Chapter 18

Functional plasticity at dendritic synapses

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Summary

Most synapses are made onto dendrites, and most excitatory connections are made onto dendritic spines. Synaptic plasticity is thus an intrinsically dendritic phenomenon, but the functional significance of the structural, electrical, and molecular properties of dendrites for synaptic plasticity is still very poorly understood. Do dendrites have a computational or cell biological role in the modification of synaptic strength that is more than circumstantial? The aim of this chapter is to summarize experimental data and theoretical considerations that may be relevant to the role of dendrites in synaptic plasticity. The focus is on associative Hebbian synaptic plasticity, including spike-timing-dependent forms, mediated by NMDA receptor activation.

Introduction

Synapses channel information between neurons in the brain, and are dynamically strengthened and weakened by the patterns of neuronal activity flowing through them. Activity-dependent synaptic plasticity is thought to be fundamental to many brain functions, including refinement of connections during development (reviewed in Katz and Shatz 1996; Cline 1998; see Chapter 3), learning and memory and other forms of information storage (reviewed in Martinez and Derrick 1996; Stevens 1998), and, by extension, many higher cognitive functions.

In this chapter, we first discuss the idea of Hebbian synaptic plasticity and the key biophysical characteristics of the NMDA receptor relevant to its role in Hebbian or associative long-term potentiation. The NMDA receptor is sensitive to the conjunction of neurotransmitter release and membrane depolarization and can therefore detect the conjunction of presynaptic and postsynaptic neuronal activity. The location of the receptors on dendritic spines allows Ca^{2+} signals resulting from NMDA receptor activation to be localized, likely contributing to synapse-specific plasticity. In addition to this primary model, issues concerning other sources of spine Ca^{2+} (e.g. voltage-sensitive Ca^{2+} channels) and other possible coincidence detectors are also raised.

We next discuss how the Hebbian plasticity involving NMDA receptors on spines depends on two roles of dendrites: *integration* of the electrical activity that is detected by the receptor, permitting cooperativity and associativity of synaptic inputs, and

compartmentalization of chemical messengers or signal transduction cascades, permitting synapse specificity. While the basic aspects of these functions are well understood, the impact of the detailed aspects of the integration and compartmentalization provided by dendrites is just beginning to be explored. We focus in particular on recent experiments concerning the role of dendritic action potentials in plasticity.

We argue that the major role of dendrites in synaptic plasticity may be in modifying the strength of interactions between particular subsets of synapses by virtue of their relative locations within the dendritic tree. This could occur either due to inhomogeneities of electrical signaling across the dendrites or breakdown of chemical compartmentalization between synapses. The complex architecture of dendritic arbors would facilitate the formation of associations between synapses on the same dendritic branches or subparts of the dendritic tree while suppressing associations between synapses located on different dendritic branches.

In addition to these spatial aspects of associative synaptic plasticity, there are important temporal features as well. A form of long-term synaptic plasticity called spike-timing-dependent plasticity (STDP) may play an important role in such basic tasks as distinguishing cause and effect and predicting future outcomes on the basis of previous experience.

Dendritic spine NMDA receptors as Hebbian coincidence detectors

Hebb's postulate

Donald Hebb (1949) postulated the following synaptic strengthening rule: 'When the axon of cell A is near enough to excite cell B or 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.' As a candidate mechanism for information storage in the brain, Hebb's postulate has withstood several generations of experimental and theoretical scrutiny like very few other principles of brain function (reviewed in Brown *et al.* 1990; Cooper 2005). Nevertheless, as a computational or mechanistic description, Hebb's rule clearly demands much further interpretation and fleshing out. How does a synapse 'know' when it has taken part in firing a cell? How are presynaptic and postsynaptic firing encoded in molecular events at the synapse? What molecules detect the conjunction of these events? How are the pre- and postsynaptic signals corresponding to one synapse kept separate from those belonging to other synapses? How does a neuron determine which inputs 'took part' in firing it?

Discovery of NMDA receptor-dependent LTP has led to a theory of synaptic plasticity that describes how neurons, dendrites, and synapses implement Hebbian plasticity. This theory, which we will refer to as the 'spine-NMDA receptor theory' of LTP, will guide most of the discussion of synaptic plasticity in this chapter. Although the theory is still unproven and is lacking in many details, it is by far the most widely accepted and thoroughly documented account of the mechanisms by which synaptic connections between neurons are strengthened.

The primary omission from Hebb's rule is often considered to be the lack of a provision for decreases in synaptic efficacy. Without a mechanism for depression to complement synaptic potentiation, the brain would eventually face saturation of synaptic efficacy and consequent loss of stored information. What conditions allow for the undoing of synaptic strengthening or the weakening of connections? A number of different generalizations of the Hebb rule have been proposed on theoretical grounds (reviewed in Brown *et al.* 1990). Two forms of synaptic depression have received particular experimental attention: homosynaptic long-term depression (LTD) at hippocampal and neocortical synapses (reviewed in Bear and Malenka 1994), and associative LTD at cerebellar parallel fiber to Purkinje cell synapses (reviewed in Linden 1994). Of particular interest with respect to the role of dendrites is depression that is triggered by pairing of action potentials and EPSPs.

Hebb's postulate contains an element of causality that has often been overlooked, the requirement that the presynaptic cell 'takes part in firing' the postsynaptic cell (Hebb 1949), which implies that it causes that firing. One way to identify causal, as opposed to accidental, correlations in firing is through temporal ordering. A presynaptic action potential that occurs after a postsynaptic response could not have caused that response, but if presynaptic action potentials at a given synapse consistently arrive immediately before each postsynaptic spike, they are likely to be causal agents in generating that response. STDP, a spike-timing-dependent form of long-term plasticity, has exactly the properties needed to identify such causal relationships. In STDP, pairs of pre-postsynaptic action potentials that occur in the causal order, pre-before-post, strengthen the synapse; whereas those that occur in the acausal order, post-before-pre, weaken it.

Long-term potentiation

Long-term potentiation (LTP) is a particular form of synaptic strengthening (reviewed in Bliss and Collingridge 1993) that has been recognized as displaying the essential elements of Hebb's rule (Kelso *et al.* 1986; Malinow and Miller 1986; Gustafsson *et al.* 1987; Brown *et al.* 1990). LTP was originally described at synapses made between neurons in the entorhinal cortex and the granule cells in the dentate gyrus of the hippocampus (Bliss and Lømo 1973). When this pathway was activated with a brief, high-frequency stimulus train, a rapid and sustained increase in the strength of subsequent test stimuli was observed. Subsequent studies revealed similar forms of long-lasting, activity-dependent synaptic enhancement in all three of the major synapses of the hippocampal formation, as well as in numerous neocortical regions (reviewed in Bear and Kirkwood 1993; Kirkwood and Bear 1995), amygdala (Chapman *et al.* 1990; Rogan and LeDoux 1995; Huang and Kandel 1998), striatum (Kombian and Malenka 1994; Calabresi *et al.* 1996), and other central as well as peripheral synapses (e.g. Brown and McAfee 1982).

The best-studied form of LTP is that which occurs at synapses of Schaffer commissural-collateral axons from CA3 to CA1 neurons in the hippocampus. The nature of LTP at other synapses, such as in the dentate gyrus or different neocortical synapses, may differ in various details that have not been thoroughly characterized. In general, neocortical LTP appears to have many similarities to CA1 LTP (Bear and Kirkwood 1993).

Pyramidal cells in many brain regions appear similarly equipped in terms of plasticity machinery: NMDA receptors, spines, key protein kinases, etc. Nevertheless, it is worth keeping in mind the example of LTP at the mossy-fiber to CA3 synapse, which is mechanistically quite dissimilar to CA1 LTP (reviewed in Johnston *et al.* 1992; Nicoll and Malenka 1995), but may display many of the same essential features (Derrick and Martinez 1996). Unless noted, when speaking of LTP, we refer to CA1 LTP, or in some cases neocortical LTP, throughout this chapter.

In contrast to the general agreement about how LTP is triggered or induced, there is much more controversy over the nature of the changes underlying synaptic strengthening, generally referred to as the 'expression mechanism'. Whether expression involves presynaptic or postsynaptic changes, or changes on both sides of the synapse, has significant consequences for information processing (Otmakhov *et al.* 1993; Markram and Tsodyks 1996; Abbott *et al.* 1997; Tsodyks and Markram 1997), but is somewhat more removed from the function of dendrites than are the mechanisms of induction. This chapter focuses primarily on induction mechanisms or conditions under which LTP is triggered.

NMDA receptor properties

A Hebbian synaptic modification requires the detection of coincident presynaptic and postsynaptic activation (Hebb 1949). The response of a coincidence detector in the presence of both signals should be qualitatively different from the response to either signal alone. Some form of coincidence detection can be accomplished relatively simply by a response element with a supralinear response function such as a threshold. A number of examples of molecules capable of functioning in this way are discussed in Bourne and Nicoll (1993).

The NMDA receptor is a remarkable macromolecular complex with a strong claim to be the Hebbian detector underlying LTP. Sensitivity to specific NMDA receptor antagonists (e.g. 2-amino-5-phosphonovalerate (APV)) is usually considered the sine qua non of the main form of LTP (Bliss and Collingridge 1993), although NMDA receptor-independent dependent forms of LTP have also been described (reviewed in Johnston *et al.* 1992; Nicoll and Malenka 1995). By virtue of an unusual set of biophysical characteristics, the NMDA receptor opens only when both the presynaptic and postsynaptic neurons are activated. Specifically, receptor opening requires both a presynaptic chemical signal (neurotransmitter) and a postsynaptic electrical signal (local membrane depolarization). When both occur together, the opening of the receptor allows Ca^{2+} ions to enter the postsynaptic neuron and activate Ca^{2+} sensitive enzymes that eventually lead to synaptic potentiation or depression.

