from different stimuli may differ by as much as an order of magnitude.

These spatial- and frequency-dependent effects are responsible for activation of different downstream targets since calcium sensors have sharp thresholds for Ca^{2+} level sensing. The multitude of responses that Ca^{2+} mediates as a second messenger is a function of these biophysical properties.

Although most studies have focused on NMDA receptors as the source of Ca^{2+}, it is now known that there are other modes of Ca^{2+} entry at the synapse (FIGURE 1). In the lateral amygdala synapses, for example, Ca^{2+} influx into the postsynaptic neuron is carried out by voltage-gated Ca^{2+} channels (83). Certain stimulus patterns favor VGCC contributions to plasticity (16). In the hippocampus, at mossy fiber synapses, NMDA receptors and metabotropic glutamate receptors (mGluRs) fulfill this function. mGluRs are activated by glutamate, but they employ a downstream cascade of events that eventually results in release of Ca^{2+} from the IP3-gated intracellular stores. Some simulations of CA1 neurons have studied the role of intracellular calcium sources during synaptic plasticity (71). These simulations suggest that an intracellular source is necessarily involved during the induction of LTP, as the duration of Ca^{2+} elevation required for LTP cannot be accounted for by NMDA receptors alone. Simulations of calcium dynamics in Purkinje neurons also suggest that an intracellular Ca^{2+} source may be essential for spike timing detection (25).

Overall, it is now clear that the induction of plasticity is triggered by calcium influx into postsynaptic cells. The mechanistic details of Ca^{2+} influx depends on cell

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type and the type of stimulus used, but in most cases this initial step embodies associativity between pre- and postsynaptic activity. The time course and amplitude of calcium buildup is strongly dependent on input pattern, geometry, and other synaptic details (18). As discussed below, this is critical for determining the nature of the resultant synaptic plasticity.

Input selectivity in space and time

One of the most intriguing aspects of induction of synaptic plasticity is that the same second messenger Ca^{2+} is required for both LTP and LTD. In particular, both forms of plasticity can be blocked by intracellular Ca^{2+} chelators (52, 63). This raises a fundamental issue: How can the same second messenger mediate two opposing forms of plasticity? The growing understanding of the mechanism behind this dual function of Ca^{2+} activity is an example of a particularly fruitful collaboration between theory, simulations, and experiments.

Theoretical and simulation studies suggested that the calcium waveform can act as a determinant between the two forms of plasticity (49). According to this hypothesis, strong and rapid increase in Ca^{2+} levels results in LTP induction, whereas slower and more moderate increases in Ca^{2+} result in LTD. Experimental verification of this proposal followed. It was demonstrated that the amplitude of Ca^{2+} rise was indeed different during induction of different forms of plasticity (55, 85). Ca^{2+} imaging experiments further corroborate this, as they show that even in the case of STDP asymmetric Ca^{2+} influx occurs during LTP compared with LTD induction (45, 72). Simulations also suggested that distinct downstream biochemical sensors for Ca^{2+} may explain differential responsiveness to these Ca^{2+} waveforms (3, 49). Many experiments since then have demonstrated that kinases and phosphatases differentially respond to the amplitude and time course of Ca^{2+} signals (Ref. 63, reviewed in Ref. 51). Other candidates, such as calmodulin, have been proposed to be Ca^{2+} sensors that could sense Ca^{2+} waveforms and mediate different outcomes through a separate set of downstream targets (24). Based on these diverse studies, it is clear that there are multiple targets for Ca^{2+} during a plasticity event, and selective activation of these players determines the direction of plasticity.

Another aspect of input selectivity is detection of repetitive stimulus patterns on the time scale of tens of seconds to minutes (FIGURE 1). Spaced stimuli repeated at 5- to 10-min intervals have been found to be more effective for learning than the same number of stimuli massed together in time. This form of selectivity has been observed in animals ranging from flies to rodents (35, 59, 60, 79). These tasks are much slower than the millisecond-range dynamics of electrical activity and Ca^{2+} influx. Simulations and experiments have been combined in several studies to suggest that biochemical cascades might be involved in such slow computation tasks. The first molecule to be implicated in such a role was CaMKII, which has been shown to play a role as a frequency decoder (22). Other simulations of biochemical networks at synapses suggest that pattern detection is an emergent property of the network (6). In one such simulation, a specific prediction was that ERK II is preferentially activated by LTP-inducing stimuli that are spaced apart by ~10 min (8). Experiments designed to test these predictions corroborated the simulation results (2).

