Review

Long-Term Plasticity of Intrinsic Excitability: Learning Rules and Mechanisms

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Spatio-temporal configurations of distributed activity in the brain is thought to contribute to the coding of neuronal information and synaptic contacts between nerve cells could play a central role in the formation of privileged pathways of activity. Synaptic plasticity is not the exclusive mode of regulation of information processing in the brain, and persistent regulations of ionic conductances in some specialized neuronal areas such as the dendrites, the cell body, and the axon could also modulate, in the long-term, the propagation of neuronal information. Persistent changes in intrinsic excitability have been reported in several brain areas in which activity is elevated during a classical conditioning. The role of synaptic activity seems to be a determinant in the induction, but the learning rules and the underlying mechanisms remain to be defined. We discuss here the role of synaptic activity in the induction of intrinsic plasticity in cortical, hippocampal, and cerebellar neurons. Activation of glutamate receptors initiates a long-term modification in neuronal excitability that may represent a parallel, synergistic substrate for learning and memory. Similar to synaptic plasticity, long-lasting intrinsic plasticity appears to be bidirectional and to express a certain level of input or cell specificity. These nonsynaptic forms of plasticity affect the signal propagation in the axon, the dendrites, and the soma. They not only share common learning rules and induction pathways with the better-known synaptic plasticity such as NMDA receptor dependent LTP and LTD, but also contribute in synergy with these synaptic changes to the formation of a coherent engram.

What Are the Cellular Learning Rules?

The most remarkable feature of the brain is its capacity to collect new information from the environment and to store it in order to produce changes in the behavior. Over the last decades, the aim of most neuroscientists in the field of brain plasticity has been to establish learning rules that could account for this storage at the cellular level. 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 active simultaneously. This learning rule has been verified and extended over the last two decades (for review, see Sourdet and Debanne 1999; Abbott and Nelson 2000; Bi and Poo 2001; Sjöström and Nelson 2002). One of the goals of this review is to discuss whether the learning rules and inductions mechanisms defined for synaptic plasticity also apply to other forms of plasticity that affect ion channels in nonsynaptic structures of the neuron.

Synaptic and Nonsynaptic Plasticity

The synapse is the anatomical and functional interface between individual nerve cells, and thus occupies a strategic position. It is generally considered as a privileged element involved in short- or long-term modifications of the transmission of neuronal message in the brain. The efficacy of synaptic transmission is highly regulated by network activity. These modifications may occur rapidly, within a few seconds to minutes, but may last from minutes to hours. The large number of presynaptic boutons that contact a single neuron offers a wide range of functional diversity, but also insures spatial specificity of the modified input. It has been shown that modifications of the probability of transmitter release at the presynaptic site are involved in some types of long-term plasticity of synaptic strength. The best example of long-lasting modification of this type is long-term potentiation (LTP) of the mossy fiber synapse in the area CA3 of the hippocampus (Zalutsky and Nicoll 1990). This LTP does not result from the activation of NMDA receptors (NMDAR) and is thought to be initiated by a rise in presynaptic calcium (Castillo et al. 1994; but see Yeckel et al. 1999 for data supporting a postsynaptic calcium rise).

Changes in synaptic transmission may also occur postsynaptically. The well-known NMDAR-dependent LTP and long-term depression (LTD) in the area CA1 represent two forms of activity-dependent plasticity that are mediated in part by changes in the number or properties of postsynaptic AMPA receptors. One feature of Schaffer collateral-CA1 cell synapses in the adult rat is that 20% of the synapses express only functional NMDAR. This ratio is much larger in younger animals. Prior to LTP induction, afferent stimulation does not evoke any postsynaptic response at the resting membrane potential. Following induction of LTP, these silent synapses become functionally active, probably because of the de novo insertion of AMPA receptors by exocytosis (for review, see Malinow and Malenka 2002). Recent investigations indicate that mirror modifications (i.e., endocytosis of AMPA receptors) might account for the expression of LTD (for review, see Carroll et al. 2001). However, at the Schaffer collateral-CA1 synapse, changes in presynaptic glutamate release may also underlie LTP and LTD (Emptage et al. 2003; Stanton et al. 2003). Finally, LTP promotes formation of new dendritic spines (Engert and Bonhoeffer 1999) or multiple spine synapses between a single axon terminal and a dendrite (Toni et al. 1999).

