REVIEW

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The Role of Dendritic Filtering in Associative Long-Term Synaptic Plasticity

Abstract

Several forms of synaptic plasticity in the neocortex and hippocampus depend on the temporal coincidence of presynaptic activity and postsynaptic trains of action potentials (APs). This requirement is consistent with the Hebbian, or correlational, type of cellular learning rule used in many studies of associative synaptic plasticity. Recent experimental evidence suggests that APs initiated in the axosomatic area are actively back-propagated to the dendritic arborization of neocortical and pyramidal cells. High-frequency trains of postsynaptic APs that are used as conditioning stimuli for the induction of Hebbian-like plasticity in both neocortical and hippocampal pyramidal cells display attenuation of the dendritic AP amplitude during the train. This attenuation has been shown to be modulated by neurotransmitters and by electrical activity. We suggest here that both spike train attenuation in the dendrite and its modulation by neurotransmitters and electrical activity may have important functional consequences on the magnitude and/or the sign of the synaptic plasticity induced by a Hebbian pairing procedure.

Introduction

The idea that memory storage in the brain results from activity-dependent changes in synaptic strength was developed by Hebb (1949), who proposed that excitatory synapses linking two cells could be strengthened if both cells were simultaneously active. Over the last decades, the aim of many neuroscientists in the field of synaptic plasticity has been to confirm Hebb's hypothesis and to determine the cellular mechanisms responsible for the induction of persistent facilitation of synaptic transmission (for review, see Frégnac and Shulz 1994). It is now well established that induction of long-term potentiation (LTP) in neocortical and hippocampal pyramidal neurons results from the conjunction of synaptic activation and sufficient depolarization of the postsynaptic membrane to allow NMDA receptor activation (for review, see Brown et al. 1990). This form of potentiation is defined as associative LTP (see section I). Postsynaptic depolarization in nerve cells can be induced either by a sustained activity of an heterosynaptic pathway or by a train of action potentials (APs) initiated in the axosomatic area. Because the neuronal geometry is complex, a key question today is how postsynaptic depolarization spreads from the area of initiation to a specific synapse in the distal dendritic tree. What are the mechanisms underlying the required spread of depolarization, and what are the consequences of their modulation on the induction of long-term synaptic plasticity?

LTP and long-term depression (LTD) of excitatory synaptic transmission are induced when single APs or spike trains evoked postsynaptically by current pulses to the soma are paired with a synaptic stimulation with an appropriate phase delay (for review, see Debanne 1996; Debanne et al. 1998a). Important findings have been reported recently concerning dendritic back-propagation of AP trains used as a conditioning stimulus for associative plasticity in hippocampal and neocortical pyramidal cells (for review, see Stuart et al. 1997a; Johnston et al. 1999). In particular, the basic mechanisms underlying the back-propagation and back-attenuation of postsynaptic APs have been characterized. More recently, the modulation of spike train back-propagation has been investigated (Johnston et al. 1999). However, the possible consequences of postsynaptic spike train attenuation on induced plasticity have not yet been considered and discussed. We will present recent data on the modulation of spike train attenuation and consider their subsequent possible effects on plasticity induced through coactivation of a glutamatergic synapse and a train of postsynaptic APs.

I. Associative Synaptic Plasticity

THE HEBB PRINCIPLE AS A CELLULAR LEARNING RULE

External and internal events are represented in the brain as spatiotemporal patterns of neural activity, which are determined by the integration of diverse synaptic inputs. For more than a century, it has been thought that the fundamental mechanism underlying the persistent memory of previous events, that is, the engram, must reside at the synapse and be formed by activity-dependent changes in synaptic efficacy (James 1890; Konorski 1948; Hebb 1949; Stent 1973). Most theoretical schemes of synaptic plasticity incorporate a principle of association originally proposed by a number of psychophysicists and especially by Donald Hebb. Hebb's hypothesis can be summarized as follows: Long-lasting synaptic potentiation of an excitatory connection results *"...when an axon of cell A is near enough to excite a cell B and repeatedly and persistently takes part in firing it..."*. That is, synchronous pre- and postsynaptic activation represents the sufficient and required condition for the induction of persistent facilitation of the considered synapse (Fig. 1A). This temporal association represents the basis of the *associative* nature of this form of potentiation of synaptic transmission and has been described in several brain areas including the neocortex and the hippocampus both in vivo and in vitro (for reviews, see Frégnac and Shulz 1994; Montague and Sejnowski 1994; Debanne et al. 1995).

SYNCHRONOUS PRE- AND POSTSYNAPTIC ACTIVITY INDUCES LTP IN PYRAMIDAL NEURONS

LTP is induced associatively when a large postsynaptic depolarization is synchronously and persistently paired with the activation of a synaptic input. Presynaptic activation can include sensory stimuli (Frégnac et al. 1988, 1992; Shulz and Frégnac 1992; Debanne et al. 1995, 1998b), low-frequency electric shocks delivered to afferent fibers (Baranyi and Feher 1981; Sastry et al. 1986; Stanton and Sejnowski 1989; Hirsh and Gilbert 1993; Debanne et al. 1994; Frégnac et al. 1994), high-frequency stimulation of afferent fibers (Kelso et al. 1986; Murphy et al. 1997), or

Figure 1: A schematic representation of associative LTP and LTD induction. Two neurons (1 and 2) establish a monosynaptic excitatory connection. A heterosynaptic pathway (presynaptic neuron 3) is added in C and D. The temporal pattern of activity is represented underneath the neurons. Vertical bars represent spiking activity. (A) Hebb's postulate. Synchronous activation of pre- and postsynaptic neurons (1 and 2, respectively) results in associative LTP. (B) Stent's postulate. Asynchronous activation of pre- and postsynaptic (1 and 2, respectively) results in associative LTD. (C,D) A neuron (2) is shown receiving two sets of nonoverlapping synaptic input, one weak (1) and the other strong (3) (reflecting different numbers of afferent fibers). Tetanic stimulation of input 1 alone causes neither LTP nor LTD. (C) Concurrent tetanic stimulation of 3 and 1 causes associative LTP between 1 and 2. (D) Asynchronous activation of tetanic stimulation of 3 and 1 induces associative LTD between 1 and 2.

single APs in a presynaptic cell in the case of paired recordings of monosynaptically connected neurons (Malinow 1991; Debanne et al. 1996, 1997; Debanne et al. 1998a; Bi and Poo 1998). Most important is the temporal conjunction of the presynaptic stimulation with the activation of the postsynaptic neuron.

