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Active dendrites, potassium channels and synaptic plasticity

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The dendrites of CA1 pyramidal neurons in the hippocampus express numerous types of voltage-gated ion channel, but the distributions or densities of many of these channels are very non-uniform. Sodium channels in the dendrites are responsible for action potential (AP) propagation from the axon into the dendrites (back-propagation); calcium channels are responsible for local changes in dendritic calcium concentrations following back-propagating APs and synaptic potentials; and potassium channels help regulate overall dendritic excitability. Several lines of evidence are presented here to suggest that back-propagating APs, when coincident with excitatory synaptic input, can lead to the induction of either long-term depression (LTD) or long-term potentiation (LTP). The induction of LTD or LTP is correlated with the magnitude of the rise in intracellular calcium. When brief bursts of synaptic potentials are paired with postsynaptic APs in a theta-burst pairing paradigm, the induction of LTP is dependent on the invasion of the AP into the dendritic tree. The amplitude of the AP in the dendrites is dependent, in part, on the activity of a transient, A-type potassium channel that is expressed at high density in the dendrites and correlates with the induction of the LTP. Furthermore, during the expression phase of the LTP, there are local changes in dendritic excitability that may result from modulation of the functioning of this transient potassium channel. The results support the view that the active properties of dendrites play important roles in synaptic integration and synaptic plasticity of these neurons.

Keywords: hippocampus; CA1 neurons; long-term potentiation; long-term depression; Ca^{2+}

1. INTRODUCTION

The dendrites of neurons in the central nervous system have been studied for many years because of their presumed role in coordinating synaptic input and in regulating the strengths of those inputs. Historically, there have been great debates about whether dendrites were active or passive, and whether synaptic inputs on the distal portions of dendritic trees were too far away from the cell body to have much effect on neuronal excitability (for reviews, see Shepherd 1991; Johnston *et al.* 1996). In the hippocampus, CA1 pyramidal neurons have received the most attention in this regard. The dendrites of these neurons, as well as many other neurons in the hippocampus, neocortex, olfactory bulb and cerebellum, are now known to express a wide array of voltage-gated ion channels (reviewed in Magee 1999). For example, in CA1 pyramidal neurons Na^+ channels, which support the active back-propagation of APs, are expressed at a relatively uniform density from the initial segment of the axon to at least three quarters of the length of the main apical dendrite (Magee & Johnston 1995; Colbert & Johnston 1996; Mickus *et al.* 1999; Colbert & Pan 2002; Gasparini & Magee 2002). Ca^{2+} channels, which are opened by both synaptic potentials and dendritic APs, are also at a relatively uniform total density from the soma into the distal dendrites, but the distribution of the various subtypes of Ca^{2+} channel is quite heterogeneous—L- and N-type channels are more numerous in the soma and proximal dendrites, whereas R- and T-type channels are more numerous in the distal dendrites (Magee *et al.* 1995; Sabatini & Svoboda 2000). Hyperpolarization-activated h-channels, which affect temporal summation of synaptic inputs and overall neuronal excitability (Poolos *et al.* 2002), are expressed non-uniformly with a very high density in the distal dendrites (Magee 1998). Finally, there are two broad classes of K^+ channel in the dendrites of these neurons, inactivating and non-inactivating, both of which have profound effects on dendritic signalling. The non-inactivating class is expressed with a uniform density, while the inactivating class is non-uniformly distributed with the highest density in the distal dendrites (Hoffman *et al.* 1997). Clearly, CA1 pyramidal neuron dendrites cannot be considered passive.

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One contribution of 30 to a Theme Issue 'Long-term potentiation: enhancing neuroscience for 30 years'.

Based on these and other findings, the issues about dendritic function have moved significantly past the active versus passive debate and have become much more complicated and specific. For example, some of the more recent questions about how dendrites work relate to:

(i) which molecular subunits are responsible for the dendritic channels;
(ii) how are they targeted to dendrites;
(iii) what is the smallest synaptic integration zone (for example, spines, side branches or main trunk);
(iv) what is the function of dendritic APs;
(v) how do dendritic channels affect the spatial and temporal summation of synaptic inputs;
(vi) do dendritic channels undergo activity-dependent modification; and
(vii) do dendritic channels regulate the induction of various forms of synaptic plasticity?