Synaptic plasticity is also highly selective for the

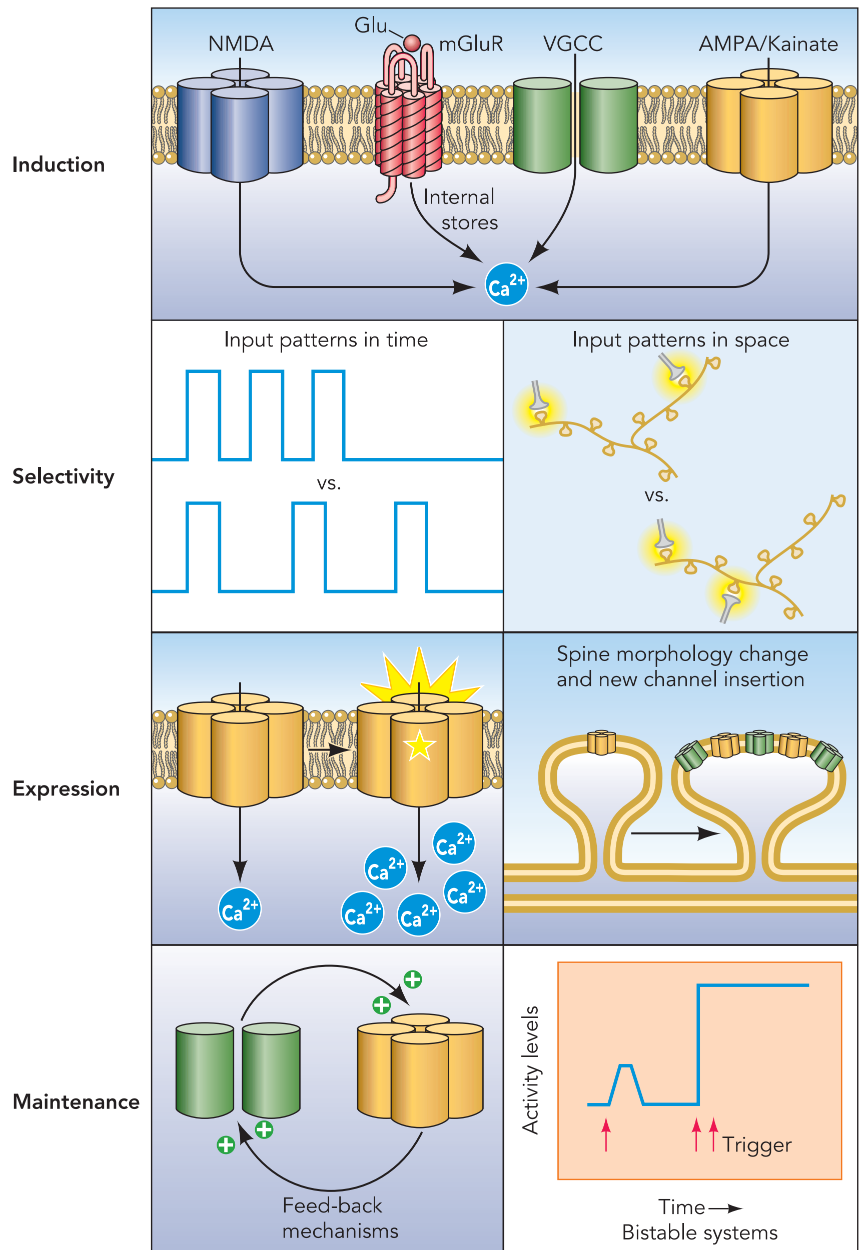

FIGURE 1. **Functional modules in synaptic plasticity**
The topmost panel (Induction) shows that, during induction of synaptic plasticity, there are multiple sources of Ca^{2+}. The second panel (Selectvity) shows examples depicting the selection of input patterns in time (*left*) and in space (*right*). The third panel (Expression) has two examples that depict the different mechanisms for expression of synaptic plasticity. The last panel (Maintanence) has two possible mechanisms for maintenance of synaptic plasticity.