Postsynaptic activation of hippocampal or neocortical neurons results naturally from the synaptic activation of a separate synaptic pathway, which may or may not produce a suprathreshold response. Hebbian potentiation is induced when postsynaptic activation (membrane depolarization) results from the tetanization of a heterosynaptic group of fibers (Levy and Stewart 1979; Barrionuevo and Brown 1983; Gustafsson and Wigström 1986; Stanton and Sejnowski 1989; Fig. 1C), a coherent theta rhythm oscillation induced by cholinergic agonists (Huerta and Lisman 1993) or a train of postsynaptic APs (Baranyi and Feher 1981; Kelso et al. 1986; Sastry et al. 1986; Gustafsson et al. 1987; Hirsch and Gilbert 1993; Debanne et al. 1994, 1995; Frégnac et al. 1994; Fig. 1A). The associative nature of these protocols is demonstrated by the fact that no potentiation is induced when the test input is stimulated alone (Barrionuevo and Brown 1983; Gustafsson et al. 1987; Debanne et al. 1994) or when the stimulation is delivered out of phase with the theta oscillation (Huerta and Lisman 1993, 1995). Finally, the postsynaptic

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depolarization may be controlled directly through instrumental means by voltage-clamping the cell using the patch-clamp technique. Large and constant depolarizations (in the range of $-20/0$ mV) concomitantly applied with repeated synaptic activation result in LTP induction in both hippocampal (Malinow 1991; Isaac et al. 1995) and neocortical (Yoshimura and Tsumoto 1994; Otsu et al. 1995; Isaac et al. 1997; Rumpel et al. 1998) neurons.

Compared with forms of synaptic plasticity induced either by tetanization of the synaptic pathway (homosynaptic plasticity) or by the conjunction of presynaptic trains of activity with high levels of constant postsynaptic depolarization (Malinow 1991; Isaac et al. 1995), associative long-term plasticity induced by pairing of synaptic inputs and bursts of postsynaptic APs presents several important features. First, this form of plasticity is the most physiological: Plasticity is assessed in current-clamp mode with natural stimuli. This is not the case in pairing procedures in which the postsynaptic neuron is continuously voltage-clamped to maintain a depolarized membrane potential. Moreover, tetanic stimuli protocols used in homosynaptic plasticity frequently do not correspond to physiological patterns of activation. Second, the use of trains of postsynaptic APs (induced by injecting current into an intracellularly recorded neuron) provides a major advantage in that postsynaptic activity can be modulated independently of the presynaptic pattern and the temporal phase between the two can be defined precisely. The magnitude of potentiation has been found to depend on both the degree of synchrony (time interval) and the amplitude of the postsynaptic depolarization (Gustafsson et al. 1987). In contrast, the role of temporal synchrony is not critical in pairing protocols with constant depolarizations. Finally, the neuronal pathway and the occurrence of electrical events can be controlled accurately in pairing protocols. The synaptic pathway remains constant because the frequency of stimulation is kept the same before, during, and after induction of potentiation. This is not the case with homosynaptic plasticity as undefined polysynaptic pathways may be recruited during the tetanus and uncontrolled action potentials may be triggered during temporal summation of the excitatory postsynaptic potentials (EPSPs). Postsynaptic APs elicited during tetanus enhance homosynaptic potentiation (Scharfman and Sarvey 1985; Thomas et al. 1998).

In conclusion, Hebb's principle represents a cellular learning rule that has been largely verified in pyramidal neurons from the neocortex and the hippocampus with the use of various protocols exhibiting the common feature that a postsynaptic depolarization must be temporally associated with the synaptic stimulation (Fig. 1A,C). In nonpyramidal neurons, including cerebellar cells and stellate cells from the cortex, the Hebbian rule does not apply, however, because the conjunction of pre- and postsynaptic spiking activity paradoxically results in LTD induction (Crépel and Jaillard 1991; Bell et al. 1997; V. Egger, D. Feldmeyer, D. Spergel, and B. Sakmann, unpubl.).

HEBBIAN SYNAPSES, NMDA
RECEPTORS,
AND POSTSYNAPTIC
CALCIUM INFLUX

In most of these examples, the various forms of postsynaptic depolarization are applied to relieve the Mg^{2+} block of NMDA receptor-gated channels (NMDARs) (Mayer et al. 1984; Nowak et al. 1984) to allow NMDA receptor-mediated calcium influx into the dendritic spine

(Alford et al. 1993). This calcium entry represents the first step in the cascade leading to associative LTP expression, either induced by a pairing procedure (Gustafsson et al. 1987; Zalutski and Nicoll 1990; Debanne et al. 1994) or by the conjunctive tetanization of a weak and a strong input (Gustafsson and Wigström 1986; Murphy et al. 1997). In addition to the NMDAR-mediated calcium influx, postsynaptic depolarization used for induction of associative LTP also activates L-type voltage-dependent calcium channels (VDCCs). This calcium influx is per se responsible for a short-term component of associative potentiation (Kullmann et al. 1992).

INCREASED TEMPORAL PRECISION WITH SINGLE BACK-PROPAGATED APS

In early studies of associative LTP, the duration of the postsynaptic depolarization used in pairing presynaptic stimulation with postsynaptic APs varied between 50 and 240 msec, eliciting 7–12 APs (Kelso et al. 1986; Sastry et al. 1986; Gustafsson et al. 1987; Hirsch and Gilbert 1993; Frégnac et al. 1994). Our recent findings indicate that the ability to induce potentiation by synchronous pairing depends on the number of APs produced by the depolarizing pulse (Fig. 2D). LTP is always induced when long depolarizing pulses producing 10–12 APs (240 msec) are used (Fig. 2A,D; Debanne et al. 1994). When the duration of the depolarization is limited to a 50-msec pulse eliciting 3–4 APs; however, no significant change can be observed (Fig. 2A,D). For even shorter pulses (10 msec) that elicit single APs, LTD induction is observed if the pre- and postsynaptic APs are synchronously paired (0-msec delay) (Debanne et al. 1998a; Fig. 2B,D). In this case, the ability of the synaptic input to express LTP is not an issue because LTP can be induced at these inputs when longer pulses or appropriate pairing protocols are used. For example, in the pairing procedure using single postsynaptic APs, potentiation is induced if the postsynaptic AP is paired with the late component of the synaptically evoked EPSP (delay of 15 msec between the pre- and postsynaptic APs, Fig. 2B). These original findings, confirmed by later studies (Bi and Poo 1998; but see Pike et al. 1999), show that the temporal sensitivity is highly increased in the millisecond range when single postsynaptic spikes are used as conditioning events to induce associative long-lasting synaptic changes. Thus, single AP discharge in pyramidal cells may permit greater temporal accuracy in the discrimination and stabilization of neuronal inputs than bursts of APs (see also, Softky 1994; Gerstner et al. 1996; Kempter et al. 1999).

What is the mechanism responsible for this time dependence? As suggested in a recent study (Debanne et al. 1998a), the limiting factor might be the NMDA receptor-mediated component of the EPSP. NMDA receptors can be activated by backpropagating APs in the case of synchronous pairing (0-msec delay) with 10–12 APs or when single APs are timed with the late component of the EPSP (15-msec delay). In contrast, synchronous pairing with only 1–4 APs results in conjunction of the back-propagated APs with the AMPA receptor-mediated component of the EPSP, preventing LTP induction.