The excitatory neurotransmitter glutamate activates two primary ion channel-coupled (ionotropic) receptors, the AMPA and NMDA receptors (named for their artificial agonists, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate and *N*-methyl-D-aspartate, respectively; reviewed in Edmonds *et al.* 1995). The AMPA receptors are generally seen as providing the primary depolarization associated with synaptic activation, while the NMDA receptors are viewed as a secondary source of depolarization, being primarily involved in plasticity.

The sensitivity of the NMDA receptor to glutamate is high (EC_{50} in the 1 μM range; Patneau and Mayer 1990), making the receptor more sensitive to lower concentrations of transmitter than the AMPA receptor (EC_{50} > 100 μM; Patneau and Mayer 1990). The high affinity of the NMDA receptor is also associated with a slow deactivation rate following brief applications of glutamate (multiple time constants from 100 ms to > 1 s; Spruston *et al.* 1995a); meaning that once presynaptically released glutamate binds to the receptor, it remains bound for a lengthy time period. Therefore, the NMDA receptor acts as a long-lasting indicator of presynaptic activity. However, these decay-time constants are more rapid at physiological temperatures, resulting in a briefer NMDA current (25–50 ms; Feldmeyer *et al.* 2002).

A crucial and unusual biophysical characteristic of the NMDA receptor is that it remains 'silent' at normal resting potentials and does not pass current unless the membrane is depolarized. When the receptor is bound by glutamate, the pore of the receptor opens, but conduction of the channel is blocked by extracellular Mg^{2+} ions (Mayer *et al.* 1984; Nowak *et al.* 1984). Depolarization of the postsynaptic membrane expels Mg^{2+} from the channel, allowing it to conduct a mixture of Na^+, K^+, and Ca^{2+}. Thus, due to the voltage-sensitivity of the Mg^{2+} block, the conductance of the NMDA receptor is a supralinear function of postsynaptic voltage over the range of potentials from rest to around −20 mV. The kinetics of the Mg^{2+} block are rapid (Nowak *et al.* 1984), so, in contrast to the slow deactivation of the receptor, the coupling of depolarization to channel block is generally quite rapid (sub-ms), allowing postsynaptic depolarization to quickly open the channel tens of milliseconds after the presynaptic action potential (Spruston *et al.* 1995a). However, the kinetics of Mg^{2+} unblock also have slow components (Spruston *et al.* 1995a), which interact with channel kinetics in a time-dependent fashion (Vargas-Caballero and Robinson 2003, 2004; Kampa *et al.* 2004), and the effect is to narrow the effective time window by which postsynaptic depolarization can trigger NMDA channel opening (Kampa *et al.* 2004). It should also be noted that in addition to activation by glutamate and modulation by Mg^{2+}, the NMDA receptor is sensitive to a large and diverse array of molecular signals, including glycine, zinc, polyamines, histamine, pH, redox agents, neurosteroids, calmodulin, kinases, phosphatases, etc. (reviewed in McBain and Mayer 1994).

NMDA receptors display considerable molecular diversity. Functional receptors are composed of NR1 subunits in combination with members of the NR2 gene family. Different NR2 subunits confer different physiological and pharmacological properties on the receptor (reviewed in Feldmeyer and Cull-Candy 1996). In addition, the NR1 subunit also exists in a variety of different splice variants that confer different properties on the receptor (reviewed in Zukin and Bennett 1995). Developmental and cell-type specific regulation of subunit composition and splicing give rise to diversity in the functional properties of NMDA receptors across different neuronal populations. Of particular interest with respect to NMDA receptor plasticity are subunit-specific differences in deactivation and Mg^{2+} sensitivity (Monyer *et al.* 1994). Cells expressing NMDA receptors with different subunit composition may exhibit shorter or longer integration times or sensitivity to postsynaptic depolarization. Diversity of subunit composition

within single neurons may also be important, perhaps depending on the class of presynaptic afferent (cf. Maccaferri *et al.* 1998).

The second crucial property of the NMDA receptor is its permeability to Ca^{2+} ions (MacDermott *et al.* 1986; Ascher and Nowak 1988). It is through this second messenger that the receptor couples its activation to downstream enzymes. For example, blockade of potentiation by intracellular postsynaptic application of Ca^{2+} chelators blocks LTP (Lynch *et al.* 1983; Malenka *et al.* 1988). The location of the synaptic NMDA receptors on dendritic spines is thought to restrict the increase in intracellular $[Ca^{2+}]$ to the vicinity of the activated synapse (reviewed in Koch and Zador 1993). The basic structural feature of a head separated from the parent dendrite by a thin neck has been shown, by computer simulations (Holmes and Levy 1990; Zador *et al.* 1990) and direct experimental measurement (Svoboda *et al.* 1996; Häusser *et al.* 1997), to hinder diffusion of molecules between the spine head and the dendritic shaft (and vice versa). Theoretical and experimental issues regarding the role of dendritic spines and other dendritic compartments in compartmentalizing Ca^{2+} and other (bio)chemicals are the subject of Chapters 10 and 11.

Electrical integration and compartmentalization by dendrites

The requirement for both glutamate and postsynaptic depolarization for NMDA receptor activation, and the location of these receptors on dendritic spines, form the basis for a 'spine-NMDA receptor' model of Hebbian plasticity. This model can explain three central aspects of the phenomenology of LTP induction: *cooperativity*, *associativity*, and *synapse-specificity* (Figure 18.1). We will discuss these properties in some detail, as they are essential to the role of dendrites in synaptic plasticity. Two other primary characteristics of NMDA receptor-dependent LTP, its rapid induction and persistent expression, while critical to the possible function of LTP in memory storage, are relatively less important with regard to dendritic function.

Cooperative interactions mediated by dendrites

Cooperativity refers to the requirement for the near-simultaneous activation of a threshold level of synaptic input necessary in order to induce LTP. In practice, cooperativity has been interpreted as sensitivity either to the frequency of stimulation delivered during the shock (Bliss and Lømo 1973; Colino *et al.* 1992) or to the intensity of the extracellular stimulus used to activate presynaptic axons during a tetanization protocol (Bliss and Gardner-Medwin 1973; McNaughton *et al.* 1978; Barrionuevo and Brown 1983).

Consistent with the spine NMDA receptor theory, LTP induction does not appear to require a certain density of activated synapses or frequency of synaptic activation other than what is necessary to produce the requisite NMDA receptor activation. Direct experiments demonstrate that depolarization (applied by a postsynaptic recording electrode) combined with low-frequency stimulation of presynaptic afferents is sufficient to induce LTP (Kelso *et al.* 1986; Wigström *et al.* 1986; Colino *et al.* 1992). Conversely, membrane hyperpolarization is sufficient to prevent LTP from taking place during

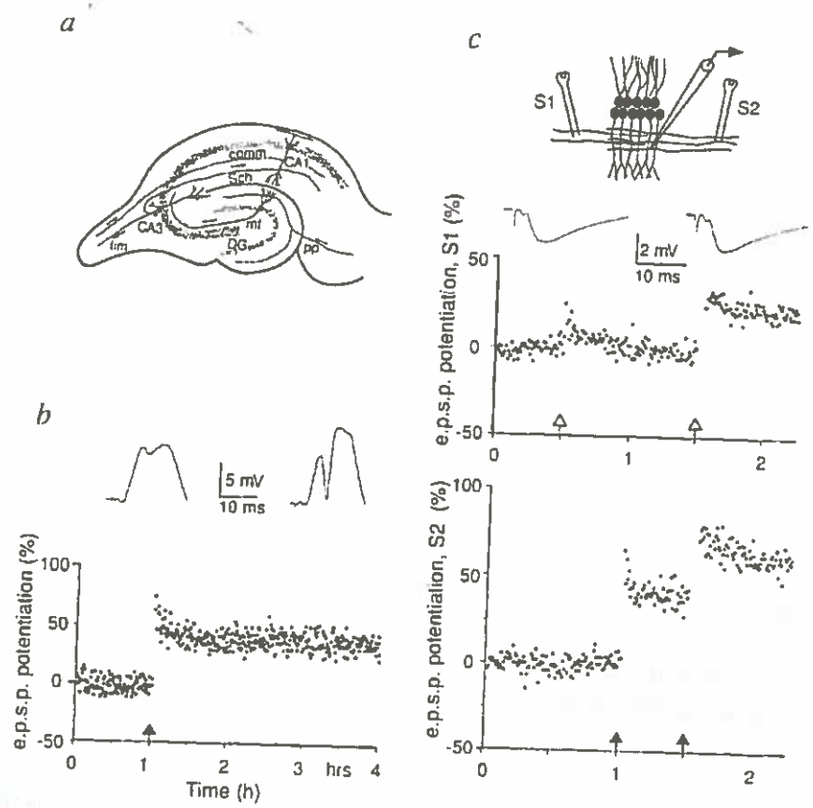

Fig. 18.1 The basic features of LTP in the hippocampus. (A) Schematic diagram of the hippocampus, showing the principal regions (CA1, CA3, and dentate gyrus (DG)) and excitatory pathways (perforant path, pp; mossy fibers, mf; fimbria, fim; Schaffer collaterals, Sch; commissural fibers, comm). (B) Field potential recordings in the somatic region of the dentate gyrus *in vivo* in response to perforant path stimulation recorded before (left) and 3 h after (right) LTP induction, using a 250-Hz, 200-ms tetanus. Note the increase in slope of the population EPSP and in the size of the population spike (downward deflection). The graph plots the slope of the rising phase of the population EPSP following LTP induction (at the time of the arrow). (C) Demonstration of cooperativity, associativity, and synapse-specificity of LTP. The top diagram is a schematic diagram of the arrangement of recording and stimulation electrodes in the CA1 region of a hippocampal slice. Two independent inputs (S1 and S2) are activated by stimulation electrodes placed on either side of the extracellular recording electrode in the dendritic field. The stimulus intensities are adjusted so that S1 provides a weak input, and S2 a strong input. The slopes of the population EPSPs for the two pathways are plotted as a function of time in the lower panels. Tetanic stimulation of S1 (first open arrow) produced no long-lasting increase in synaptic efficacy, since the synaptic drive was below the cooperativity threshold for LTP. A tetanus to S2 (first closed arrow) produced robust LTP in this pathway, but no change in S1, demonstrating synapse-specificity of the potentiation. When both pathways were tetanized together (second open and closed arrows), this coincident activation produced associative LTP in the weak pathway, S1. Representative field EPSPs following S1 stimulation, taken before and after potentiation, are shown above the graphs. Taken, with permission, from Bliss and Collingridge (1993).