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spatial organization of inputs (FIGURE 1). At a small scale, this involves localization of inputs to spines and dendrites. A recent simulation study shows the role of compartmentalization of biochemical space in imparting specificity to plasticity changes. Ca^{2+} forms micro-domains and nano-domains due to localized influx and diffusive barriers, which also limit the activity of Ca^{2+} effecter proteins such as calmodulin. Such compartmentalization in combination with Ca^{2+} amplitudes modulates properties of synaptic plasticity like strengthening or weakening and the extent of strengthening (64). At a larger spatial scale, there is emerging evidence for plasticity spread along dendrites for 50—70 μm (29). This issue has recently been addressed through simulations (80). This study suggests that local synaptic potentials coincident with action potentials reaching back to these synapses in dendrite result in supralinear changes of membrane potential, eventually triggering biochemical cascades responsible for induction of synaptic plasticity. This conclusion is in line with STDP experiments (43).

A crucial combination of spatial and temporal patterning is the phenomenon of synaptic tagging. In this situation, strong activity in one synapse can lead to plasticity in a weakly stimulated second synapse. This will happen only in the conditions that the second synapse is both in close proximity of the first synapse and was stimulated within a certain window of stimulating the first synapse (32). The protein kinase activity of PKC and ERK II is thought to play a role in such tagging process, although the exact mechanism is still a topic of active research (65, 69). A recent study suggests that phosphorylation of as yet unidentified tag proteins by these kinases and CaMKII could account for several aspects of synaptic tagging (74).

From this wide range of studies, it is clear that synapses and dendrites have remarkable pattern recognition capabilities. Synapses act as stringent gatekeepers for specific sequences of inputs, contingent on location and timing of other inputs to the cell. Many signaling molecules play a role in these processes. It is likely that different synapses are specialized with distinct molecular players to build up their own repertoire of responses.

Expression and modulation of plasticity

Many biochemical players participate in the expression of synaptic plasticity once induced. These processes can be subdivided into processes acting at different temporal durations: immediate to short-term, and middle- to longer-term changes. Short-term processes can be extremely rapid, of the order of a few seconds to minutes, whereas middle- to longer-term changes can happen over many hours or even days. Changes in the conductive properties of channels and receptor-ligand interaction fall under the immediate to short-term changes (FIGURE 1). For example, AMPA receptor phosphorylation can increase the current flowing through these receptors (5). This offers a simple mechanism for increasing the synaptic response to a fixed level of presynaptic signal. Such a possibility was first suggested from simulations of AMPA receptor conductivity (5). The authors then verified this possibility by performing electrophysiological experiments to record changes in the channel conductivity. Earlier experiments had suggested that such a change can be brought about by the action of kinases (CaMKII and PKC) (78). K^+ channels are another prominent target for phosphorylation leading to modulation of plasticity (86). These authors experimentally demonstrated the reduction of K^+ channel conductivity as a consequence of ERK II kinase-mediated phosphorylation. This reduction in K^+ conductivity has two synaptic effects. First, the local potential is less hyperpolarized. Second, it leads to an increase in the local resistance of the synapse so that the same depolarizing current causes a greater rise in potential. Na^+ channel activity is also modulated by phosphorylation by PKA and PKC. Experimental and modeling studies show that many channel properties, including open kinetics, inactivation properties, conductivity, and gating voltage, can be modulated by phosphorylation of channels (20).

Beyond the phosphorylation of channels, the recruitment or removal of receptors to the synapse is now believed to be a primary mechanism for plasticity (FIGURE 1) (56). Both the AMPA and the NMDA receptors move between the postsynaptic density and a vesicular pool. The insertion of AMPA receptors is believed to be the key event in converting unresponsive, "silent" synapse into active synapses. This process switches on new synapses and hence increases the efficiency of synaptic transmission. The process is also likely to be reversible and may thus account for bidirectional synaptic plasticity (46). Another mode of expression of plasticity is changes in the physical features, such as spine shape and morphology (FIGURE 1). These changes influence synaptic properties such as degree of compartmentalization and electrical continuity. The "twitching spine" hypothesis of Crick, which suggests that rapid changes in spine morphology could be a way of changing synaptic efficacy, was based on these ideas and the finding that actin is present in spines (19). Observation of spine structure using fluorescent markers reveals that these changes can indeed happen very fast, sometimes within a few minutes (28). Simulations studying the spine motility and twitching suggest that the process of twitching results in a rapid transfer of calcium transients to the parent dendrite (37). This rapid transfer would enhance the coupling of spine to dendrite, hence increasing synaptic efficacy. Other simulations of change of synaptic morphology show that the effect of such changes can be more than just local change in synaptic strength, but it can affect the output of an entire dendritic branch (81).