ASSOCIATIVE LTD

It has been proposed, on theoretical grounds, that temporal asynchrony should result in LTD of synaptic transmission (Stent 1973; Levy and Stewart 1983; see Fig. 1B,D). The role of temporal asynchrony in hippocampal synaptic plasticity in vitro had been suggested experimentally by Stanton and Sejnowski (1989), who reported that

Figure 2: Induction of associative LTP and LTD is dependent on the number of postsynaptic APs. (A) Summary of the change in EPSP amplitude as a function of the time interval between depolarizing pulses in the postsynaptic neuron and synaptic activation (except for the 0 msec interval, depolarization always precedes synaptic activation). The pulses are either 50 msec (broken line) or 240 msec (solid line) in duration (adapted from Debanne et al. 1994). For the 240-msec pulse, LTP was obtained when synaptic activation and postsynaptic depolarization were simultaneous whereas a delay in synaptic activation of 800 or 1600 msec resulted in LTD. For 50-msec depolarizing pulses, in contrast, no significant LTP was obtained with simultaneous pairing, whereas weak LTD was obtained when the interval between the depolarizing pulse and synaptic activation was 800 msec. Significant LTD was elicited with a 400-msec interval. The time windows for LTD induction are delimited by a horizontal blue line. The inset shows the data for the EPSP amplitude (as percentage control) after asynchronous pairing with 240-msec pulses replotted as a function of the instantaneous frequency ($1/\text{interval}$) to facilitate comparison with homosynaptic LTD. Low frequencies lead to LTD, whereas higher frequencies result in LTP. (B) Changes in synaptic efficacy as a function of the time interval between single pre- and postsynaptic action potentials in pairs of CA3 pyramidal neurons (adapted from Debanne et al. 1998a). Potentiation was induced only when the presynaptic action potential preceded the postsynaptic action potential (-15 -msec delay). Depression was induced for synchronous (0 msec) and asynchronous (15–70 msec) pairing, where the postsynaptic AP preceded the presynaptic AP. The change in unitary EPSP amplitude observed when the time interval was increased to 200 msec was not significant. The time window for LTD is delimited by a horizontal blue line. The inset illustrates the timing of the NMDA receptor-mediated component of a unitary EPSP relative to the pre- and postsynaptic APs when they are synchronous or when the delay is -15 msec. (C) Time window after postsynaptic spiking during which associative LTD can be induced, as a function of the number of APs. For a 240-msec pulse (~ 10 APs) LTD was obtained with a delay of 400–2400 msec (time window = 2000 msec); for a 50-msec pulse (~ 4 APs), with a delay between 0 and 800 msec (time window = 800 msec); and with a single AP, depression was induced only between 0 and 200 msec of delay (time window = 200 msec). Note that the time window for LTD induction is not only reduced with the reduction of postsynaptic APs but also shifted towards small interstimulus intervals (see A, B). These results indicate that synapses are more sensitive to temporal correlation of pre- and postsynaptic activity when the postsynaptic activity decreases during the asynchronous pairing. (D) Changes in synaptic efficacy as a function of the number of APs for synchronous pairing (0-msec delay). For the 240-msec pulse that evoked 10 APs, LTP was obtained with simultaneous synaptic activation. No significant LTP was obtained with synchronous pairing between the synapse and 50-msec depolarizing pulses that elicited four APs. Depression was induced when single pre- and postsynaptic APs were synchronously paired.

repeated stimulation of a test input 100 msec after the tetanization of a conditioning input led to the induction of LTD in area CA1 (see Fig. 1D). The relative patterns of activity in the two pathways apparently determined the sign of the induced synaptic changes, because synchronous pairing of the test pathway with tetanization of the other input induced associative LTP as described earlier (Barrionuevo and Brown 1983). This study remains contentious because the replication of some of these findings has been difficult (Kerr and Abraham 1993; Paulsen et al. 1993). Moreover, the associative nature of this protocol is not clearly established. Little or no depression should be induced when the temporal association between the two neuronal events is reduced with increasing time intervals, but this was not demonstrated in the original study.

There is now evidence for a reproducible associative LTD in area CA1 of both organotypic slice cultures (Debanne et al. 1994) and acute slices (D. Debanne and G. Daoudal, unpubl.). When presynaptic activity repeatedly follows a postsynaptic discharge of 7–12 APs by a delay of 800–1600 msec, LTD of the synapse occurs (Fig. 2). If the synaptic pathway is not activated following injection of depolarizing pulses, no depression is observed, thus demonstrating its associative character (n.p. in Fig. 2A). Moreover, LTD is only induced when postsynaptic depolarization is followed by synaptic activation at defined intervals within a precise time window. As indicated in Figure 2, the temporal relationship between pre- and postsynaptic activity determines the sign and magnitude of the changes induced.

The time window for LTD induction is not absolute and critically depends on the magnitude of the induced postsynaptic activity. Indeed, LTD is observed at shorter intervals (<800 msec) if the depolarizing pulse duration is decreased from 240 to 50 msec (Fig. 2C). The time window for associative LTD is even narrower (~200 msec) when single postsynaptic spikes are used in the asynchronous pairing protocol (Debanne et al. 1998a; Fig. 2B,D). Importantly, extrapolation of the curve to higher levels of postsynaptic activity predicts that the critical time window for LTD induction could be further increased. In general, the minimal time interval allowing LTD induction depends on the level of postsynaptic activity. As illustrated in Figure 2, this initial point moves toward large values when the postsynaptic activity is augmented.

The profile of the synaptic change expressed as a function of the pre- and postsynaptic degree of synchrony obeys the general rules formulated for homosynaptic plasticity. Transposed as a function of the instantaneous frequency between pre- and postsynaptic activity (1/interstimulus interval), the curve for associative plasticity fits well with the plasticity curve predicted by the theory of Bienenstock and coworkers (1982) (Fig. 2A, inset; see also Fig. 2 in Debanne 1996). Moreover, the requirements for induction of associative LTD regarding NMDA-receptor activation and the postsynaptic calcium rise are similar to those described for the induction of homosynaptic LTD (Debanne and Thompson 1994). In particular, associative LTP is induced when a strong postsynaptic calcium entry is temporally associated with a synaptic activation whereas a moderate and persistent elevation in calcium concentration decreases synaptic strength at the active synapse. For example, associative LTD is induced in hippocampal (Selig et al. 1995; Goda and Stevens 1996) and cortical (Feldman et al. 1998) synapses when constant depolarization to

–50 mV of the postsynaptic neuron is paired with the synaptic stimulation. The existence of two thresholds for the respective induction of LTD and LTP is widely accepted today (Lisman 1989; Artola et al. 1990; Artola and Singer 1993; Bear and Malenka 1994; Debanne and Thompson 1994; Bear 1996; Hansel et al. 1997) and has been verified recently with direct elevations of calcium concentration in hippocampal neurons (Yang et al. 1999).