high-frequency stimulation that would normally elicit LTP (Kelso *et al.* 1986; Malinow and Miller 1986). These findings provide key support for the idea that the role of synaptic activation in cooperativity is mediated through synaptic depolarization (and possible subsequent electrogenesis) and the relief of the NMDA receptor Mg^{2+} block that follows. Conversely, cooperativity does not appear to be related to a threshold for some other signal (e.g. glutamate, presynaptic Ca^{2+}). Nevertheless, under more physiological conditions, active dendritic conductances strongly shape the amplitude and kinetics of postsynaptic depolarization, adding an important additional dimension (see *Spike-timing-dependent plasticity*, below).

Dendrites mediate the *spatial* and *temporal* integration of depolarization produced by active synapses, and therefore dendritic integration shapes the cooperativity property of LTP induction. Without dendritic electrical integration, multiple synapses within a pathway would not sense each other's activity. The simplest form of cooperativity just requires that dendrites sum their synaptic inputs. But what exactly are the detailed spatial and temporal properties of the integrative process? How does spatial or temporal proximity affect the summation (or other interactions) of active inputs? In order to understand the full nature of cooperativity and the rules for when LTP will be generated, a better understanding of dendritic integration is necessary.

If the dendritic arbor were effectively isopotential (i.e. voltage uniformity in all dendritic branches), then the spatial aspect of dendritic integration would be negligible. All synapses, regardless of location, would experience the same postsynaptic depolarization. As discussed in Chapters 12–14, dendrites are seldom isopotential. As passive electrical compartments, dendrites low-pass filter signals temporally and attenuate their spread spatially (Chapters 13 and 14). When the active (voltage-dependent) electrical properties of dendrites are also considered, the rules become potentially much more complex (Chapter 14). The initiation of action potentials and the extent of their propagation into the dendritic tree may make an important contribution to the depolarization seen by a synapse. The upshot of these considerations is that the location of a synapse within the dendritic tree may determine to some degree how that synapse will interact with other active synapses (Chapters 13 and 14). Computer simulations suggest that active dendritic conductances (e.g. voltage-gated Na^+ channels or NMDA receptors) increase cooperativity (depolarization) among 'clustered' compared to 'diffuse' synaptic inputs (Mel 1993), and that this may lead to selective strengthening of synapses whose activity is both correlated and dendritically clustered (Mainen *et al.* 1990; Pearlmutter 1995; Golding *et al.* 2002; Mehta, 2004; Polsky *et al.* 2004).

The limits of cooperativity requirements have been tested in a variety of experiments. Frequency of presynaptic activation is certainly an important parameter of LTP induction under most circumstances. This is expected for a number of different reasons, including the frequency-dependence of presynaptic release probability, the integration time constant of the postsynaptic membrane, and the sensitivity of Ca^{2+}-dependent enzymes such as CaMKII (De Koninck and Schulman 1998). Nevertheless, it has been shown that single, very strong afferent stimuli (Abraham *et al.* 1986), as well as weak stimuli paired with maintained intracellular depolarization (Colino *et al.* 1992), can induce LTP even when these stimuli are separated by as much as 1 min. The low success rate of such protocols would be expected from the low probability of transmitter release occurring on a given stimulus. With respect to the role of the number of activated synapses required for the induction process, it has been shown that activation of even a single presynaptic neuron is sufficient to induce LTP if postsynaptic depolarization is applied via a recording pipette (Malinow 1991). Together, these findings form an extremely important foundation for the spine NMDA receptor theory, as they appear to exclude quite convincingly the necessity of activating other coincidence detectors that could mediate cooperativity and associative synaptic interactions by sensing the number of activated synapses through some signal other than depolarization.

Associative interactions mediated by dendrites

In the context of LTP experiments, associativity refers to the ability of a 'test' pathway to be potentiated when activated together with a separate 'conditioning' pathway (e.g. Barrionuevo and Brown 1983). The test pathway is stimulated weakly so that LTP is not induced by this stimulus alone. The conditioning pathway is given strong stimulation, providing sufficient depolarization to induce LTP. The 'associative interaction' describes the ability of the strong pathway to provide the postsynaptic signal needed by the weak pathway so that it too undergoes LTP during coactivation. In general, then, associative interaction refers to cooperation (via postsynaptic depolarization) between different sets of synapses. Associativity can also refer to the ability of some other source of postsynaptic depolarization (e.g. by an electrode or by postsynaptic action potentials) to provide the postsynaptic depolarization needed to trigger LTP. Cooperativity between synapses, as discussed above, is essentially the same process.

The associative properties of LTP were first described in the dentate gyrus *in vivo* by pairing weak input from contralateral entorhinal cortex with a strong ipsilateral input (McNaughton *et al.* 1978; Levy and Steward 1979; 1983). Concurrent activation of both pathways achieved potentiation where stimulation of either pathway alone failed to potentiate the weak input. These experiments naturally also demonstrated the synapse specificity of LTP (see below). Later, associativity was also demonstrated in the CA1 region of the hippocampal slice (Barrionuevo and Brown 1983), a preparation in which the effects of inhibition and potential circuit complexities were minimized.

Mechanistically, the properties of the NMDA receptor explain in a simple manner the ability to form associative interactions through the summation of postsynaptic depolarization. Stimulation of the test input provides the release of glutamate required for binding to NMDA receptors. Concurrent stimulation of the conditioning input provides the postsynaptic depolarization, which is also experienced by the test input, necessary to activate the glutamate-bound NMDA receptors by relieving Mg^{2+} block.

Spatial limits on associativity

As with cooperativity, dendritic electrical integration mediates the associative interactions between sets of synapses. Assuming perfect spatial integration (i.e. an isopotential dendritic tree), the relationship of synapses in the test and conditioning inputs

(other than shared identity of synapses) is irrelevant — all associations between different synapses or pathways onto a cell are equivalent. But if neurons are not isopotential, then the spatial relationship of synapses in the two pathways will modify the associative interaction. Electrically proximal synapses would be more likely to share depolarization than electrically remote synapses. The contribution of non-isopotential postsynaptic compartments to a Hebbian plasticity rule has been simulated (Mainen *et al.* 1990) and analyzed mathematically (Pearlmutter 1995). Although these studies suggest that electrotonic attenuation will affect patterns of synaptic strengthening, empirical verification of this possibility is very interesting but technically challenging.

Very few experimental data are available on the spatial parameters of associative LTP. One difficulty with this class of experiment is that the locations of active synapses are not well known with most electrophysiological techniques. In a structure with laminated afferents, such as the hippocampus or cerebellar cortex, the position of an extracellular stimulating electrode can be used to try to localize activated afferents (e.g. Andersen *et al.* 1980), but the spatial specificity is nevertheless limited, and the precise dendritic locations of synapses are unknown. It is also unclear how results obtained with synchronous activation of relatively large numbers of synapses will resemble physiological (*in vivo*) patterns of activity.

A notable set of studies by Levy and colleagues (White *et al.* 1988; 1990) demonstrated a spatial specificity of associative LTP in the dentate gyrus *in vivo*. Using current source density analysis to map the location of active synapses along the proximo-distal axis of the granule cells, the authors determined the degree of overlap between various pairs of stimulated pathways from the entorhinal cortex. The ability of a strong ipsilateral conditioning input to potentiate a weak contralateral test input depended on the amount of overlap between the two sets of inputs, with an overlap of >50% needed for significant potentiation (White *et al.* 1990).

Although it might have been surmised that this spatial specificity arose simply from voltage attenuation between synaptic populations, further studies actually pointed to a critical role of inhibition in the spatial specificity. Blockade of inhibition enhanced associative interactions between non-overlapping synapses (Tomasulo *et al.* 1993). These results were supported by computer simulations showing that massive local shunting inhibition, but not voltage attenuation alone, would be required to decouple different groups of synapses in these electrotonically compact cells (Holmes and Levy 1997). The role of action potentials in dentate associative LTP remains somewhat unclear (Holmes and Levy 1997; see below). In disinhibited CA1 slices, associative LTP can be produced between basal and apical dendritic inputs separated by hundreds of microns (Gustafsson and Wigström 1986).