It is now well known that the AP of these neurons is actively propagated into the apical dendrites as well as being locally generated under certain conditions (Jaffe *et al.* 1992; Spruston *et al.* 1995; Golding & Spruston 1998; Golding *et al.* 2001, 2002). The so-called b-AP is an attractive candidate mechanism for regulating certain forms of Hebbian-type synaptic plasticity (Magee & Johnston 1997), but many questions remain concerning precise mechanisms.

We have addressed some of these questions in recent years, and although the picture is far from clear, some answers are beginning to emerge. We have focused much of our attention on a particular type (or class) of K^+ channel, the A-type K^+ channel. This channel shows rapid activation and inactivation and, as mentioned above, is expressed at a high density in apical dendrites of CA1 pyramidal neurons. We will review some of the recent work related to active dendrites and their role in synaptic plasticity in CA1 neurons, paying particular attention to this transient, A-type K^+ channel.

2. LONG-TERM DEPRESSION

Work on LTD was the first to show that b-APs could play an integral role in the induction of long-term synaptic plasticity. This work stemmed from studies showing that low-frequency stimulation (LFS: 1–3 Hz) provides a reliable means to induce LTD in the CA1 region of the hippocampus (Dudek & Bear 1992; Mulkey & Malenka 1992). When small, sub-threshold EPSPs are evoked with LFS and recorded at the resting membrane potential, LTD is not usually induced in CA1 neurons (Christie *et al.* 1996*b*; figure 1*a*). When these same synaptic stimuli are paired with APs triggered with somatic current injection, however, LTD is reliably elicited (figure 1*c*). Administration of b-APs at 1–3 Hz alone does not produce LTD, indicating that there is some need for coincident pre- and postsynaptic activity. This requirement may also be met by giving an intensity of synaptic stimulation sufficient to elicit APs (suprathreshold EPSPs). This procedure also elicits a robust LTD that is indistinguishable from that observed with the pairing protocol (figure 1*d*).

The role of $[Ca^{2+}]_i$ in LTD comes from a variety of observations. First, LTD can be blocked by the intracellular injection of postsynaptic Ca^{2+} chelators (Mulkey & Malenka 1992). Second, the LTD from pairing sub-threshold EPSPs and APs is correlated with rises in $[Ca^{2+}]_i$ in the dendritic regions produced by the b-APs during the induction protocol (Christie *et al.* 1996*b*). Finally, LFS-induced LTD is also blocked by Ca^{2+} channel blockers and NMDA antagonists (Camodeca *et al.* 1998; Christie *et al.* 1996*a*,*b*, 1997; Dudek & Bear 1992; Mulkey & Malenka 1992; Mockett *et al.* 2002).

When similar pairings of sub-threshold EPSPs and b-APs were given over a wide range of frequencies (1–200 Hz), a transition from LTD to LTP was observed in the 10–30 Hz range (Schexnayder 1999; figure 2). The transition from LTD to LTP was also correlated with the rise in dendritic $[Ca^{2+}]$ (figure 3). Although higher concentrations of D,L-APV (50 μM) blocked the plasticity at all frequencies (figure 2), lower concentrations (10 μM), or the addition of the L-type Ca^{2+} channel blocker nimodipine to the bath, shifted the transition in the plasticity–stimulus frequency curve to higher frequencies so that in the range of 10–100 Hz, LTD was induced instead of LTP (Schexnayder 1999). These data again suggested a role for dendritic Ca^{2+} influx via b-APs in the induction of both LTD and LTP in CA1 neurons.