Associative LTD in neocortical neurons *in vivo* of either visually evoked responses (Frégnac et al. 1988, 1992; Shulz and Frégnac 1992; Debanne et al. 1998b) or auditory responses (Cruikshank and Weinberger 1996) has also been reported following a supervised cellular learning protocol. The rationale for these protocols is based on the covariance hypothesis of separate inputs converging onto a postsynaptic neuron (for review, see Frégnac and Shulz 1994). Two separate synaptic inputs that correspond to different visual or auditory characteristics of the stimulation are respectively paired with high and low levels of postsynaptic activity imposed by iontophoretic means (see Frégnac et al. 1988; Cruikshank and Weinberger 1996; Debanne et al. 1998b). In all of these studies, potentiation of the positively covaried input is observed, whereas the input associated with low postsynaptic activity is depressed. Associative interactions leading to LTD induction have also been reported in *in vitro* experiments (Frégnac et al. 1994; Markram et al. 1997), but the associative nature of this depression is not clearly established. The extent of the time window for induction of depression has never been carefully explored in neocortical cells. Moreover, some *in vitro* protocols lack accurate control of the temporal interactions between pre- and postsynaptic activity because multiple pre- and postsynaptic APs are used for the induction of synaptic plasticity (Markram et al. 1997).

In conclusion, associative LTP and LTD are induced in pyramidal cells from the neocortex and hippocampus when postsynaptic APs elicited in the soma are synchronously or asynchronously paired with synaptic stimulation. This relatively simple view is complicated by recent findings showing that different rules may apply at excitatory synapses formed by nonpyramidal cells in the neocortex (V. Egger, D. Feldmeyer, D. Spergel, and B. Sakmann, unpubl.).

II. Geometrical Constraints in the Spread of Postsynaptic Depolarization

Although the rules for induction of associative synaptic plasticity are relatively well established, the cellular mechanisms need to be reconsidered with the geometry of the cortical pyramidal neuron. In most of the experiments reported before, postsynaptic depolarization and elevation of postsynaptic calcium are required for the induction of both associative LTP and LTD (for review, see Debanne 1996). The question that must be answered is: How does the required depolarization reach remote synapses on the distal dendritic tree?

GEOMETRICAL FACTORS

The dendritic arborization of neocortical or hippocampal pyramidal cells occupies a large volume of brain tissue, and apical dendrites can spread up to several hundred micrometers from the soma (Ramón y Cajal 1911). The physical distance between individual synapses in the dendritic tree, or between a given synapse and the AP initiation zone in the axon, implies a strong electrotonic attenuation of the electrical signals according

to cable theory (Rall 1977). Associative interactions required for the induction of associative LTP can occur only if the distance does not impede a sufficient depolarization of the dendritic spine. These geometrical constraints may be circumvented in the case of a complete or theoretical voltage clamp of the whole neuron (see Spruston et al. 1993), but they remain critical parameters in the case of associative LTP induced either by tetanic stimulation of a synaptic pathway or by synchronous pairing between the synaptic activation and a postsynaptic train of APs.

In neuronal membranes not expressing voltage-dependent conductances (referred to as passive membranes), a depolarization generated in a neuronal compartment is attenuated according to the capacitive and resistive properties of the membrane (Rall 1977). The question we address now is whether the passive (or electrotonic) spread of the depolarization evoked by tetanic stimulation of an input or by an AP initiated in the soma is sufficient to induce a local depolarization required for the induction of associative plasticity.

ELECTROTONIC SPREAD OF DEPOLARIZATION AND ACTIVE FORMS OF PROPAGATION

According to cable equations, the electrotonic spread of a somatic depolarization is insufficient to fully preserve somatic steady-state or transient depolarizations (in the form of synaptic potentials or APs) in all the dendrites (Rall 1977; Spruston et al. 1994; Korogod et al. 1996; Hoffman et al. 1997; Stuart et al. 1997b). Passive attenuation of APs may be examined experimentally in soma-dendrite paired recordings of cortical neurons in the presence of the sodium channel blocker tetrodotoxin (TTX) to eliminate fast sodium conductances. Under these conditions, a voltage command that mimics a somatic AP (~80 mV) is greatly attenuated (<25 mV) in the dendrite recorded ~300 μ m from the soma (Stuart and Sackmann 1994). Passive attenuation can also be studied in realistic models of CA1 pyramidal cells. Sodium APs of 80 mV in the soma are attenuated passively to <20 mV in dendrites located 400 μ m from the soma, unless sodium channels are inserted in the modeled dendrites (Hoffman et al. 1997; Fig. 3). These studies indicate that electrotonic attenuation of APs is significant in the passive dendrite and may not depolarize remote dendritic elements sufficiently to activate NMDA receptors or high-threshold VDCCs (see section I). It is interesting to note that hippocampal synapses, such as the mossy fiber-CA3 cell synapse, that require activation of VDCCs rather than NMDA receptors for the induction of Hebbian potentiation (Jaffe and Johnston 1990; Urban and Barrionuevo 1996) occupy a privileged location in the dendritic tree. Mossy terminals impinge on the very proximal area of CA3 apical dendrite (20–150 μ m; Johnston and Brown 1983). This results in little electrotonic attenuation, allowing strong depolarization of the spines during cell firing and activation of high- and low-threshold VDCCs even without active signal propagation.

For remote synapses, NMDA receptors can only be activated through active spread of the depolarization. In neocortical and hippocampal pyramidal cells, this spread can be achieved by calcium APs initiated in the dendrites (Benardo et al. 1982; Andreassen and Lambert 1995). But the voltage commands required for their induction are generally of large amplitude because high-threshold VDCCs are involved (Benardo et al. 1982; Kim and Connors 1993). The most efficient active spread of depolarization can be achieved by the sodium AP because the threshold

Figure 3: Schematic representation of passive and active propagation of a single AP in the apical dendrite of pyramidal neurons. (*Left*) In passive dendrites, an AP initiated in the axosomatic area is electrotonically attenuated (solid line) to <20% of its normalized amplitude in the apical dendrite. (*Middle*) When Na^+ channels are homogeneously present in the dendrites, the amplitude of the somatic AP (solid line) is conserved in the remote apical dendrite. (Dotted line) The AP amplitude with electrotonic attenuation only. (*Right*) Addition of transient K^+ channels in the distal dendrites actively reduces the AP amplitude (solid line, adapted from Hoffman et al. 1997). (Dotted lines) The AP amplitude with electrotonic attenuation (*left*) and with Na^+ channels only (*right*).

for its activation is low in hippocampal pyramidal cells (~ -60 mV; Fricker et al. 1999). In section III, we will therefore consider the mechanisms underlying the propagation of sodium APs in the dendritic arborization.