Modification of associativity by inhibition

These results stress that inhibition may critically regulate the induction of dendritic synaptic plasticity. Feed-forward and feedback inhibitory circuits are often recruited in experimental induction paradigms (unless inhibition is pharmacologically blocked) and are certainly also critical in the physiological activation of local circuits in the hippocampus, neocortex, and other brain regions. Blockade of inhibition changes considerably the stimulus conditions necessary for LTP induction and raises the probability of LTP induction in a slice preparation. For example, 'primed burst' (Larson and Lynch 1986) or 'theta burst' stimulation (brief bursts delivered at 200-ms interstimulus interval, corresponding to the endogenous theta frequency) is particularly effective in inducing LTP because it results in effective disinhibition of the slice (Pacelli *et al.* 1989) through presynaptic $GABA_B$ autoreceptors on GABAergic terminals (Davies and Collingridge 1996). These studies strongly suggest that dynamic changes in inhibitory circuitry due to activity patterns or neuromodulation provides an important influence on dendritic integration mediating synaptic plasticity *in vivo*.

Inhibition may severely alter the integrative properties of dendritic trees (Häusser and Clark 1997; Holmes and Levy 1997; Pare *et al.* 1998). At a gross level, inhibition interacts with excitatory synaptic drive by summation (hyperpolarizing the membrane) or multiplication (shunting inhibition), lowering the voltage levels reached postsynaptically or preventing the initiation of action potentials. More complex roles of inhibition depend on the precise location of inhibitory synapses within the dendritic tree and temporal relationship of their activation to the activation of excitatory synapses (Raastad *et al.* 1998). Tonic synaptic activity (both inhibition and excitation) can substantially alter the cable properties of dendrites, reducing the effective membrane resistance and thereby increasing electrotonic attenuation (Bernander *et al.* 1991; Häusser and Clark 1997; Pare *et al.* 1998; but see Raastad *et al.* 1998).

The results of Levy and colleagues (White *et al.* 1988; 1990) make a fairly strong case that at least under some conditions, excitatory and inhibitory EPSPs effectively carve out multiple semi-independent units within the dendritic tree. It will be interesting to test whether these results can be extended to other synapses and to finer dendritic subregions. Computer simulations suggest that semi-independent synapse 'clusters' may form across individual dendritic branches (Mainen *et al.* 1990). These effects can be expected due to passive electrotonic structure (Korogod *et al.* 1994; Vetter *et al.* 2001) or the amplification of local postsynaptic depolarization by dendritic nonlinearities and local action potentials (Mel 1993; Mel *et al.* 1998; Goldberg *et al.* 2002; Poirazi *et al.* 2003a; 2003b; Mehta 2004). The prediction of these models is that statistical properties (i.e. the correlation structure) of the set of inputs to the neuron are represented in the spatial location of the synapses (Chapter 14). Means for local stimulation and optical monitoring of synaptic activity may be useful in testing these possibilities.

Spike-timing-dependent plasticity (STDP)

As mentioned previously, STDP has the potential, through its spike-timing dependence, of realizing the causal aspect of Hebb's hypothesis. The introduction of timing dependence into synaptic potentiation allows for the memorization and learning of temporal sequences, not merely associations, and can help control some of the destabilizing effects of Hebbian plasticity, such as all of the synapses onto a particular neuron becoming excessively strong.

STDP has been seen in a variety of different preparations (reviewed in Abbott and Nelson 2000), including cortical slices (Markram *et al.* 1997; Feldman 2000), hippocampal dissociated and slice cultures (Bi and Poo 1998; Debanne *et al.* 1998), and *in vivo* tectal synapses (Zhang *et al.* 1998). In ordinary STDP, synapses are strengthened by repeated pairings of spikes in the pre-before-post order and weakened by pairings in the reverse order. In addition, a form called anti-STDP with the opposite temporal dependence (pre-before-post weakens synapses) has been observed in the electrosensory lobe of electric fish (Bell *et al.* 1997; Han *et al.* 2000), the cerebellum (Wang *et al.* 2000) and dorsal cochlear nucleus (Tzounopoulos *et al.* 2004).

Early in the study of long-term synaptic plasticity, it was observed that backward conditioning between weak and strong pathways fails to generate LTP (Levy and Steward 1983; Gustafsson and Wigström 1986; Kelso and Brown 1986). This matches, at the biophysical level, properties of the NMDA receptor and, at the behavioral level, aspects of classical conditioning. Recall that the effect of presynaptic glutamate is long-lasting (the channel deactivates slowly), while postsynaptic depolarization affects the channel essentially instantaneously through rapid Mg^{2+} block and unblock (although see discussion of slow Mg^{2+} unblock under *NMDA receptor properties* above), but only when it is bound to glutamate. Therefore, one would predict the temporal order of pre- and postsynaptic signals to be critical. The presynaptic signal must precede the postsynaptic signal by a time window less than the decay time of NMDA glutamate binding to achieve receptor unblocking, and the reverse order would not be effective.

More recent studies pairing postsynaptic action potentials (APs) with EPSPs have mapped the temporal sensitivity of STDP more precisely (Markram *et al.* 1997; Bi and Poo 1998; Debanne *et al.* 1998; Zhang *et al.* 1998; Feldman 2000). As in two pathway experiments (Levy and Steward 1983; Gustafsson and Wigström 1986; Kelso *et al.* 1986), an asymmetrical window of coincidence is seen in EPSP-AP pairing studies: the EPSP must precede the postsynaptic action potential in order to induce LTP. In layer 5 neocortical pyramidal neurons, a 100-ms interval produced no plasticity regardless of order, while a 10-ms interval produced potentiation when EPSPs preceded action potentials (Markram *et al.* 1997). In cultured hippocampal neurons, a similar protocol also produced LTP with forward pairing and LTD with backward pairing, but with an even more refined temporal requirement — a conjunction window of ~20 ms (Figure 18.2) (Bi and Poo 1998). Although, as discussed above, this result roughly matches the properties of NMDA receptors, this time window is shorter than the time scale of NMDA receptor glutamate unbinding, but could reflect the effect of slow Mg^{2+} unblock (Kampa *et al.* 2004). It is also likely that the efficacy of EPSP–AP pairing depends in part on other time-dependent effect of the EPSP arrival, such as the inactivation of dendritic K^+ channels by the EPSP (Hoffman *et al.* 1997; Magee and Johnston 1997), or the recruitment of Na^+ channels by the cooperative interaction of EPSPs and backpropagating APs. This interaction boosts AP backpropagation in the distal dendrites but only within a narrow time window (Stuart and Häusser 2001; Sjöström and Häusser 2005). STDP requires that synapses detect postsynaptic action potentials, and backpropagation of action potentials into the dendrites appears to be an important element in this. The role of backpropagating action potentials in plasticity in general and in STDP is examined in more detail below.

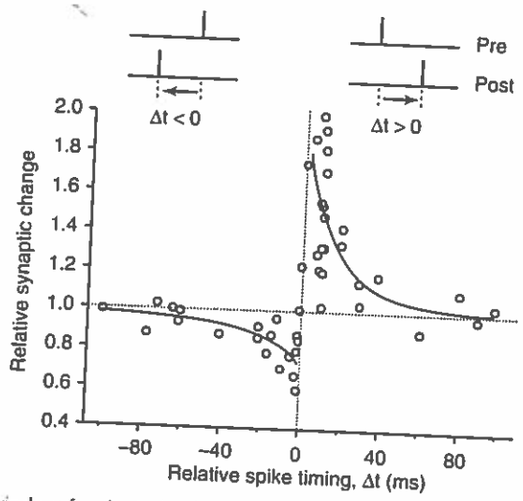

Fig. 18.2 Temporal window for the induction of synaptic potentiation and depression in hippocampal neurons. Persistent potentiation and depression of glutamatergic synapses were induced by correlated spiking of presynaptic and postsynaptic neurons in paired recordings from pyramidal neurons in dissociated hippocampal cultures. The graph shows the percentage change in the postsynaptic EPSC amplitude 20–30 min after repetitive correlated spiking (60 pulses at 1 Hz) plotted against the relative timing of pre- and postsynaptic activity. Action potential timing was defined by the time interval (Δt) between the onset of the EPSP and the peak of the presynaptic action potential during each cycle of repetitive stimulation, as illustrated by the traces above the graph. Only synapses with initial EPSC amplitude of <500 pA were included, and all EPSPs were subthreshold for data associated with negatively correlated action potential timing. Taken, with permission, modified from Bi (2002) with permission from the author.

Interestingly, exactly synchronous pairing may not be effective in inducing potentiation (Debanne *et al.* 1998). This could perhaps be caused by the time needed for NMDA receptors to begin opening (rise time is around 10 ms) or a consequence of the EPSP facilitating the backpropagation of a subsequent action potential (Stuart and Häusser 2001; and see below). The delay due to conduction of the action potential (velocity ~500 μm/ms along the main apical trunk) (Stuart *et al.* 1997a) would seem to be relatively short even for distal synapses.

If the order of action potential and EPSP is reversed, so that the action potential precedes synaptic stimulation, LTP does not occur. However, whereas reverse pairing typically produces no changes in two-pathway associative LTP (Gustafsson and Wigström 1986; Kelso *et al.* 1986; Levy and Steward 1983), reverse AP–EPSP pairing produces depression of the paired synapses (Markram *et al.* 1997; Bi and Poo 1998; Debanne *et al.* 1998; Zhang *et al.* 1998; Fedman 2000). A similar result was originally observed with asynchronous pairing of EPSPs and depolarizing pulses in CA1 neurons of cultured

hippocampal slices (Debanne *et al.* 1994; 1997). Remarkably, the switch from maximal potentiation to maximal depression may occur with a time shift of <5 ms (Bi and Poo 1998). In addition, spike pairing with random temporal ordering equally likely to produce pre-before-post and post-before-pre orderings has been observed to generate LTD (Debanne *et al.* 1994; Feldman 2000).