Whereas LTP and LTD are computationally appealing (in part because of synapse-specific changes among a large array of inputs), there are also reasons to believe that they are not the

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whole story. The synapse cannot be considered as the only neuronal element that contributes efficiently to the filtering of the neuronal message in the network on a long-term scale. In the following sections, we will briefly review the literature showing that neuronal activity persistently regulates voltage- or calcium-dependent ion channels. Any modifications in the properties and/or number of these ion channels may affect the propagation of neuronal activity.

Historically, the postulate that modifications in intrinsic excitability could underlie the formation of functional neuronal assemblies, and may thus contribute to a specific memory trace has its origin in invertebrate neural systems. The first evidence came from the pioneering work of D. Alkon who showed that phototaxic learning in a marine mollusk involved the regulation of A-type K^+ (Alkon et al. 1982) and Ca^{2+} currents (Alkon 1984). Later, J. Byrne and colleagues (Scholz and Byrne 1987) showed that several forms of learning in *Aplysia* (sensitization and operant conditioning) are associated with persistent changes in neuronal excitability (Cleary et al. 1998; Brembs et al. 2002). Then, E. Marder and colleagues in the early nineties, showed that network activity in the stomatogastric system of crustaceans could regulate ion channels (for review, see Le Masson et al. 1993; Turrigiano et al. 1994; Golowasch et al. 1999). Interest in the intrinsic excitability of mammalian neurons was for a long time occluded by the challenge of dissecting the mechanisms that determine the induction and expression of LTP and LTD. Recently, a new interest has flourished in the study of the induction and expression mechanisms underlying the plasticity of intrinsic excitability in the mammalian brain (see Table 1; Spitzer 1999).

Neuronal Excitability, Ionic Channels, and Input–Output Function

Neuronal excitability is determined by the properties and distribution of ion channels in the plasma membrane. Excitability can be defined as a propensity of the neuron to generate, beyond a certain threshold, an output signal—the action potential (AP)—from a given input signal (usually an excitatory postsynaptic potential, EPSP). At the mechanistic level, this process requires the opening of voltage-gated ion channels located in the neuronal membrane when an excitatory synapse is activated. The operation of coupling between the EPSP and the AP is essential for the neuron, as it couples its input to its output. Although this concept is rather simple, the input–output function of the neuron involves complex operations and significant shaping of the EPSP by ion channels located in the dendritic, somatic, and axonal compartments. The locus of neuronal excitability cannot be restricted to the axon hillock, in which the action potential is initiated as processes relevant to neuronal excitability have already been brought into play at the level of the dendritic spine. In fact, the use of patch-clamp recordings and/or imaging techniques have identified voltage-gated Ca^{2+}, Na^+, and K^+ channels in dendritic spines (for review, see Nimchinsky et al. 2002) and dendritic shafts of hippocampal and neocortical pyramidal neurons (for a recent review, see Reyes 2002). Functionally, all of these channels, located in the membrane of the dendritic spine or shaft and the cell body, play a crucial role. They either amplify (persistent sodium current and T-type calcium channels) or attenuate (A-type K^+ current and H-type cationic current) the EPSP amplitude (Reyes 2002). Consequently, these operations, achieved by ion channels, affect the input–output function of the neuron. It