III. The Role of AP Back-Propagation in Associative Synaptic Plasticity

BIOPHYSICS OF DENDRITE BACK-PROPAGATION OF SINGLE APS

APs are regenerative electrical events, mediated by voltage-activated Na^+ channels, which are initiated following depolarization of the axosomatic membrane potential to a threshold level (for review, see Stuart et al. 1997b). During the normal functioning of the central nervous system (CNS), this threshold is reached after temporal and/or spatial summation of synaptic inputs impinging on the whole neuron's dendritic tree. As the axon usually originates from the soma of neurons, this site provides a natural focal point for summation of synaptic inputs from different locations in the dendritic tree. APs are usually initiated first in the axon hillock or at the first node of Ranvier and propagate actively along the axon (Combs et al. 1957; Gogan et al. 1983; Stuart et al. 1997b). Furthermore, once initiated, sodium-dependent APs also actively back-propagate from the soma to the dendrites of CA1 (Miyakawa and Kato 1986; Richardson et al. 1987; Turner et al. 1991; Jaffe et al. 1992; Spruston et al. 1995) and neocortical pyramidal neurons (Stuart and Sakmann 1994; Buszáki and Kandel 1998), hippocampal granule cells (Jefferys 1979), substantia nigra neurons (Häusser et al. 1995), spinal cord neurons (Larkum et al. 1996), and mitral cells of the olfactory bulb (Bischofberger and Jonas 1997; Chen et al. 1997).

Direct recordings from dendrites of neocortical and hippocampal pyramidal neurons have demonstrated that these neuronal processes express various types of ion channels that endow them with active membrane properties (Huguenard et al. 1989; Stuart and Sakmann 1994; Magee and Johnston 1995a,b; Hoffman et al. 1997; Magee 1998). The active back-propagation of APs was demonstrated by comparing back-propagation of a somatic AP under control conditions with that of a simulated AP waveform when voltage-activated Na^+ channels were blocked by TTX (Stuart and Sakmann 1994). These experiments show that the amplitude of a back-propagating AP waveform is greatly reduced when dendritic Na^+ channels are blocked by TTX in those neurons with a similar density of dendritic and somatic Na^+ channels (Stuart and Sakmann 1994; Häusser et al. 1995; Spruston et al. 1995). Dendritic APs are smaller and broader than somatic APs, and the greater the distance from the soma, the greater the attenuation (Turner et al. 1991; Stuart and Sakmann 1994; Spruston et al. 1995; Stuart et al. 1997a; Fig. 3). In fact, dendritic AP attenuation along hippocampal dendrites is active and attributable to the increasing density of transient A-type K^+ channels with greater distance from the soma (Hoffman et al. 1997; Fig. 3). In contrast, APs are not back-propagated in cerebellar neurons because focal application of TTX has little effect on fast APs recorded in the dendrite (Stuart and Häusser 1994) and somatic APs are passively attenuated along the dendrites (Llinas and Sugimori 1980). This cell-specific difference, essentially resulting from a difference in sodium channel density, suggests that active back-propagation of APs into the dendritic tree is functionally important in those neurons where it occurs. Back-propagating APs may provide a retrograde signal to the dendritic tree that indicates the level of neuronal output, as the relatively large physical distance separating the input from the output could create the need for a rapid feedback signal.

Single back-propagating APs also interact with dendritically initiated Ca^{2+} APs (Andreassen and Lambert 1995; Schiller et al. 1997; Larkum et al. 1999). Larkum and coworkers have shown that single APs elicited in the soma of single cortical cells facilitate the initiation of calcium spikes when they coincide with distal dendritic input within a time window of a few milliseconds. The dendritic calcium wave is propagated to the soma, causing the neuron to fire a burst of APs, thus allowing all-or-none amplification of synaptic inputs (Larkum et al. 1999). Several points concerning the implications of this boosting mechanism in the function of cortical circuits remain to be clarified, however (Frégnac 1999). It is not known whether this process is relevant for unitary EPSPs as only EPSPs $> \sim 10$ mV were able to induce this boosting. Moreover, because of the late development of dendritic calcium APs (J.J. Zhu and B. Sakmann, unpubl.), this amplification mechanism has thus far only been studied in the adult neocortex. It therefore may not play a significant role in the induction of associative synaptic plasticity in the developing cortex or hippocampus. Indeed, strong boosting has never been observed in young cortical neurons when single pre- and postsynaptic APs were elicited with such short delays (Markram et al. 1997; Bi and Poo 1998; Debanne et al. 1998a). In the study of Larkum and coworkers (1999) the lowered threshold for calcium spike induction was found for small delays of ~ 5 msec between the back-propagating AP and the EPSP. In the context of Hebbian-like plasticity, this amplification might serve as a mechanism to prevent LTD induction when an AP-EPSP sequence occurs with very brief

delays and could contribute to prolong the critical time window for LTP induction when somatic and dendritic inputs are coactivated.

Active properties of cortical dendrites are also thought to play an important role in coincidence detection of neural events. The presence of voltage-gated sodium and potassium conductances in the dendrites allows discrimination, by the neuron, of events with a temporal accuracy in the submillisecond range (Softky 1994). Dendritic action potentials may therefore increase the computation capability of individual cortical pyramidal neurons.

IS BACK-PROPAGATION OF SODIUM APS REQUIRED FOR INDUCTION OF ASSOCIATIVE POTENTIATION?

This question was first addressed by Kelso and coworkers (1986) and by Gustafsson and coworkers (1987), at a time when back-propagated APs in the dendrites were suspected but not yet demonstrated. Both studies show that the intracellular blockade of postsynaptic spiking activity by lidocaine derivatives (QX222 or QX314) does not impede associative LTP induction. Similar findings have been reported more recently in visual cortical neurons (Harsanyi and Friedlander 1997). Blocking sodium spiking activity leaves the possibility of triggering calcium APs (Kelso et al. 1986; Stuart and Sakmann 1994), which probably serve to replace sodium spike depolarization functionally. However, it is worth noting that these studies used very large amplitude currents in the postsynaptic neuron (4–6 nA in the study by Gustafsson et al. 1987); under these conditions, the somatic depolarization could be of sufficient magnitude to allow electrotonic depolarization of some of the proximal dendrites and activation of dendritic calcium spikes (Benardo et al. 1982; Andreassen and Lambert 1995). Therefore, one can not exclude the possible contribution of back-propagating APs elicited under more moderate depolarization.

Magee and Johnston (1997) reconsidered this question using an elegant combination of electrophysiological recordings from dendrites or soma in CA1 pyramidal neurons with the measurement of intracellular calcium concentration using a fluorescent calcium probe. In this study, pairing of axonally initiated APs with subthreshold EPSPs induced an increase of dendritic AP amplitude and a supralinear Ca^{2+} influx that is larger than the algebraic sum of Ca^{2+} influx induced by either presynaptic or postsynaptic activation alone. This pairing also induced a robust LTP. To examine the nature of the associative signal for LTP, the back-propagation of somatic APs was blocked by transient application of TTX in a restricted region of the proximal apical dendrite just before AP initiation. APs failed to back-propagate distal to the blocked region, as evidenced by the lack of $[\text{Ca}^{2+}]_i$ elevation in the distal but not proximal dendrites. Pairing of EPSP trains with non-back-propagating postsynaptic APs prevented the induction of LTP (Magee and Johnston 1997). Thus, a role for back-propagating APs in the induction of LTP has been demonstrated with moderate postsynaptic depolarizations of the soma.