The observation of bidirectional plasticity might be explained by findings that potentiation follows from a large increase in $[Ca^{2+}]$ while LTD follows from a smaller sustained increase (Yang *et al.* 1999), as has been explored in a number of modeling studies (Karmarkar and Buonomano 2002; Shouval *et al.* 2002; Rubin *et al.* 2005; Badoual *et al.* 2006). Ca^{2+} imaging suggests that the spine $[Ca^{2+}]$ achieved is greater during forward than backward pairing (Koester and Sakmann 1998; Yuste *et al.* 1999; Nevian and Sakmann 2004). Whether such differences could account for a radical change in the effect on synaptic transmission is unclear, and is the target of simulation studies (Franks and Sejnowski 2002). It seems apparent that various combinations of stimuli (for example, postsynaptic action potentials of varying number) could lead to similar amplitudes of spine $[Ca^{2+}]$ increase. How, then, could peak spine $[Ca^{2+}]$ alone reliably distinguish a particular AP-EPSP sequence? Activation of downstream enzymes, particularly CaMKII, may sense not only amplitude but also temporal properties of $[Ca^{2+}]$ transients (De Koninck 1998). Issues regarding Ca^{2+} signaling are discussed in more detail below (*Synapse specificity* section). In slices, induction of LTP by spike-timing protocols requires pairs with the appropriate timing to be repeated at a minimum rate of about 10 Hz. Alternatively, a transient, weak depolarization of the postsynaptic neuron can be combined with spike pairs at lower frequencies (Sjöström *et al.* 2001). Both of these requirements suggest that $[Ca^{2+}]$ levels must be elevated to a certain threshold. *In vivo*, the transient depolarizations required for low-frequency LTP might be supplied by the barrage of synaptic activity that neurons continually receive. Interestingly, retrograde signaling through cannabinoid pathways has been implicated in the generation of LTD by spike-timing protocols (Sjöström *et al.* 2003). This pathway is likely to be relatively slow, suggesting that the rapid switch-over from LTP to LTD around zero spike-timing difference arises from a more slowly varying LTD component combining with the sudden onset of LTP.

Simple forms of learning such as classical conditioning display associative and temporal effects that appear analogous to those of STDP (reviewed in Quinn 1998). This connection assumes that presynaptic input corresponds to or in some way represents the conditioned stimulus (CS), while postsynaptic stimulation is produced by the unconditioned stimulus (US). Following pairing of CS and US, the CS response becomes potentiated and can now evoke the response previously exclusive to the US. The temporal requirements of these learning paradigms (CS must predict or precede US) qualitatively match the temporal requirements of STDP. In fact, it has even been observed that the reverse ordering, US before CS, can cause an aversive CS to become attractive (Tanimoto *et al.* 2004), analogous to the switch from LTP to LTD when spike ordering is reversed. Several studies have provided remarkable evidence that just such an associative LTP-like phenomenon in the lateral amygdala mediates the acquisition of fear conditioning

(Rogan and LeDoux 1995; McKernan and Shinnick-Gallagher 1997; Rogan *et al.* 1997). In addition, the appropriate spike ordering has been found during remapping of somatosensory cortex after whisker clipping in rats (Celikel *et al.* 2004), suggesting a role of STDP in this phenomenon (Feldman 2000). Nevertheless, in classical conditioning, it is not clear whether depolarization rather than, for instance, a neuromodulatory signal carries information in the US. More complex forms of learning have even less clear relationships with the cellular properties of synaptic plasticity induction and may call for entirely new mechanisms, such as the provision of a global reinforcement signal that is not computed locally by the cell (reviewed by Schultz *et al.* 1997).

The temporal contingencies introduced by STDP lead to predictions of timing effects during learning (Minai and Levy 1993; Abbott and Blum 1996; Blum and Abbott 1996; Gerstner *et al.* 1996). For example, theoretical analysis led to the prediction that receptive fields would shift backward upon repeated stimulation in a particular temporal sequence (Abbott and Blum 1996; Blum and Abbott 1996). This effect has been observed in a remarkably large number of different contexts (Wilson and O'Neill 1998; Mehta *et al.* 2000; 2002; Engert *et al.* 2002; Fu *et al.* 2002; Yao *et al.* 2004), and it implies that neural systems can spontaneously develop predictive encodings of sensory data on the basis of experience. While it is clear that the timing dependence of STDP might play a role in temporal sequence learning and prediction, there are more subtle effects introduced by STDP as well. Hebbian plasticity tends to be unstable because strong synapses keep getting stronger and weak ones weaker. Timing effects in STDP can relieve some of these instabilities (Kistler and van Hemmen 2000; Song *et al.* 2000; van Rossum *et al.* 2000; Kempter *et al.* 2001; Rubin 2001; Gütig *et al.* 2003). The role of anti-STDP, with its temporally reversed dependency, has been explored in the cancellation of self-generated electric fields in electrosensing in fish (Roberts and Bell 2000) and in the equalization of synaptic efficacies along complex dendritic trees (Holmgren and Zilberter 2001; Goldberg *et al.* 2002; Rumsey and Abbott 2004).

If repeated pre- and postsynaptic spike pairs are well separated in time, their effects on synaptic efficacy roughly sum linearly, at least until saturation occurs. If, however, multiple spike pairs appear within the duration of the temporal window for STDP induction, nonlinear interactions become apparent (Senn *et al.* 2001; Sjöström *et al.* 2001; Froemke and Dan 2002; Wang *et al.* 2005; Froemke *et al.* 2006; Kampa *et al.* 2006). Models of these nonlinear effects are still being developed (Senn *et al.* 2001; Badoual *et al.* 2006), and their functional implications have yet to be worked out. However, it seems that at least some of the nonlinearities are due to activity-dependent regulation of the backpropagation of action potentials, which is discussed in the following section.

Dendritic excitability and synaptic plasticity

The presence of voltage-gated Na^+, K^+, and Ca^{2+} channels in the dendritic arbor may profoundly change the function of the dendrites in synaptic integration (Chapters 9 and 14). It follows directly that the integrative function of the dendrites in synaptic plasticity will also be critically shaped by these active channels. The function of active dendritic

processing may have as much impact on signaling between synapses as on conveying synaptic signals to the soma — or somatic signals back to the synapses.

Action potentials are usually initiated in the axon (reviewed by Stuart *et al.* 1997b), but the presence of voltage-gated Na^+ channels throughout the dendritic arbor of hippocampal and neocortical pyramidal cells (along with favorable electrical load considerations) promotes the propagation of regenerative currents 'backward' into the dendritic arbor (Chapters 9 and 14). Thus, a backpropagating action potential may serve to notify synapses throughout the dendritic tree when a spike has been emitted from the axon. The role of backpropagating action potentials in synaptic plasticity has recently become a topic of considerable interest. Under physiological conditions, do these action potentials mediate the postsynaptic depolarization necessary for NMDA receptor opening? If so, this finding would bring the physiology even closer to Hebb's principle requiring firing of both presynaptic and postsynaptic neurons (Hebb 1949).

Are backpropagating action potentials necessary?

It has been demonstrated that action potentials are not strictly necessary for the induction of CA1 LTP (McNaughton *et al.* 1978; Kelso *et al.* 1986; Gustafsson *et al.* 1987; Golding *et al.* 2002). The depolarization necessary for NMDA receptor opening can be directly supplied by current injected through a recording pipette under conditions where spikes are absent postsynaptically. Indeed, a common procedure for inducing LTP in whole-cell recordings is to voltage clamp the neuron at around 0 mV while stimulating presynaptic afferents at low frequency (Malinow and Tsien 1990). The fact that LTP can be readily induced in the absence of postsynaptic firing suggests the simple explanation that the main influence of backpropagating action potentials on LTP is their depolarization of the NMDA receptor and the consequent amplification of NMDA-receptor mediated Ca^{2+} influx (Koch and Zador 1993; Yuste and Denk 1995; Koester and Sakmann 1998; Schiller *et al.* 1998; Yuste *et al.* 1999; Nevian and Sakmann 2004), rather than a secondary mechanism such as activation of voltage-gated Ca^{2+} channels (but see below).

While postsynaptic action potentials may not be strictly necessary, it is an important and difficult problem to determine under what conditions postsynaptic action potentials are in fact involved in the normal (*in vivo*) induction of LTP. Blockade of postsynaptic action potentials (Scharfman and Sarvey 1985) or specific blockade of their dendritic backpropagation (Magee and Johnston 1997) can prevent LTP induction under some conditions. In some preparations, AP–EPSP pairing can induce LTP where pairing EPSPs and prolonged depolarization or high-frequency stimulation fails (Markram *et al.* 1997; Zhang *et al.* 1998). A *requirement* for action potentials might be interpreted in the context of the spine NMDA receptor theory as a finding that subthreshold summation of EPSPs cannot produce enough depolarization to open NMDA receptors sufficiently to generate potentiation. Thus, synaptic cooperativity under physiological conditions could reflect the necessity for sufficient synaptic depolarization to elicit spikes, whether initiated axonally and backpropagating to the dendrites or initiated locally (see below). Likewise, associative interactions would depend not on direct sharing of depolarization between synapses, but on the ability of one input to generate the postsynaptic action potentials necessary to bring about NMDA receptor depolarization. Understanding these phenomena will ultimately demand monitoring *in vivo* patterns of pre- and postsynaptic activity and their consequences for the strength of synaptic connections (e.g. Thomas *et al.* 1998).