Table 1. Long-Term Plasticity of Intrinsic Excitability

Brain area	Induction	Excitability	References
NMDAR dependent intrinsic plasticity			
Hippocampus (DG)	HFS	+	Bliss et al. (1973)
Hippocampus (CA1)	HFS	+	Andersen et al. (1980) Hess and Gustafson (1990) Chavez-Noriega et al. (1990)
Cerebellum (DCN)	HFS	+	Aizenmann and Linden (2000)
Cerebellum (granule cell)	HFS	+	Amano et al. (2000)
Hippocampus (CA1)	Pairing	+	Jester et al. (1995)
Hippocampus (slice)	HFS	+ (presyn.)	McNaughton et al. (1994)
Hippocampus (culture)	Paining	+ (presyn.)	Ganguly et al. (2000)
Hippocampus (CA1)	HFS/LFS	+/−	Daoudal et al. (2002)
Hippocampus (CA1)	STDP	+/−	Wang et al. (2003)
mGluR-dependent Intrinsic plasticity			
Hippocampus (CA1)	ACPD	+	Cohen et al. (1999)
Hippocampus	DHPG	+	Ireland and Abraham (2002)
Cortex (L5)	10 Hz., ACPD/CHPG	+	Sourdet et al. (2003)
Kainate R-dependent intrinsic plasticity			
Hippocampus CA1	KA	+	Melyan et al. (2002)
Glutamate receptor-independent intrinsic plasticity			
Hippocampus	Postsyn. Depol. Ca^{2+}	+ (back-propag.)	Tsubokawa et al. (2000)
Cerebellum (DCN)	Postsyn. Depol. Ca^{2+}	+	Aizenmann and Linden (2000)
Cortex (culture)	Postsyn. Depot	+	Cudmore et al. (2001)
Entorhinal cortex	Postsyn. depol./hyperpol.	+/−	Egorov et al. (2002)
Compensatory Intrinsic plasticity			
Cortex (culture)	TTX (48 h)	+	Desai et al. (1999a)
Visually driven intrinsic plasticity			
Optic tectum (Xenopus)	Visual stimulation	+	Aizenman et al. (2003)

HFS, high-frequency stimulation; LFS, low-frequency stimulation; STDP, spike timing-dependent plasticity; KA, kainate; Bic, bicuculline; TTX, tetrodotoxin.

is therefore reasonable to assume that any long-lasting modifications of their properties or their density will affect the neuronal output. In particular, regulation of ion channel properties near the synapse (i.e., the bouton and the spine) might have powerful consequences on the spread of neuronal information.

Plasticity of Intrinsic Excitability: A Cellular Correlate of Learning?

What is the evidence for the implication of intrinsic excitability in learning and memory? Several studies with invertebrates point to a role of K^+ channel modulation in these processes. For instance, classical conditioning of the phototaxic response of the marine mollusk *Hermissenda crassicornis* correlates with a second messenger-induced reduction of K^+ currents in photoreceptor cells (Alkon 1984). In *Drosophila melanogaster*, several mutations of K^+ channel genes lead to impaired associative learning. A *Shaker* mutation that alters the fast-inactivating K^+ current reduces olfactory conditioning performances (Cowan and Siegel 1986), and a mutation of the *eag* K^+ channel gene leads to deficits in courtship conditioning (Griffith et al. 1994). It is important to note that the first *Drosophila*-learning mutants described, *dunce* and *rutabaga*, have alterations in K^+ currents (Zhao and Wu 1997) that may contribute to the learning impairments. All of these cellular correlates of learning are associated with an increase in neuronal excitability. Interestingly, bidirectional changes in excitability are induced concomitantly with sensitization and habituation in the leech (Burrell et al. 2001).

In the mammalian brain, the search for cellular excitability correlates of learning and memory has focused on neurons that are specifically active during learning. Eye-blink conditioning in the cat or the rabbit is well documented in this respect, as it involves specific circuits in the cerebellum and hippocampus that have been thoroughly characterized. In conditioned animals, neurons that are active during the conditioning exhibit an excitability that is significantly higher than that of neurons recorded from naive or pseudo-conditioned animals. Cortical, hippocampal, and cerebellar neurons of conditioned mammals display an increased intrinsic excitability at the somatic (Disterhoft et al. 1986; Coulter et al. 1989; Aou et al. 1992; Moyer et al. 1996; Saar et al. 1998) or dendritic level (Schreurs et al. 1997; Quirk et al. 2001). In several cases, the after-hyperpolarizing (AHP) current was found to be depressed. These observations therefore suggest that the memory trace could be not only supported by selective changes in synaptic strength, but that modifications in neuronal excitability might contribute to the cellular substrate of the memory trace in the brain. However, this conclusion must be qualified, because in hippocampal and cortical neurons, increased neuronal excitability is no longer detectable 8 d after conditioning, although learning is still established (Moyer et al. 1996; Saar et al. 1998). Thus, an alternative and possibly complementary view is that this persistent increase in excitability allows or facilitates modifications of synaptic strength in a defined time window following the training. This mechanism may represent a substrate for the dynamic control of synaptic plasticity (i.e., metaplasticity; Abraham and Bear 1996).