Changes in the basal properties of neurons account for several manifestations of middle- to long-term

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plasticity. Such changes are distinct from alterations in synaptic properties. It is now clear that neuronal activity during plasticity events is capable of changing intrinsic properties of neurons, including channel density, conductivity, and activation/inactivation properties of voltage-gated channels across the entire cell. These changes may be long-term and may exert significant effects on cellular responses and circuit dynamics. These possibilities have been explored in a combination of experimental and simulation studies (47, 57). The major implication of these studies is that long-term changes in intrinsic properties, such as excitability of neurons, have a large impact on the induction and expression of future plasticity events. This property is referred to as metaplasticity. Since metaplastic changes depend on the previous history of the synapse, it has been often referred to as higher-order synaptic plasticity (1, 23). Compared with synaptic plasticity processes that are rapid and synapse specific, metaplastic changes occur at a slower rate and can affect a large number of synapses or even the whole neuron at the same time (66, 82). Changes in the overall excitability of neurons as a consequence of synaptic potentiation have recently been reported to occur in the mammalian hippocampus (30). Intrinsic plasticity along with synaptic plasticity adds to the repertoire of changes that can account for information storage mechanisms at the cellular level. These processes also double as mechanisms to normalize neuronal output and improve network stability (21). However, only a small fraction of these possibilities have been tested experimentally.

Expression and modulation of synaptic plasticity are therefore just as rich a locus of molecular variety as induction or pattern selectivity. Receptors and voltage-gated channels both in the synapse and elsewhere in the cell may become biochemically modified to affect their responses. Expression levels both of receptors and voltage-gated channels may be altered to influence cellular responses. Cells as a whole may elaborate new spines or alter the geometry of existing ones.

Maintenance of synaptic changes

As discussed above, expression of plasticity is brought about through multiple molecular players. However, molecules have a short lifetime (minutes to days), whereas memories may be retained for years (27). A plausible solution to this paradox is the concept of a molecular switch (FIGURE 1). Such switches can recruit newly synthesized molecules to adopt a particular "remembered" state and thus retain state information despite molecular turnover. Theoretical and experimental studies suggest that feedback circuits of signaling pathways may form switches that are bistable, that is, can remain stably in either of two states (10).

The first strong candidate for a molecular switch was CaMKII. Simulation and theoretical studies in the 1990s led to the proposal that CaMKII activation after Ca^{2+} influx was sufficient to explain expression and maintenance of LTP. On the basis of simulation studies, it was suggested that CaMKII can be involved in a self-renewing, autophosphorylation cascade once triggered so that there is a long-term increase in synaptic strength (50). However, experiments since then have revealed that the molecular targets of activated CaMKII are also subject to modulation by other kinases and phosphatases triggered by the same Ca^{2+} influx and are capable of reversing the changes introduced by CaMKII. In addition, this proposal did not account for LTD. One elaboration of the original CaMKII model was the proposal that calmodulin can be trapped into an active association with CaMKII. This interaction results in active forms of CaMKII that last at the synapse for different durations (38). Experimentally, such a trapping mechanism may be a possible explanation for NMDA receptor-dependent activation of CaMKII for a long-lasting synaptic plasticity (4).

The role of other signaling pathways has also been explored, and new mechanisms of maintenance of synaptic change have come to light from these simulation studies. Notable among these has been the bistable feedback loop involving p42-ERK II and PKC (9, 46). The essence of this proposal is that both ERK II and PKC can activate each other through cascades of molecules. This biochemical loop can be bistable with respect to ERK II activity levels; that is, a weak or brief stimulus would activate ERK II, but it will come back to baseline on removal of the stimulus. However, if there is a strong stimulus, then the feedback loop kicks in, switching ERK II stably to the high activity state. A similar kinase feedback mechanism has been suggested from simulations of intracellular signaling in the mollusk *Aplysia*. According to this proposal, PKA activity is responsible for long-term changes such as CREB activation; however, the duration of PKA activity is "gated" or restricted to a time window of 3—6 h by ERK II (67). Thus four of the major kinases thought to have a role in learning and memory have been implicated in putative memory switches (77).