Relatively few studies have yet tested pairing of presynaptic EPSPs and postsynaptic action potentials to induce LTP. The results of recent experiments in a range of preparations, including neocortical slices (Markram *et al.* 1997; Feldman 2000), acute hippocampal slices (Magee and Johnston 1997), cultured hippocampal slices (Debanne *et al.*1998) and dissociated cultures (Bi and Poo 1998), and frog tectal neurons *in vivo* (Zhang *et al.* 1998), are mostly consistent. LTP induced by pairing EPSPs and postsynaptic action potentials is usually (Markram *et al.* 1997; Bi and Poo 1998; Debanne *et al.* 1998; Zhang *et al.* 1998; Feldman 2000), but not always (Magee and Johnston 1997; see below) blocked by NMDA receptor antagonists. Synapse specificity of EPSP–AP pairing was demonstrated in tectal neurons (Zhang *et al.* 1998). Given that the vast majority of our knowledge of LTP mechanisms stems from experiments using tetanic stimuli (and a smaller amount from low-frequency pairing with prolonged depolarization), it will be very important to determine whether mechanisms of EPSP–AP-induced LTP are indeed similar. Experiments such as verifying synapse specificity of induction, establishment of the duration of potentiation, and occlusion of tetanically induced LTP and action potential pairing-induced potentiation would be useful in this regard.

Extracellular monitoring of EPSP–AP pairing-induced LTP would provide a simple experimental protocol that could facilitate the study of issues such as the temporal coincidence windows and sensitivity to pharmacological agents. In whole-cell pairing experiments, postsynaptic action potentials are generated by intracellular current pulses, but they can also be elicited by antidromic activation of postsynaptic cell axons. Perhaps surprisingly, such a protocol has not been successfully used. In one study examining orthodromic–antidromic paring (Jester *et al.* 1995), conventional NMDA receptor-dependent LTP was not induced, but a form of potentiation known as 'EPSP-spike' (E-S) potentiation (Bliss and Lømo 1973) was seen. This type of potentiation is expressed as an increase in the size of an extracellular population spike relative to the size of the extracellular field EPSP, and it is neither dependent on NMDA receptor activation nor restricted to active synapses. Changes in inhibitory circuitry (Chavez-Noriega *et al.* 1990) and increases in dendritic excitability (Wathey *et al.* 1992) were proposed to explain the coupling of EPSPs to spike initiation, and a large number of recent experimental studies have supported both intrinsic and circuit mechanisms (reviewed in Daoudal and Debanne 2003; Xu and Kang 2005).

Regulation of backpropagating action potentials

A variety of mechanisms have been shown to be capable of modulating the spatial extent of dendritic action potential invasion in CA1 pyramidal neurons (Chapter 14). Differential modulation of backpropagating action potentials is a mechanism that can limit or reinforce the associations between particular synapses on the basis of their dendritic location. Indeed, the properties of spike-timing-dependent plasticity vary

depending on the location of the activated synapses (Froemke *et al.* 2005; Sjöström and Häusser 2005). Generally speaking, synapses on a particular dendritic branch are likely to experience identical action potential signals, while synapses on different branches may experience distinct action potential signals. For example, under resting conditions in pyramidal neurons, action potentials typically do not fully invade the dendritic tree (Spruston *et al.* 1995b; Stuart *et al.* 1997a); only synapses within the proximal regions of the dendritic tree would thus be subject to action potential depolarization and experience potentiation. These proximal synapses would therefore form associations with each other, but not with more distal (uninvaded) synapses. It is possible that invasion of action potentials may be controlled on a much more local level by up- or downregulation of the activity of voltage-dependent Na^+ and K^+ channels. Thus, similar considerations might apply to individual subtrees of secondary or even tertiary branches rather than simply to large-scale proximo-distal specificity. Candidate mechanisms for branch-specific regulation of backpropagating action potentials include branch-point failures (Jaffe *et al.* 1992; Regehr and Tank 1992; Spruston *et al.* 1995b; Magee and Johnston 1997), excitatory (Hoffman *et al.* 1997; Magee and Johnston 1997; Magee *et al.* 1998; Stuart and Häusser 2001) or inhibitory (Buzsaki *et al.* 1996; Tsubokawa and Ross 1996) synaptic input, phosphorylation (Hoffman and Johnston 1998; Magee *et al.* 1998), neuromodulatory transmitters (Tsubokawa and Ross 1997; Hoffman and Johnston 1999; Sandler and Ross 1999), and action potential-dependent inactivation (Colbert *et al.* 1997; Jung *et al.* 1997; Mickus *et al.* 1999).

Whether selective amplification and suppression of the invasion of different regions of the dendritic tree plays an important role in dendritic plasticity still remains an intriguing conjecture. However, one very exciting set of studies (Hoffman *et al.* 1997; Magee and Johnston 1997; Magee *et al.* 1998) has gone some way toward demonstrating the possibility of branch-specific EPSP–AP pairing in CA1 pyramidal neurons. First, subthreshold EPSPs boost the amplitude of backpropagating action potentials (Magee and Johnston 1997) by inactivating transient A-type K^+ channels, which are present at high density in CA1 pyramidal cell dendrites and can control backpropagating action potential amplitude there (Hoffman *et al.* 1997). Second, dendritic hyperpolarizing current injections can prevent induction of LTP by EPSP–AP pairing (Magee and Johnston 1997), perhaps because such injections can prevent action potential boosting by EPSPs (Magee and Johnston 1997). Third, at the fork of the primary apical dendrite of CA1 neurons, branch-specific boosting of action potentials can be produced by direct depolarizing pulses applied to one branch (Figure 18.3) (Magee and Johnston 1997; Magee *et al.* 1998). It appears to follow logically, but remains to be demonstrated experimentally, that branch-specific associative LTP can be induced in this way. This might be accomplished by monitoring two weak (subthreshold and non-EPSP-boosting) test pathways applied to separate branches and inducing potentiation by pairing with a strong (supra-threshold and EPSP-boosting) pathway confined to a single branch (or, alternatively, direct dendritic depolarization could substitute for the strong pathway). What has been established is that the magnitude, temporal dependence, and even the sign of spike-timing-dependent plasticity depends strongly on synaptic location

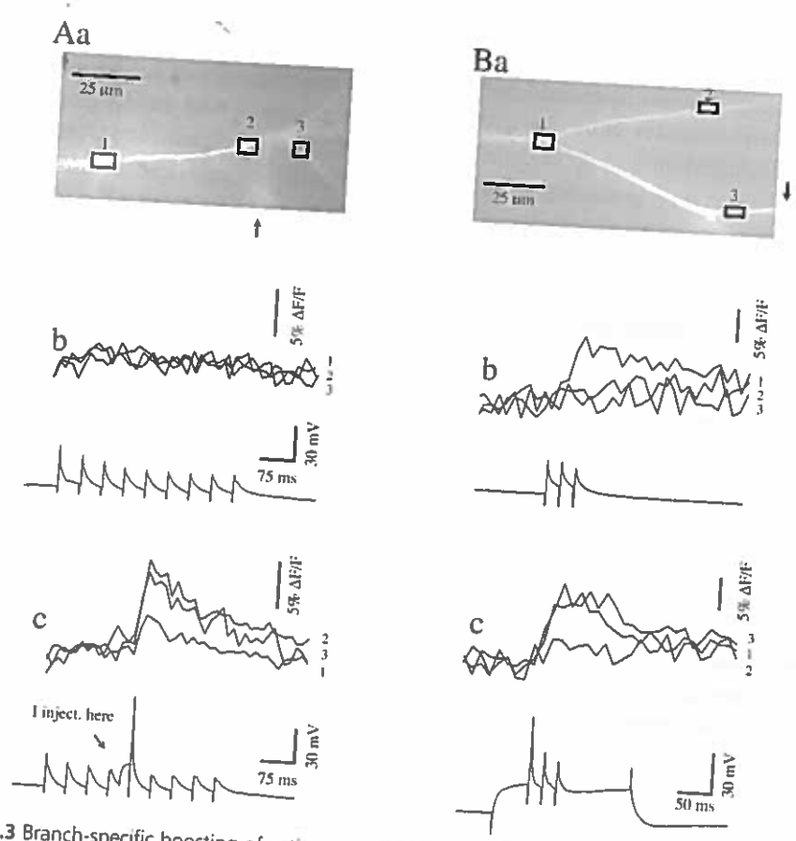

Fig. 18.3 Branch-specific boosting of action potentials in dendrites. (A) *(a)* CA1 pyramidal cell filled with Fura-2 via a dendritic patch pipette (arrow), located ~290 μm from the soma. The image is oriented so that the more proximal regions of the neuron are located toward the left. *(b)* Optical recordings (average ΔF/F) from regions of the neuron delimited by the numbered boxes in *(a)*, with dendritic voltage trace shown below. A train of nine antidromic action potentials (*bottom line*) triggers a very small Ca^{2+} signal in the distal dendrites. *(c)* A 40-ms, 0.3-nA current injection causes an increase in dendritic action potential amplitude and associated Ca^{2+} signal. The largest Ca^{2+} signal is located nearest the dendritic pipette, suggesting that the largest increase in action potential amplitude is near the point of current injection. A trace with only the current injection was used to correct for bleaching and for any small Ca^{2+} signals (<1% ΔF/F) caused by the current injection. (B) *(a)* In a different pyramidal cell, a dendrite was filled with Fura-2 via a patch pipette located ~280 μm from the soma on the lower branch (*arrow*), ~50 μm distal to the site shown. The major branch point is ~150 μm away from the soma. *(b)* Optical recordings (average ΔF/F) from regions of the neuron delimited by the numbered boxes in *(a)*, with the dendritic voltage shown below. A train of three antidromic action potentials (*bottom line*) induces a Ca^{2+} signal primarily localized to regions of the dendrite proximal to the branch point. *(c)* Current injection (0.2 nA) into the lower branch (*arrow*) causes an increase in the amplitude of the first dendritic action potential and a large increase in the Ca^{2+} signal in the dendritic branch that received the current injection, whereas only a very small signal is evident in the other branch. This profile suggests that coincident synaptic input can influence back-propagating action potentials to preferentially invade synaptically active regions of the dendrite. The current injection by itself did not produce a Ca^{2+} signal in the displayed regions. Reprinted, with permission, from the *Annual Review of Physiology*, Volume 60

(Froemke *et al.* 2005; Letzkus *et al.* 2005; Sjöström and Häusser 2005). The induction of plasticity appears to depend both on the backpropagation of action potentials (Stuart and Häusser 2001; Sjöström and Häusser 2005) and on the generation of dendritic calcium spikes (Golding *et al.* 2002; Kampa *et al.* 2006). Insofar as dendritic electrogenesis is spatially cooperative, spike-timing-dependent plasticity could exhibit a complex dependence on the spatial pattern of activated synapses within the dendritic tree.