3. LONG-TERM POTENTIATION

Strong support for the importance of back-propagating APs and LTP induction was provided by a technically challenging set of experiments carried out by Jeff Magee (Magee & Johnston 1997). Dendritic recordings were made during synaptic stimulation alone, and when EPSPs were paired with b-APs. When the EPSPs and b-APs were paired, the amplitudes of the b-APs in the distal dendrites were boosted in a supralinear fashion, and LTP was induced. The key experiment in that study was the local and reversible application of TTX to the proximal apical dendrites during the LTP induction protocol. Such local application of TTX blocked the propagation of the b-APs from the soma to the site of the stimulated synapses. Although APs still occurred in the cell body and synaptic input was still elicited in the dendrites, the TTX prevented (disconnected?) the b-APs from reaching the synapses during the pairing paradigm. When the propagation of the APs into the dendrites was interrupted in this fashion, LTP induction was prevented. After a few minutes the local TTX washed away and an identical pairing of EPSPs and b-APs was given. The b-APs now fully propagated into the dendritic regions of the stimulated synaptic input (demonstrated by Ca^{2+} imaging), and LTP was induced. This experiment led to the conclusion that, at least for this type of LTP protocol in which small EPSPs are paired with postsynaptic APs, the back-propagation of the APs is required for the induction of LTP. Furthermore, the strict notion of Hebbian plasticity, in which APs in the postsynaptic neuron are critically important, received strong support from these results.

These experiments, however, also raised many other important questions about the nature of the mechanisms boosting the b-APs during the pairing protocol and whether the boosting was somehow necessary for the LTP induction. At approximately the same time as the Magee experiments, Dax Hoffman discovered a very high density