RECONSIDERING HEBB'S PRINCIPLE

Magee and Johnston (1997) demonstrated the importance of AP amplification by synaptic activation, without which the amplitude of back-propagating APs would be insufficient to evoke a large influx of Ca^{2+} and to induce LTP in the distal dendritic region. What are the mechanisms underlying the back-propagating AP amplification by synaptic activation? Rapid inactivation of transient A-type K^+ channels by EPSPs may underlie the AP amplification described by Magee and Johnston

(Hoffman et al. 1997). Indeed, when back-propagating APs are paired with a localized synaptic input, AP amplitude is boosted in the branch receiving synaptic input, but not in another branch that does not receive any synaptic input (Hoffman et al. 1997). The susceptibility of A channels to rapid inactivation during subthreshold synaptic input could provide a mechanism for coincidence detection, whereby back-propagating APs will preferentially invade synaptically active regions of the dendritic arborization. The synaptically regulated propagation of APs into specific dendritic branches may thus play a role in Hebbian synaptic plasticity (Magee and Johnston 1997).

Also, supralinear accumulation of calcium in dendrites has been shown during associative pre- and postsynaptic activation (Yuste and Denk 1995; Magee and Johnston 1997), but the underlying mechanisms were poorly understood at the time of these studies. How does extracellular Ca^{2+} enter into dendritic spines during the pairing protocols? One possible source is through VDCCs, as their activation leads to Ca^{2+} influx into dendrites, including the spines (Yuste and Denk 1995). In addition, blocking subpopulations of VDCCs eliminates the induction of associative LTP in CA1 hippocampal pyramidal neurons (Magee and Johnston 1997). A second source of Ca^{2+} influx is mediated by NMDA receptors. Recently, using two-photon confocal microscopy, Schiller and coworkers (1998) measured dendritic $[\text{Ca}^{2+}]_i$ in response to the focal release of caged glutamate, back-propagating APs, or both, in layer V cortical neurons. They found that most of the calcium entry in response to glutamate alone is mediated by VDCCs, NMDA receptors accounting for <20% of the total Ca^{2+} entry (see also Magee et al. 1995). Also, they confirmed that Ca^{2+} transients evoked by back-propagating APs are largely due to VDCCs (Magee and Johnston 1995a; Markram et al. 1995; Yuste and Denk 1995). When glutamate release is paired with postsynaptic APs, however, the NMDA receptor-dependent component is selectively amplified (Schiller et al. 1998). In contrast to the spatially uniform rise of Ca^{2+} evoked by APs, increases of $[\text{Ca}^{2+}]_i$ were restricted to spines and short portions of the dendritic shaft close to the activated spines during focal synaptic stimulation or pairing procedure (Yuste and Denk 1995, Schiller et al. 1998). Moreover, Ca^{2+} transients in active spines preceded those developing in the adjacent parent dendrite (Schiller et al. 1998). Thus, local and supralinear Ca^{2+} influx through NMDA receptor pores in the dendritic spines could represent a cooperative accumulation of Ca^{2+} , which could be used to register the temporal coincidence of the input and output of the neuron and may serve as the molecular basis of associative LTP.

The summation of Ca^{2+} transients in the spines of neocortical pyramidal neurons has been found to depend on the temporal interactions of coincident EPSPs and APs. Supralinear summation is observed when the AP follows the EPSP by 50 msec, whereas pairing between an AP and an EPSP interestingly evokes a sublinear summation of calcium influx when the EPSP follows the AP by 50 msec (Koester and Sakmann 1998). This sublinear response is caused by a reduction of the EPSP-evoked Ca^{2+} transient by a preceding AP. The mechanism underlying the reduction of synaptic Ca^{2+} influx by an AP could be an inactivation of NMDAR channels by a brief and localized rise in $[\text{Ca}^{2+}]_i$ (Legendre et al. 1993). In contrast, the increased Ca^{2+} influx when the AP followed the EPSP could be caused by a transient alleviation of the Mg^{2+} block of NMDARs

resulting in an amplification of Ca^{2+} influx through NMDARs (Mayer et al. 1984; Schiller et al. 1998). The precise timing between pre- and postsynaptic activity may therefore determine the sign of the change in synaptic strength. Functionally, supralinear and sublinear summations of calcium influx mediated by NMDARs and VDCCs could represent mechanisms to enhance the contrast between high and low elevations of $[\text{Ca}^{2+}]_i$, which then independently activate different calcium sensors involved in LTP and LTD induction, respectively (Lisman 1989). This enhancing mechanism could explain why small differences in the degree of synchrony between single pre- and postsynaptic APs induces strong and opposite effects on synaptic strength. Indeed, Debanne and coworkers (1998b) have demonstrated that LTP between pairs of monosynaptically coupled CA3 cells is only induced when postsynaptic AP occurs 15 msec after the presynaptic AP, whereas LTD is induced when the postsynaptic AP occurs 0–70 msec before the presynaptic AP (Debanne et al. 1998a; Fig. 2). Consequently, we propose that the key parameter for LTP or LTD induction is not the degree of temporal coincidence between the pre- and postsynaptic APs per se, but rather the degree of coincidence of the NMDA receptor-mediated EPSP and the postsynaptic depolarization achieved by single back-propagating APs (Debanne et al. 1998a).

IV. Attenuation of a Spike Train in Hippocampal and Neocortical Apical Dendrites

CA1 and neocortical pyramidal neurons in vivo can fire long bursts of APs in response to natural stimulation (Douglas et al. 1991; Bland and Colom 1993). Similar bursts of APs induced postsynaptically by current injection in intracellularly recorded nerve cells are used as conditioning events to induce associative plasticity (Baranyi and Feher 1981; Gustafsson et al. 1987; Bindman et al. 1988). The interest in AP train back-propagation in dendrites is more recent than in back-propagation of a single AP. In contrast to the case of single back-propagating APs, which only activate fast conductances, back-propagating spike trains into dendrites can activate both rapid and slow conductances. In particular, slow voltage-dependent K^+ , Na^+ , and Ca^{2+} conductances that have been reported in hippocampal and neocortical neurons could interfere with subsequent APs in a train (for review, see Johnston et al. 1996).

BIOPHYSICS OF SPIKE TRAIN BACK-PROPAGATION

In hippocampal (Callaway and Ross 1995; Spruston et al. 1995; Tsubokawa and Ross 1996) and neocortical (Stuart et al. 1997a; V. Sourdet, N. Ferrand, and D. Debanne, unpubl.) pyramidal cells, the amplitude of back-propagating APs decreases during a high-frequency train (Fig. 4A). In CA1 hippocampal pyramidal neurons, somatic APs remain relatively constant in amplitude during a train (Andreasen and Lambert 1995; Callaway and Ross 1995; Spruston et al. 1995), whereas dendritic APs decrease progressively in amplitude (Andreasen and Lambert 1995; Callaway and Ross 1995; Spruston et al. 1995), stabilizing toward the latter part of the train (Callaway and Ross 1995; Spruston et al. 1995). At higher frequency, the rate of the amplitude decay is enhanced and the last APs of the train show the lowest amplitude (Callaway and Ross 1995). Similar observations have been obtained in layer V neocortical pyramidal neurons (Fig. 4A; V. Sourdet, N. Ferrand, and D. Debanne, unpubl.). Furthermore, APs may fail to actively propagate into much of the