"Theoretical and experimental studies suggest that feedback circuits of signaling pathways may form switches that are bistable..."

Simulation studies done in the recent past have explored the issue of maintenance further by introducing structural and physical constraints on synaptic function. Synaptic size is a critical constraint. Typical synaptic volumes are very small, of the order of 0.1 fl. Only a few molecules of each biochemical species are present in the synapse. For example, there are likely to be only five or six free Ca^{2+} ions. At these scales, sto-

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chastic effects pose a serious problem for reliable functioning of these cascades (7, 12). How does the synapse overcome such effects in maintaining plasticity changes? Two recent simulation studies suggest possible biochemical and cell-biological solutions in these conditions of very small molecule numbers (33, 62). In one, the cooperative action of several CaMKII holoenzymes was found to be sufficient to retain information for periods of years. In the second study, the traffic of AMPA receptors itself was found to be a bistable event. When coupled with CaMKII autophosphorylation, this study too predicted stable times of over a year. An interesting point to be noted here is that phosphorylation state may not be an accurate indication of enzymatic activity, since it has been experimentally demonstrated that CaMKII enzymatic activity decreases to baseline within ~15 min after LTP induction (48).

A further possible bistable mechanism has been suggested that involves local protein synthesis. Recent experiments suggest that the process of local protein synthesis might be important for two attributes of plasticity: *1*) tagging synapses that have recently undergone plastic changes and *2*) maintenance of plasticity changes by replacing proteins required for plasticity (15, 44). These experiments suggest a possibility of a positive feedback loop involving local protein synthesis and synaptic plasticity, both reinforcing each other locally at the synapse.

Other mechanisms that may contribute to long-term maintenance of synaptic changes underlying memory include recurrent activations of the synaptic networks that store memories, perhaps during sleep (39, 84). These episodes of activity could drive repeated synaptic plasticity events that maintain patterns of strong and weak synapses. Another possibility that has been suggested recently is modulation of trafficking rates due to clustering of receptors. This leads to metastable states that can outlast the lifetime of individual receptors, thus providing a mechanism for long-term maintenance of bidirectional synaptic changes (73).

The maintenance of memory is therefore both a theoretical and experimental challenge. This challenge is exacerbated by the small size and experimental inaccessibility of the synapse. Simulations have begun to help here by extrapolating macroscopic observations down to submicroscopic levels. Molecular switches have been proposed that may explain how synapses can "remember" despite molecular turnover and traffic. Some variants of these switches may even work in the chemically noisy environment of single synapses.

Conclusion

Synaptic plasticity has turned out to be a far more complex process than envisioned some 60 years ago by Donald Hebb. Nevertheless, a sparse set of fundamental operations seems to account for most aspects of synaptic change. Here, we suggest that this basic set consists of the operations of induction, pattern selectivity, expression of change, and maintenance of change. It is clear that nature has diversified each of these operations with the usual extravagance of molecular players. There are many molecular circuits that appear to be able to take up the above four basic roles, and often these circuits seem to be deployed in parallel. Such complexity in implementation is likely to be critical for robustness, fine-tuning of responses, and explaining the manifestation of numerous neurological disorders. These details remain fruitful directions for the confluence of simulations and experiments. Simulation studies contribute to these studies in a twofold manner: *1*) by making specific predictions for experimental verification and *2*) as a means to test scenarios that are technically difficult to address experimentally. Quantitatively accurate simulations place high demands on experimental design. Synaptic signaling is already complex, and the miniscule scale of the synapse adds to the experimental challenges. It is our hope that performing in silico studies in sync with in vitro and in vivo experiments will provide greater rigor in describing the phenomenon and also pave the way for unifying the many and disparate dimensions of synaptic plasticity. We believe that the outline of such a unification can already be perceived in the four main functional roles we have examined in this review. With these as a reference, we can perhaps return to some of the conceptual simplicity of Hebb's vision.

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