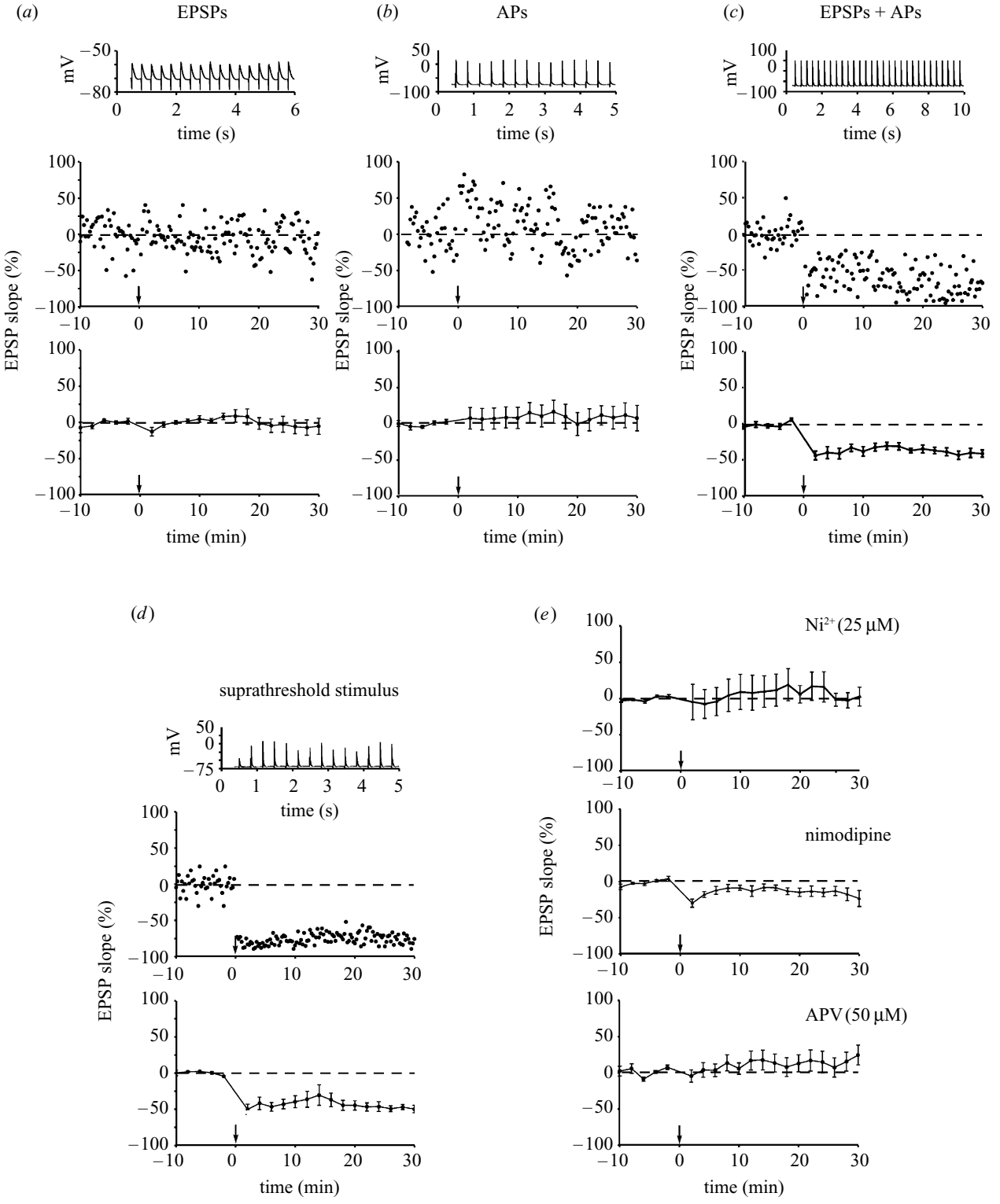

Figure 1. LTP by pairing Schaffer collateral EPSPs and APs in CA1 pyramidal neurons. (*a*) EPSPs, sub-threshold for AP generation, fail to induce LTD (3 Hz for 900 stimuli). The top trace in this and panels (*a–d*) is a portion of the stimulus train (EPSPs in this panel) recorded with a whole-cell pipette in the soma. The EPSP slope as a function of time for one experiment is shown in the middle trace, while the average for four experiments is given in the bottom trace. The arrow in this and all panels represents the time of the 3 Hz train. (*b*) Similar to (*a*) except that a 3 Hz (900 stimuli) train of postsynaptic APs was substituted for the EPSP train. The APs were triggered by 1–2 ms current pulses to the soma and back-propagated into the dendrites. (*c*) Similar to (*a*) and (*b*) except that the APs triggered by brief somatic current injections were paired with the EPSPs. LTD was induced in all experiments using this pairing protocol. (*d*) The intensity of Schaffer collateral stimulation was increased so that now the EPSPs triggered APs on their own without depolarizing current to the soma. The suprathreshold stimulus train also induced LTD in all experiments. (*e*) The protocol of sub-threshold EPSPs paired with postsynaptic APs shown in (*c*) was given with different pharmacological agents in the bath during the pairing protocol. For Ni^{2+}, $n = 5$; nimodipine, $n = 5$; and D,L-APV, $n = 6$. (From Christie *et al.* (1996*b*) and reprinted with permission from *Learning & Memory*. Copyright © 1996 Cold Spring Harbor Laboratory Press.)

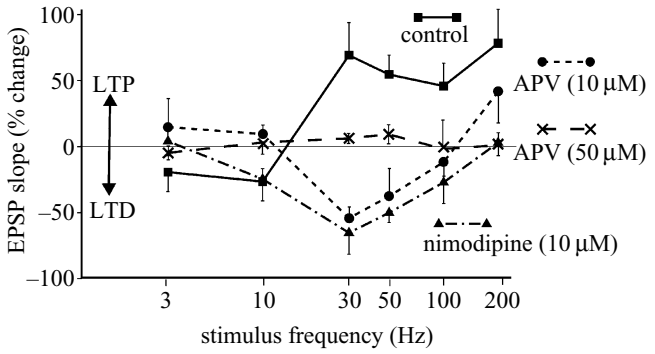

Figure 2. Changes in synaptic strength as a function of stimulus frequency. Sub-threshold EPSPs from Schaffer collateral stimulation were paired with APs triggered by brief somatic current injections (900 stimuli at each frequency, $n = 3$–7 for each point, similar protocol to that shown in figure 1*c*). Plasticity versus frequency curves were also obtained in low (filled circles; 10 μm) and high (crosses; 50 μm) APV (D,L) and in nimodipine (filled triangles; 10 μm). Although high APV blocked all plasticity, lower concentrations of APV and nimodipine shifted the transition frequency from LTD to LTP to higher frequencies. Control represented by filled squares. (Taken from Schexnayder (1999), with permission.)