Chemical compartmentalization and integration by dendrites

Synapse specificity

Synapse specificity refers to the requirement for an individual synapse to be presynaptically activated in order for it to undergo potentiation during a conditioning protocol. Lack of synapse specificity could imply a process that is not truly sensitive to the conjunction of pre- and postsynaptic activity, but could also result from the spread of a plasticity signal generated after detection of such a conjunction. Although mechanisms for regulating the overall amount of synaptic input to a cell may play an important role (Turrigiano *et al.* 1998; Turrigiano and Nelson 1998), synapse specificity is often seen as a prerequisite for a synaptically based cellular memory mechanism. The issue is basically one of computational or storage capacity. Roughly speaking, if each synapse stores one or a few bits of independent information, the storage capacity of a neuron is multiplied by the number of its synapses, typically 10^4 or more. A catastrophic breakdown of synapse specificity would clearly degrade capacity, but it has been argued that the effects of semilocal potentiation may be beneficial (e.g. Montague *et al.* 1991; Montague 1996).

In the hippocampus, synapse specificity of LTP was deduced from early studies (Andersen *et al.* 1977; Levy and Steward 1979). However, the experimental evidence demonstrating *strict* synapse specificity during LTP induction is perhaps weaker than the documentation of associative and cooperative phenomena. Numerous studies have been conducted with dual pathways of stimulated afferents. Typically, in the hippocampus, these are stimulated by large extracellular electrodes placed some distance (around 0.5–1 mm) apart from one another, either on opposite sides of the recording site or at separate locations along the proximo-distal axis of the cell. Thus, the precise spatial location of activated synapses is not known, but could generally involve either partially interdigitated or mostly segregated populations of synapses. With the location of active synapses unknown, it remains possible that specificity breaks down on a spatial scale that is small relative to these distances (e.g. between neighboring spines on a small dendritic branch). Notably, in one of the most careful examinations of this issue, the authors found a *lack* of synapse specificity at distances of <150 µm (Engert and Bonhoeffer 1997). This study used local perfusion to pharmacologically isolate groups of nearby synapses in cultured hippocampal slices. Because there was no obvious dependence of the amount of cross-potentiation on the relationship of the groups of synapses to dendritic branching, these results could be interpreted as supporting an extracellularly diffusing messenger rather than intradendritic diffusion. Similar conclusions were drawn from studies describing intercellular spread of potentiation between synapses on nearby neurons (Kossel *et al.* 1990; Schuman and Madison 1994).

According to the spine NMDA receptor model, synapse specificity begins with the requirement for the presynaptic terminal to release glutamate directly onto NMDA receptors in order to bind and open them. Nonactivated synapses may receive strong postsynaptic depolarization, but, without glutamate binding to NMDA receptors, will not receive the necessary NMDA receptor-mediated Ca^{2+} influx. From this point, synapse specificity is believed, first, to rely on the ability of the postsynaptic dendrites to localize this $[Ca^{2+}]$ signal, and some portion of the signal transduction cascade that it activates, to the locale of the synapse. Ultimately, the plasticity is expressed as a change in one or several local synaptic properties (e.g. number of functional postsynaptic receptors in the postsynaptic density). Second, this theory also relies implicitly on an inability of other sources of spine Ca^{2+} (particularly VSCCs) to provide an adequate $[Ca^{2+}]$ signal for potentiation (discussed below).

Achieving synapse specificity may be most problematic with respect to those synaptic modifications that require *de novo* synthesis of plasticity-related proteins. It is believed that the initial maintenance of synaptic potentiation is provided by covalent modifications or translocation of synaptic proteins, but that maintenance of the potentiation beyond a period of some hours requires the recruitment of newly synthesized proteins (reviewed in Bliss and Collingridge 1993). Given that protein synthesis begins with transcription in the nucleus followed by ribosomal translation (either in the cell body or in the dendrites (Chapter 5)), the machinery cannot be contained entirely within a given spine synapse. Therefore, some provision must be made for targeting the newly synthesized proteins preferentially or exclusively to potentiated synapses. A number of hypotheses for how this might be achieved have been proposed (for example, through a synaptic 'tag') (reviewed in Frey and Morris 1998). Quasi-synapse-specific protein delivery might be achieved by upregulating translation in a branch-specific manner. True synapse specificity would still require spine-specific markers or tags, such as a particular phosphorylated protein.

Dendritic spine $[Ca^{2+}]$

NMDA receptors have an unusually high permeability to Ca^{2+} ions (Mayer and Westbrook 1987; Ascher and Nowak 1988). The only well-recognized 'output' of the NMDA receptor is the flux of Ca^{2+} ions into the dendritic spine on which the receptors are located. Insofar as the NMDA receptor is the principal pathway for rises in spine $[Ca^{2+}]$, NMDA receptor activation and spine $[Ca^{2+}]$ activation could be considered equivalent coincidence detectors (but see below). The chemical compartmentalization provided by the spine (Chapters 10 and 11) would provide a means of restricting the rise in $[Ca^{2+}]$ and subsequent activation of Ca^{2+}-sensitive enzymes that would catalyze the enhancement of synaptic strength.

A simple and popular hypothesis concerning the transduction of Ca^{2+} signals into different forms of synaptic plasticity is that the amplitude and duration of local

spine [Ca^{2+}] rises determine whether potentiation or depression (or nothing) will occur (Lisman 1989; Bear and Malenka 1994). A rise in postsynaptic [Ca^{2+}] is necessary for LTP and LTD induction, as chelation of Ca^{2+} by intracellular buffers prevents the induction of LTP (Lynch *et al.* 1983; Malenka *et al.* 1988). Following reduction of Ca^{2+} entry through NMDA receptors (by pharmacological block using APV or hyperpolarization), a normally LTP-inducing tetanus can induce LTD (Cummings *et al.* 1996). Evidence for the sufficiency of spine [Ca^{2+}] to induce potentiation or depression has been somewhat more difficult to obtain. Many stimuli which increase spine [Ca^{2+}], such as action potentials or depolarizing voltage pulses, typically do not produce LTP, but may produce a transient potentiation (e.g. Kullmann *et al.* 1992). A difficulty in interpreting experiments of this type is that the [Ca^{2+}] actually achieved at test synapses is not known. Protocols for inducing LTP by raising intracellular Ca^{2+} with photolysis of caged-Ca^{2+} compounds have yielded mixed results (Malenka *et al.* 1988; Neveu and Zucker 1996a; 1996b). However, it appears that some of the variability observed in these studies may be avoided with a new caged-Ca^{2+} compound (Yang *et al.* 1999). As predicted, raising Ca^{2+} briefly to high levels consistently produced LTP, while raising Ca^{2+} to lower levels for a sustained period produced LTD (Yang *et al.* 1999). In these conditions, presynaptic activity and glutamate release are not necessary for potentiation to occur (but see Kullmann *et al.* 1992; Neveu and Zucker 1996b). The exact parameters of the required [Ca^{2+}] rise may also depend on the history of the synapse (i.e. 'meta-plasticity'; reviewed in Abraham and Bear 1996).

It is widely held that the main function of postsynaptic spines is to compartmentalize diffusible molecules at a single spine synapse and to prevent them from otherwise diffusing between synapses (Wickens 1988; Holmes and Levy 1990; Koch and Zador 1993; Svoboda *et al.* 1996; Häusser *et al.* 1997). Compartmentalization of synaptic Ca^{2+} transients by spines has been demonstrated with imaging techniques (Muller and Connor 1991; Denk *et al.* 1995; Yuste and Denk 1995; Koester and Sakmann 1998; Mainen *et al.* 1999; Yuste *et al.* 1999). However, it is not clear from these studies to what extent compartmentalization would hold under various stimulation conditions. Synapse-specific plasticity has recently been demonstrated at synapses on aspiny inhibitory neurons (Lamsa *et al.* 2005), a finding consistent with the possibility that compartmentalization might be achieved on a much smaller spatial scale than even the spine. There is evidence, for example, in the process of vesicular release, that Ca^{2+} signaling molecules are located within a microdomain (<100 nm; reviewed by Neher 1998) near the mouth of a Ca^{2+} channel. The role of dendrites in compartmentalizing chemical signals is treated at length in Chapters 10 and 11.