Figure 4: Attenuation of spike trains in neocortical and hippocampal pyramidal cells. (A) Whole-cell patch-clamp recordings from visually identified somata and apical dendrites of layer V pyramidal neurons in parasagittal neocortical brain slices of young rats (P8–P15). Pyramidal neurons are identified under IR-DIC (infrared differential interference contrast) video microscopy by their location in the slice and their apical dendrites that extends towards the pial surface. Dendritic APs (*bottom right*) elicited by injection of a train of current pulses are smaller and broader than somatic APs (*bottom left*). During high-frequency depolarizing current trains (50 Hz), dendritic APs (*right*) attenuated, but somatic APs (*left*) did not (V. Sourdet, N. Ferrand, and D. Debanne, unpubl.). (B) Schematic representation of voltage and $[Ca^{2+}]_i$ transients during high-frequency trains of APs in the soma (*bottom*) and proximal (*middle*) and distal (*top*) apical dendrite from a hippocampal pyramidal cell. In control conditions (*left column*), late APs in the spike train are attenuated in the distal dendrite, resulting in a small $[Ca^{2+}]_i$ profile. Up-regulation of the spike train would increase the associated calcium transients in remote dendrites (*right column*). (C) Expected synaptic changes as a function of the regulation of the dendritic attenuation of a spike train. LTP is induced when the postsynaptic calcium elevation produced by a train of APs is greater than θ^+ , the threshold for LTP induction. LTD results when postsynaptic calcium is $<\theta^+$ but $>\theta^-$ (threshold for LTD induction). A given synchronous pairing that results in weak LTP in control conditions (black vertical line) may induce a weak depression (green vertical line) or a larger potentiation (red vertical line) if the dendritic attenuation of a spike train is respectively up- or down-regulated (red and green trains). (D) Differential synaptic changes along the apical dendrite are expected to occur when synaptic inputs are synchronously paired with the last APs in a train (↑). Pairing nonattenuated APs (red trace) with glutamate release in the proximal dendrite would result in LTP induction. In contrast, pairing attenuated APs (green trace) with synaptic activation occurring with the same phase would result in LTD induction. The expected spatial gradient of synaptic change along the dendrite is illustrated at *right*.

dendritic tree at high frequency, though not at low frequency (Callaway and Ross 1995).

The degree of AP attenuation observed during a train depends on the recording site in the dendritic tree: The greater the distance from the soma, the larger the attenuation (Spruston et al. 1995, Tsubokawa and Ross 1996). In distal dendrites of hippocampal pyramidal neurons, dramatic attenuation of AP amplitude typically occurs after one or a few APs, probably because of back-propagation failures (Spruston et al. 1995; Tsubokawa and Ross 1996): The first AP is actively back-propagated, but later ones are likely electrotonically attenuated somatic APs. These apparent failures of active propagation are often observed after a branch

point (Spruston et al. 1995), as previously shown in axons (for review, see Debanne et al. 1999a). In contrast, no apparent failures of the later APs are observed in the dendrites of neocortical neurons (Stuart et al. 1997a). The activity-dependent attenuation during a train in hippocampal pyramidal neurons is voltage dependent and is due, in part, to the slow recovery from inactivation of dendritic Na^+ channels (Colbert et al. 1997; Jung et al. 1997; Mickus et al. 1999). Na^+ channels seem also to be involved in activity-dependent attenuation of dendritic APs in layer V neocortical pyramidal neurons (V. Sourdet, N. Ferrand, and D. Debanne, unpubl.). Finally, K^+ currents also mediate this form of attenuation in CA1 pyramidal dendrites (Colbert et al. 1997).

PHYSIOLOGICAL SIGNIFICANCE

The consequence of the filtering of AP back-propagation is that the spatial and temporal profiles of the $[\text{Ca}^{2+}]_i$ signals in the dendrites are likely to differ in an activity-dependent manner. Calcium transients evoked by single APs display a fast rise time (~ 2 msec) and decay within 80 msec (Markram et al. 1995). During trains of APs, the amplitude and duration of the Ca^{2+} transients is increased as compared with those produced by single APs, because of the summation of Ca^{2+} transients (Markram et al. 1995). The profile of the Ca^{2+} transients produced by a given spike train differs in the soma and in the dendrites and depends on the AP frequency. Indeed, studies show the rise of Ca^{2+} during a train is greater in the proximal dendrites and decreases gradually in size along the distal dendritic regions (Callaway and Ross 1995; Schiller et al. 1995; Spruston et al. 1995). This spatial decrease of Ca^{2+} entry can be correlated with the degree of dendritic AP attenuation observed during a train depending on the location in the dendritic tree (Spruston et al. 1995, Tsubokawa and Ross 1996).

During low-frequency (5–10 Hz) trains, dendritic Ca^{2+} transients evoked by individual spikes sum to reach a plateau level (Callaway and Ross 1995; Schiller et al. 1995). This plateau level increases at higher AP rates (20–30 Hz) (Callaway and Ross 1995; Schiller et al. 1995), but the level of Ca^{2+} influx decreases at the end of the train in dendrites. The maximal rise of Ca^{2+} is therefore found to occur in the middle of the train (Callaway and Ross 1995; Tsubokawa and Ross 1997), with the transient amplitude for each spike in the train declining, even though later spikes cause some $[\text{Ca}^{2+}]$ elevation (Callaway and Ross 1995). This frequency-dependent reduction of Ca^{2+} transients at the end of a train can be correlated with the faster and more striking decrease in dendritic AP amplitude at high frequency (Callaway and Ross 1995). The effect is even more pronounced at 50 Hz. Indeed, in distal dendrites, the rise of $[\text{Ca}^{2+}]_i$ reaches a peak after the first few spikes and rapidly declines during the rest of the train (Callaway and Ross 1995), suggesting that the later spikes do not contribute to the Ca^{2+} signal at this location. Interestingly, all-or-none filtering has been observed at dendritic branch points, producing spike train invasion failure in CA1 neurons (Spruston et al. 1995).

All of these findings have important implications for synaptic plasticity. Proximal and distal spines may not receive the same amount of Ca^{2+} influx, especially at the end of a high frequency train. In the extreme case corresponding to spines located in a very remote dendritic branch (>600 μm) where APs fail to back-propagate (Spruston et al. 1995), the voltage

and calcium profiles elicited by a single AP and a high-frequency train could actually be very similar. Therefore, the later APs would not functionally alter the dendritic membrane properties, which could account for the lack of potentiation in some pairing protocols (D. Debanne, B.H. Gähwiler, and S.M. Thompson 1999b). It would be especially interesting in this case to know whether the attenuation of the later APs could be modulated to become functional during the induction of associative plasticity. However, this relatively simple view may be complicated in the case of pyramidal cells of the adult neocortex by calcium spike-mediated boosting of sodium APs. Amplification of the output signal mediated by dendritic calcium spikes has indeed been demonstrated when single backpropagating APs are coactivated with remote synaptic depolarization (Larkum et al. 1999). It remains to be determined whether similar boosting can also be observed with late APs in a spike train.