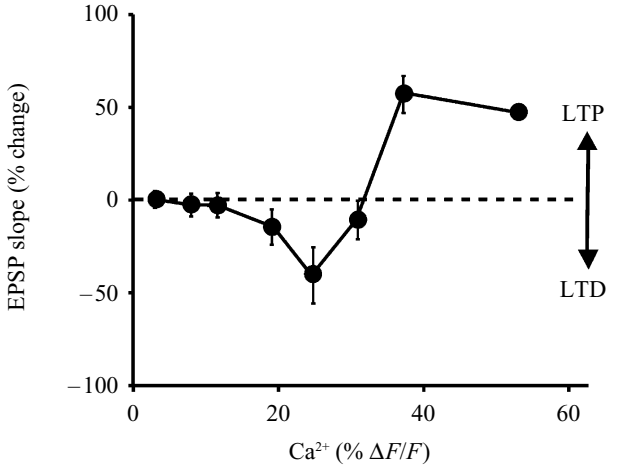

Figure 3. Relationship between synaptic plasticity and postsynaptic Ca^{2+} (measured in apical dendrites) for the experiments performed in control saline shown in figure 2. Ca^{2+} was measured with a high-speed, cooled CCD camera by using similar methods to those described in Christie *et al.* (1996*b*). (Taken from Schexnayder (1999), with permission.)

of transient, A-type K^+ channels in the distal dendrites of CA1 pyramidal neurons (Hoffman *et al.* 1997). These channels prevented the b-AP from reaching full amplitude, and suggested the hypothesis that EPSPs in dendrites could inactivate the K^+ channels, allowing b-APs occurring within *ca.* 10–15 ms following the peak of the EPSP to be boosted or increased in amplitude. The boosted b-APs could then be an effective depolarization to unblock NMDA receptors, increase the Ca^{2+} influx through voltage-gated Ca^{2+} channels, and induce LTP at the activated synapses. The theoretical basis for this hypothesis was explored in several modelling studies (Migliore *et al.* 1999; Johnston *et al.* 2000).

4. REGULATION OF DENDRITIC K^+ CHANNELS

Because the high density of A-type K^+ channels in CA1 dendrites appeared to have such a strong influence on the amplitude of b-APs, synaptic potentials, and dendritic electrical signals in general, it was of some interest to explore the regulation of these channels by neuromodulatory neurotransmitters and second messenger systems. Activation of PKA and PKC was found to shift the activation curve of the K^+ channels to more positive potentials, thereby reducing their probability of opening (Hoffman & Johnston 1998). The result of this modulation was to decrease the activity of the channels and thus to increase the amplitude of b-APs (Hoffman & Johnston 1999; Johnston *et al.* 1999). Although the molecular subunit comprising the dendritic, A-type K^+ channels is not known with certainty, there is good evidence for the involvement of Kv4.2 (Sheng *et al.* 1992; Maletic-Savatic *et al.* 1995; Serodio & Rudy 1998; Ramakers & Storm 2002). Phosphorylation sites on Kv4.2 have been identified for PKA, PKC, Ca^{2+}-calmodulin-dependent protein kinase II and MAPK (Adams *et al.* 2000; Anderson *et al.* 2000), and the phosphorylation of Kv4.2 by MAPK is regulated by both PKA and PKC (Yuan *et al.* 2002). We recently tested whether the downregulation of the dendritic, A-type K^+ channels by PKA and PKC was acting through MAPK and found that the increase in b-AP amplitude by either PKA or PKC was blocked by MAPK inhibitors in a similar manner to that shown for Kv4.2 (Yuan *et al.* 2002). These results provide further support for the role of Kv4.2 in the native K^+ current, but also highlight the complex manner in which signal transduction pathways interact to regulate dendritic channels (Schrader *et al.* 2002).