Role of voltage-sensitive Ca^{2+} channels

Although the NMDA receptor is clearly a main source of spine Ca^{2+} entry, other sources of Ca^{2+} entry into dendritic spines clearly exist — in particular, voltage-gated Ca^{2+} channels and intracellular Ca^{2+} stores. Local uncaging of neurotransmitter produces increases in spine [Ca^{2+}] that are sensitive to various Ca^{2+} channel blockers (Schiller *et al.* 1998). Blockers of Ca^{2+} release from stores can dramatically reduce spine Ca^{2+} transients under

some conditions (Emptage *et al.* 1999; but see Mainen *et al.* 1999). Backpropagating action potentials admit Ca^{2+} through voltage-sensitive Ca^{2+} channels (VSCCs) on dendrites and dendritic spines (Yuste and Denk 1995; Koester and Sakmann 1998; Magee *et al.* 1998; Yuste *et al.* 1999). The amount of Ca^{2+} entering the spine via NMDA-R activation and via VSCC activation is of comparable magnitude (e.g. Koester and Sakmann 1998), although the NMDA-R activation could in theory be greatly increased during sustained depolarization. These observations support the possibility that backpropagating APs or even local depolarization could mediate a plasticity signal independent of NMDA receptor gating.

The actual contribution of VSCCs to associative LTP is still controversial. Ca^{2+} influx through VSCCs is not strictly necessary for LTP, as voltage clamping the neuron at the synaptic reversal potential inactivates VSCCs and prevents then from being opened by EPSPs, but LTP can still be induced simply by paired EPSPs under these conditions (Perkel *et al.* 1993). Furthermore, LTP can be produced in the presence of L-type and T-type VSCC blockers (e.g. Huang and Malenka 1993; Hanse and Gustafsson 1994; Bi and Poo 1998). Blockers of other VSCC types (e.g. N, P, Q/R) affect presynaptic Ca^{2+} channels and block transmitter release, making pharmacological dissection of their roles more difficult to discern. Nevertheless, the possibility of cooperativity between NMDA receptor and VSCC mediated Ca^{2+} entry under particular stimulus conditions is not excluded by these experiments. Assuming that VSCCs are activated primarily during action potential invasion and not by subthreshold stimulation (i.e. primarily high-threshold VSCCs are involved), the participation of VSCCs in LTP induction would depend on the extent to which action potentials are elicited and backpropagated during a particular induction protocol (Markram *et al.* 1997). As NMDA receptor-mediated Ca^{2+} influx depends strongly on the extent to which action potentials are elicited and backpropagated, and blocking VSCCs may itself change AP backpropagation, it is quite difficult to disentangle the contributions of the different mechanisms. When these variables are not measured and depend on the precise stimulation delivered, inconsistent results would be expected. In EPSP–AP pairing experiments, blockade of L-type VSCCs has been shown to partially prevent potentiation (Magee and Johnston 1997; Bi and Poo 1998) and can block depression (Bi and Poo 1998). Other forms of NMDA receptor-independent (and VSCC-dependent) potentiation have been described in neurons that also show NMDA receptor-dependent potentiation. Some of these, such as TEA-induced potentiation (e.g. Hanse and Gustafsson 1994), are heterosynaptic, but an associative form that requires synaptic stimulation (but not NMDA receptor activation) has also been reported (Kullmann *et al.* 1992). The latter study points to the possibility of a secondary coincidence detector (outside the spine NMDA receptor theory).

How would the enzymes in a spine distinguish between Ca^{2+} arising from NMDA receptor influx and that arising from other Ca^{2+} sources? Is it possible that Ca^{2+} entering through the NMDA receptor has privileged access to a key enzyme by virtue of extreme proximity? The ability of EGTA to prevent LTP induction (Lynch *et al.* 1983) would suggest otherwise, as this chelator does not bind fast enough to prevent Ca^{2+} signaling

on the scale of channel 'microdomains'. Furthermore, photolytic activation of fast Ca^{2+} buffers can prevent LTP induction up to 1 s after a tetanus (Malenka *et al.* 1992), indicating that Ca^{2+} must remain elevated for enough time to equilibrate over much larger spatial domains (see Chapter 10 for a discussion of diffusion issues).

The conundrum of how a synapse could distinguish the presynaptically gated NMDA receptor Ca^{2+} from purely postsynaptic sources of Ca^{2+} raises the question as to whether a second pathway parallel to the NMDA receptor might detect presynaptic activity. The main candidates for such a detector are the metabotropic glutamate receptors (mGluRs), which are not permeable to ions but directly activate second messenger pathways. The evidence for the involvement of mGluRs in LTP induction remains controversial (Selig *et al.* 1995). mGluRs might contribute additional Ca^{2+} into the spine via activation of release of Ca^{2+} from stores (e.g. Emptage *et al.* 1999). In this case, spine $[Ca^{2+}]$ remains the coincidence detector and the problem remains unsolved. Alternatively, a downstream enzyme might integrate the Ca^{2+} signal with the mGluR-activated second messenger, thereby acting as a more precise, second-order detector of pre- and postsynaptic activity. Further downstream coincidence detectors are also called upon for mechanisms of LTP expression involving presynaptic changes.

Concluding remarks

Our understanding of the physiology of long-term synaptic plasticity has been formalized by a theory based on spine NMDA receptors as coincidence detectors. This theory proposes four main functions for dendrites in explaining the phenomenology of long-term plasticity:

1. *Electrical integration*. Synapses interact by supplying depolarization (or hyperpolarization) that is sensed eventually by the NMDA receptor. Thus, the integrative function of the dendritic tree is seen as mainly electrical. Most experimental data are consistent with cell-wide summation of synaptic activity, with little exploration to date of how the active and passive propagation of electrical signals within dendrites may give rise to more complex synaptic relationships. The contributions of voltage-sensitive Ca^{2+} channels and coincidence detectors other than the NMDA receptor are still not well understood.
2. *Chemical compartmentalization*. Once activated, the NMDA receptor mediates a highly local (spine-specific) biochemical cascade with no interaction occurring between synapses. The dendritic tree, particularly through the dendritic spines on which excitatory synapses are formed, isolates synapses from one another to provide synapse specificity. Thus, the dendrites are seen as achieving chemical compartmentalization. Determination of the net effect of synaptic plasticity by the time course and amplitude of bulk spine $[Ca^{2+}]$ is an attractive, but still unproven hypothesis. There is reason to believe that the basic dendritic functions of electrical integration and chemical compartmentalization are both subject to important qualifications that point toward the possibility that groups of neighboring synapses would form functional units.

3. *Electrical compartmentalization*. The dendritic arbor will promote not only electrical integration but inevitably some degree of compartmentalization or localization of passive and active electrical signaling. Synaptic integration and action potential backpropagation may be subject to dynamic control by a large number of modulatory influences. Associative interactions between synapses within the dendritic tree will therefore have a spatial or topological component, reinforcing synapses with nearby dendritic location and correlated activity. These possibilities remain largely in the realm of conjecture, and will require experimental means to measure and control the location of patterned synaptic activity.
4. *Chemical integration*. Dendrites and spines may not fully compartmentalize the signal transduction events downstream of NMDA receptor activation. Ca^{2+} signals may leave spines and travel between adjacent synapses under some conditions. While subsequently activated enzymes may be immobilized in spines, it is still not clear how the delivery of newly synthesized synaptic proteins is achieved in synapse-specific manner. Control of protein translation or protein trafficking may occur on a semilocal (e.g. branch-specific) scale.

In addition to the spatial aspects introduced into associative synaptic modification by dendritic structure, temporal contingencies intrinsic to the process of plasticity induction add to the richness of the basic phenomenon and to its implications for learning and memory.

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Chapter 19

Structural plasticity of dendrites

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Summary

Many lines of research have demonstrated structural plasticity of dendrites in the mammalian brain. Historically, the concept of structural plasticity has been incorporated into theories of learning in which structural changes in synaptic connections between neurons are suggested to underlie long-term information storage. However, the fact that circuits encoding learned information are likely to be distributed within and between brain regions, combined with the inability to identify individual cells and synapses involved in learning, makes it difficult to test this hypothesis directly. Even so, a number of experiments have demonstrated consistent experience- or learning-dependent structural changes in dendrites and synapses of cortical structures. Until recently, these types of studies depended upon comparisons of groups of animals, typically a control group and a group that underwent some form of training. Structural differences between groups were taken to indicate an effect of training on dendrites and synaptic connections. In the past several years, advances in time-lapse imaging approaches (i.e. multiphoton microscopy) allowed the visualization of the same dendrites in culture and *in vivo* over minutes to months, revealing the dynamic nature of dendritic spines during normal and altered neuronal activity. In addition, an appreciation of the prevalence and rapidity of structural plasticity of dendrites can be gained from studying systems with relatively simple circuitry in which a large proportion of cells are dedicated to a particular function. This approach has demonstrated that physiological stimuli such as hormonal fluctuations induce remarkable plasticity of dendrites and synaptic connectivity in multiple hypothalamic regions. The further observation of similar hormone-induced structural plasticity in the dendrites of hippocampal neurons, which are known to be important in learning, may help to bridge these two approaches by providing a context in which to study the learning- and memory-related consequences of dendritic plasticity produced by hormones.

Introduction

The wiring of the adult central nervous system (CNS) classically had been viewed as fixed and structurally stable. Indeed, it had been presumed in the past that stability in the synaptic connectivity within our brains is necessary for continuity of memory and personality. However, such a rigid picture of neural circuitry is now contradicted by over 30 years of