V. Modulation of Dendritic Back-Propagation and Attenuation of Spike Trains

MODULATION OF BACK-PROPAGATING APS

Two types of modulation will be considered: (1) modulation by neurotransmitters, and (2) modulation by electrical activity. Neuromodulation can up- or down-regulate the back-propagation of APs and the spike-associated changes in $[Ca^{2+}]_i$.

Synaptic inhibition or hyperpolarization can block the first back-propagating AP in a train and decrease dramatically the spike-associated $[Ca^{2+}]_i$ changes in distal dendrites (Miles et al. 1996; Tsubokawa and Ross 1996). However, synaptic inhibition does not change or increase AP amplitude in the dendrite and has little effect on the Ca^{2+} changes in the somatic or proximal dendritic regions (Tsubokawa and Ross 1996). Modulation by synaptic inhibition is effective in a time window of <10 msec and mediated by a conductance shunt activated by GABA_A receptors (Tsubokawa and Ross 1996).

Serotonin acts through a different mechanism as it hyperpolarizes both the soma and apical dendrites (Sandler and Ross 1999). In this study, it was shown that serotonin has varying effects on back-propagating APs, depending on the neuronal compartment. In the soma, serotonin increases AP amplitude with little effect on the peak potential, suggesting that serotonin-induced hyperpolarization deinactivates sodium channels. In the apical dendrites, serotonin decreases uniformly the relative peak potential without affecting the absolute amplitude of back-propagating APs in the train, thus reducing spike-evoked $[Ca^{2+}]$ changes (Sandler and Ross 1999).

In contrast, agonists of muscarinic cholinergic, β -adrenergic, and D1/D5-dopaminergic receptors enhance back-propagation (Tsubokawa and Ross 1997; Hoffman and Johnston 1999). The effects of carbachol are observed in the proximal and middle dendrites, with a maximal effect at a distance of between 150 and 300 μ m, but not in the distal dendrites (Tsubokawa and Ross 1997). In particular, carbachol has little effect on the first dendritic spike in the train but significantly enhances the

amplitude of the later APs (Tsubokawa and Ross 1997). However, Hoffman and Johnston (1999) found that carbachol does enhance the amplitude of single APs in distal dendrites. These discrepancies may result for two reasons: (1) the experimental conditions, and (2) the final target of the activation of muscarinic receptors. The up-regulation of the frequency-dependent decline reported by Tsubokawa and Ross (1997) involves a reduction of the slow inactivation of dendritic Na^+ channels (Colbert and Johnston 1998) mediated by the activation of protein kinase C (PKC) (Tsubokawa and Ross 1996; Colbert and Johnston 1998). Effects of carbachol on trains of dendritic APs are mediated by activation of the M1 subtype of muscarinic cholinergic receptor (Tsubokawa and Ross 1997). In contrast, carbachol potentiation of single APs in distal dendrites (Hoffman and Johnston 1999) could be mediated by down-regulation of dendritic transient K^+ channels via PKC activation (Hoffman and Johnston 1998). In association with the enhancement of spike back-propagation, carbachol increases spike-associated $[\text{Ca}^{2+}]_i$ changes (Tsubokawa and Ross 1997). Interestingly, maximum rise of Ca^{2+} is observed at the end of the spike train under carbachol application whereas without this cholinergic agonist, Ca^{2+} influx was transient (Tsubokawa and Ross 1997; Fig. 4B).

Effects of β -adrenergic and D1/D5-dopaminergic agonists have been studied only on single APs (Hoffman and Johnston 1999). These actions are found only in distal dendrites (Hoffman and Johnston 1999) and may be mediated by down-regulation of dendritic transient K^+ channels via PKA activation (Hoffman and Johnston 1998). The spatial specificity of the effects of monoamines on dendritic spikes correlates with the high density of transient K^+ channels observed in distal dendrites (Hoffman et al. 1997).

Thus, the propagation of APs along the dendrites can be modified significantly by a variety of neuromodulatory synaptic inputs. As both Na^+ and K^+ channels can be targeted by protein kinases (for review, see Johnston et al. 1999), other neurotransmitters that lead to activation of second-messenger systems and protein kinase cascades could also modulate AP back-propagation.

In addition to the neuromodulatory control of active back-propagation, electrical activity has recently been found to regulate the frequency-dependent decline of AP amplitude in the dendrites of CA1 pyramidal neurons. Strong dendritic depolarizing pulses applied in the dendrites induced an irreversible long-lasting enhancement of back-propagating spike amplitude in the apical dendrites resulting in a lack of attenuation (H. Tsubokawa, S. Offermans, M. Simon, and M. Kano, unpubl.). This new form of activity-dependent plasticity requires an increase in $[\text{Ca}^{2+}]_i$ in the apical dendrite and is mediated by the activation of Ca^{2+} -calmoduline-dependent protein kinase II. This experiment raises the fascinating idea that back-propagation of a train of APs is not fixed but also depends on the past activity of the neuron. It would be particularly interesting to determine whether this form of plasticity is reversed by prior activity or neuromodulatory actions.

PERSPECTIVES

The magnitude and the sign of the induced change in synaptic strength is thought to be largely determined by the postsynaptic Ca^{2+} influx associated with back-propagating APs according to a biphasic curve (see section I). We propose that the neuromodulatory- or activity-dependent

regulation of postsynaptic $[Ca^{2+}]_i$ transients associated with back-propagating APs determines the induced change in synaptic efficacy at a given synapse (Fig. 4C). For example, the same synchronous pairing that results in weak LTP under control conditions could induce a weak depression or a larger potentiation if the dendritic attenuation of a postsynaptic spike train is down- or up-regulated, respectively (Fig. 4C). Another prediction is that differential synaptic changes can be induced along the apical dendrite when distributed synaptic inputs are synchronously paired with the later APs of a spike train. In proximal dendrites, synaptic potentiation is expected to occur because there is little attenuation of the APs. In distal dendrites, where frequency-dependent attenuation of spike amplitude is greater (Fig. 4D), weak LTP or even LTD might occur. Changes in the amplitude of single APs or spike trains in the dendrites may therefore represent a powerful modulatory control in the induction of associative plasticity (i.e., metaplasticity, Abraham and Bear 1996).

Concluding Remarks

There has been enormous effort devoted to the understanding of the rules for induction of associative synaptic plasticity. Recently, the cellular mechanisms underlying back-propagation of single APs and trains of spikes have been described. We are beginning to understand the role of back-propagating action potential in the induction of LTP, but several points remain to be clarified. Does associative LTD also require back-propagation of somatic APs for its induction? What are the spatial limits along the apical dendritic tree within which synapses can undergo associative potentiation without active back-propagation? Does this limit depend on the level of somatic depolarization? Future research in associative synaptic plasticity will also have to verify experimentally the predictions illustrated in Figure 4, C and D. Establishing a bridge between modulatory actions of dendritic back-propagation and the subsequent changes in synaptic efficacy will elucidate new dynamic aspects in associative synaptic plasticity.

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