5. CHANGES IN DENDRITIC SIGNALLING DURING THE EXPRESSION OF LONG-TERM POTENTIATION

It is well known that several protein kinases are activated either transiently or persistently with the induction of LTP (Roberson *et al.* 1996). Because A-type K^+ channels in the dendrites are modulated by many of these same protein kinases, we tested whether a change in K^+ channel function could be detected locally in the dendrites after LTP induction. One consequence of a decrease in K^+ channel activity would be an increase in b-AP amplitude. In previous experiments we have shown that Ca^{2+} signals from b-APs in the dendrites are very good indicators of AP amplitude (Jaffe *et al.* 1992; Miyakawa *et al.* 1992; Magee & Johnston 1997; Magee *et al.* 1998). We therefore measured the amplitude of Ca^{2+} signals from b-APs before and after inducing LTP (using a similar protocol of pairing sub-threshold EPSPs with somatically triggered APs, at 100 Hz, as described in figures 1–3). The results were consistent with the hypothesis of a decrease in K^+ channel activity during the early expression phase of LTP. We found that the Ca^{2+} signals from b-APs were increased within the region of the dendrites (± 25 μm) where the synapses were stimulated (figure 4) (Schexnayder 1999).

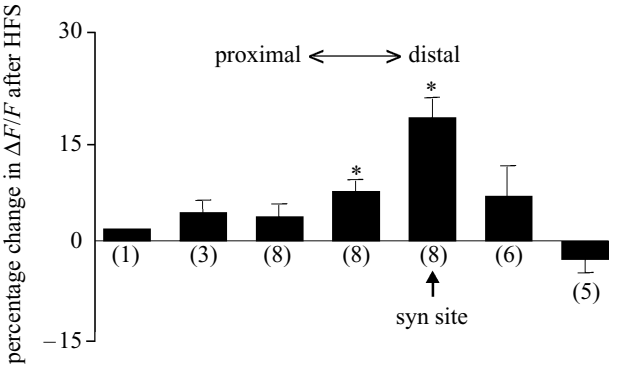

Figure 4. Changes in dendritic Ca^{2+} signals after LTP induction. The histograms represent percentage change in $\Delta F/F \pm$ s.e.m. for adjacent 25 μm segments of the dendrite before, and 5 min after, inducing LTP with a 100 Hz pairing regime (see text). The segment of the dendrite corresponding to the location of the synapse (as determined from measurements of sub-threshold Ca^{2+} signals; see Magee *et al.* 1995) is marked with an arrow (syn site). The Ca^{2+} signals resulted from a train of 5 b-APs at 20 Hz triggered by brief current injections via a whole-cell patch pipette on the soma. The distances were normalized with respect to the location of the activated synapses, and the percentage change was averaged over all experiments for each region. Significant changes are marked with an asterisk, and the number of observations is shown in parentheses. (Taken from Schexnayder (1999), with permission.)

6. K^+ CHANNELS AND INDUCTION OF LONG-TERM POTENTIATION

We investigated the role of A-type K^+ channels in LTP induction at Schaffer collateral synapses by using a theta-burst pairing (TBP) protocol (see also Hoffman *et al.* 2002). The protocol was similar to that used by Magee & Johnston (1997) and described above, except that we chose the minimum number of b-APs that would elicit reliable LTP (figure 5; Watanabe *et al.* 2002). With two b-APs timed to coincide with the last two EPSPs in the train, LTP was induced. When the EPSPs and the b-APs were unpaired, however, no plasticity was observed. Furthermore, when the pairing protocol was changed so that the b-APs were delayed by 10 ms and only one b-AP was paired with an EPSP, LTP was significantly reduced. Recordings of these b-APs in the dendrites indicated that when the two b-APs were paired with the EPSPs, they were both boosted in amplitude, as seen previously by Magee & Johnston (1997), but when shifted by 10 ms, only one b-AP was increased in amplitude.

The results of this experiment, that is, that b-APs are boosted in amplitude when they are paired with EPSPs, were in keeping with the hypothesis previously mentioned, that inactivation of dendritic K^+ channels by the EPSPs would allow b-APs to propagate at increased amplitude. The results, however, also suggested that the boosting of b-AP amplitudes was essential for LTP induction. We further tested the proposed role of the K^+ channels by taking advantage of the finding that MAPK inhibitors shift the activation curve for A-type K^+ channels in the hyperpolarized direction and thereby increase their probability of opening (Watanabe *et al.* 2002). We found that the MAPK inhibitor U0126 decreased the amplitude of b-APs, decreased the boosting of b-APs during the TBP protocol, and decreased LTP induction. Although the MAPK inhibitor could be having multiple effects on channels and other signal transduction pathways, we did find that we could overcome the block of LTP by increasing the number of APs given during the TBP paradigm. The results are consistent with the hypothesis that the A-type K^+ channels in dendrites regulate the induction of LTP under certain conditions.

7. DISCUSSION

Given the numerous types of voltage-gated channel in dendrites, important questions exist concerning the function of these channels in regulating synaptic integration and synaptic plasticity. The b-AP is an attractive candidate for providing a feedback signal from the cell body to the synaptic regions of the dendrites to show that an output of the neuron has occurred. Such a feedback signal may be an important enabler for LTP and LTD induction at active synapses and in certain dendritic branches, although b-APs are certainly not required for LTP/LTD induction under all conditions (e.g. Brown *et al.* 1990). The Ca^{2+} influx that accompanies the b-APs, and which occurs during the LTP induction protocols, may also regulate the expression and/or modulation of dendritic ion channels. Such mechanisms (e.g. figure 4) may play a role in so-called E-S potentiation where changes in the excitability of postsynaptic neurons have been shown to accompany LTP of the synaptic response (Chavez-Noriega *et al.* 1990).

In this report we have presented some of the experiments involving b-APs and LTD and LTP induction in CA1 pyramidal neurons. These experiments have demonstrated:

(i) a strong correlation between b-APs and the induction of several forms of synaptic plasticity;
(ii) that the amplitude of b-APs in the dendrites is an important variable for LTP induction;
(iii) that A-type K^+ channels in dendrites are highly regulated by several types of protein kinases and membrane potential;
(iv) that the induction of LTP using a TBP protocol depends on the activation/inactivation state of these K^+ channels;
(v) that the timing of pre- and postsynaptic events is critical for the induction of LTP and that this timing is determined in part by dendritic K^+ channels; and
(vi) that after the induction of LTP there are changes in the excitability of the dendrites in the vicinity of the activated synapses.

Several previous studies have shown that the induction of LTD/LTP depends on the relative timing of pre- and postsynaptic APs (Bi & Poo 1998, 2001; Markram *et al.* 1997; Debanne *et al.* 1998; Feldman 2000). The b-AP, and the boosting of the b-AP, may be an important mechanism in those studies as well, although there are clearly mechanisms other than dendritic K^+ channels that may be involved. For example, Stuart & Hausser (2001) have shown that the pairing of EPSPs and b-APs in neocortical pyramidal neurons boosts b-AP amplitude through an increased activation of Na^+ channels rather than the

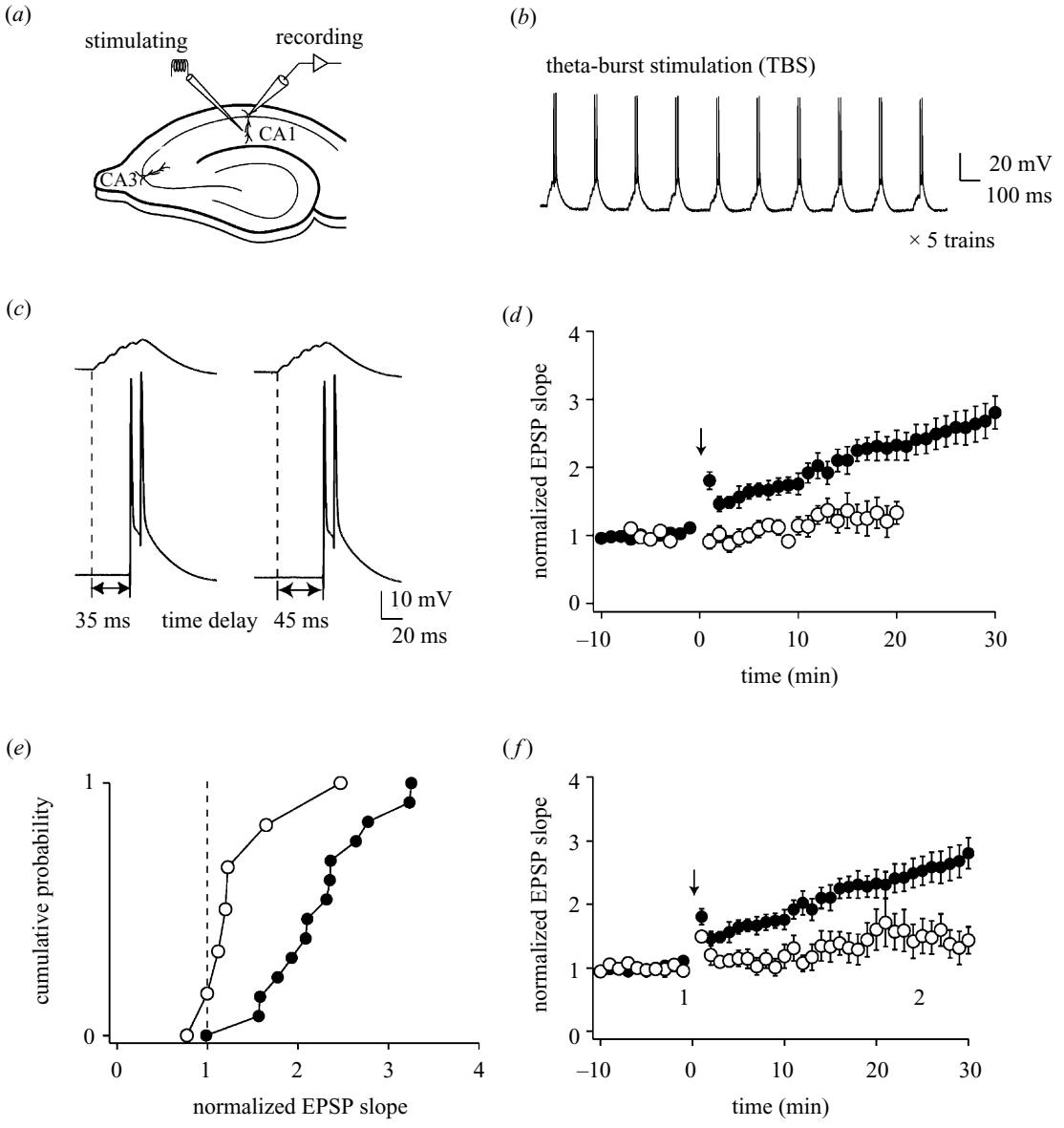

Figure 5. LTP induction by pairing sub-threshold EPSPs and postsynaptic APs in a theta-burst pattern. (*a*) Schematic of a hippocampal slice showing stimulating and recording sites. (*b*) A sample of the TBP protocol. (*c*) Representative traces of sub-threshold EPSPs and b-APs at two different time delays. (*d*) Time-course and magnitude of the test EPSP before and after the TBP (filled circles) procedure (arrow) for the 35 ms delay and for similar but unpaired (open circles) stimulation. (*e*) Cumulative probability plots (rank ordering of magnitude changes) for all experiments for TBP at 35 ms (filled circles) and 45 ms (open circles) delays. (*f*) Summary for all the experiments (35 ms, filled circles; 45 ms, open circles). (Taken from Watanabe *et al.* (2002), with permission.)

decreased activity of K^+ channels, as proposed here. Furthermore, in the most distal dendritic regions of CA1 neurons, in stratum lacunosum-moleculare, the local initiation of a dendritic AP by synaptic input rather than a b-AP propagated from the cell soma appears to be critical for LTP induction (Golding *et al.* 2002). Nevertheless, for Schaffer collateral synapses in the middle region of CA1 pyramidal neuron dendrites (stratum radiatum) from adult animals, a role for A-type K^+ channels in the induction and expression of LTP is well supported by several different types of experiment (see Ramakers & Storm 2002). Clearly, however, much more work is needed before the role of active dendrites in the induction and expression of synaptic plasticity is fully understood.

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GLOSSARY

AP: action potential
b-AP: back-propagating action potential
EPSP: excitatory postsynaptic potential
LFS: low-frequency stimulation
LTD: long-term depression
LTP: long-term potentiation
MAPK: mitogen-activated protein kinase
NMDA: *N*-methyl-D-aspartate
PKA: cAMP-dependent protein kinase
PKC: protein kinase C
TTX: tetrodotoxin