These in vivo experiments suggest that synaptic or propagated activity during training may play a role in the induction of intrinsic plasticity. However, several important questions that cannot be satisfactorily addressed in the in vivo preparation remained to be explored. Do specific regimes of synaptic activity also induce long-term plasticity of intrinsic excitability? Is it rapidly induced? Can intrinsic plasticity be reversed by a specific pattern of activity? Is there a functional synergy between synaptic and intrinsic plasticity? Some of these questions have been addressed with the use of in vitro preparations of brain tissue, in which synaptic activity and membrane potential are accurately controlled and the synaptic and voltage-gated currents can be pharmacologically isolated. Because network activity is implicated in the induction of intrinsic plasticity, synaptic receptors are potential candidates in this process. Among glutamate receptors, NMDAR, mGluR, and Kainate receptors play a central role in the induction of functional and synaptic plasticity. Interestingly, all of them are also principal actors in the induction of long-lasting modifications in neuronal excitability at the postsynaptic site.

EPSP-Spike Plasticity

It is well established today that NMDAR is a molecular detector of the coincidence of two neuronal events (i.e., the presynaptic release of glutamate and a postsynaptic depolarization) at the origin of LTP and LTD induction (Sourdet and Debanne 1999). However, its role is not limited to this side of functional plasticity, and several lines of evidence indicate that NMDAR also contributes to the induction of long-lasting plasticity of neuronal excitability in hippocampal, neocortical, and cerebellar neurons. In most cases, this was shown to occur when a synaptic pathway was tetanized. One of the best-illustrated examples of this plasticity is the increase in the probability that an EPSP will elicit an action potential (EPSP-Spike plasticity or E-S plasticity). This plasticity appears to be of fundamental importance, because it directly affects the input–output function of the neuron.

E–S Potentiation in the Hippocampus

In the dentate gyrus, homosynaptic LTP of excitatory synaptic transmission is induced by high-frequency stimulation (HFS, 100 Hz) of the afferent fibers (Bliss and Lomo 1973). In parallel, the probability of discharge of the postsynaptic neurons to a given excitatory synaptic input is enhanced (Bliss et al. 1973; Fig. 1A). This second component has been called EPSP-to-Spike potentiation (E-S potentiation), which is complementary to LTP and functionally important. E-S potentiation was also found at the Schaffer collateral-CA1 cell synapse when the afferent fibers were tetanized (Andersen et al. 1980; Abraham et al. 1987; Chavez-Noriega et al. 1990), and may be induced associatively with coincident activation of a synaptic input and antidromic APs (Jester et al. 1995). Although this protocol has not been replicated so far at the level of single CA1 pyramidal neurons, recent data indicate that associative LTP in CA1 pyramidal cells is associated with a persistent facilitation of the dendritic summation of subthreshold EPSPs (Wang et al. 2003). The underlying mechanisms could be common to those responsible for E-S potentiation. As for LTP, E-S potentiation requires the activation of NMDAR for its induction (Jester et al. 1995; Daoudal et al. 2002; Wang et al. 2003). Therefore, it is expected that the two forms of plasticity share common induction pathways.

EPSP-spike coupling is strongly determined by inhibitory synaptic transmission, but contradictory conclusions have been drawn regarding the contribution of $GABA_A$ receptor-mediated inhibition to hippocampal E-S potentiation. Early studies argued that E-S potentiation was fully abolished by the $GABA_A$ channel blocker picrotoxin (Abraham et al. 1987; Chavez-Noriega et al. 1989; Tomasulo and Ramirez 1993), whereas others reported a picrotoxin-resistant E-S component (Asztely and Gustafsson 1994; Jester et al. 1995; Daoudal et al. 2002). These later results suggested that, in addition to an imbalance between excitation and inhibition (Lu et al. 2000), intrinsic changes in excitability might have also been induced (Taube and Schartzkroin 1988). This last component was evaluated as ~40% of the total E-S potentiation (Daoudal et al. 2002; Fig. 1A), indicating that in control conditions, a substantial fraction of E-S potentiation is mediated by modifications of intrinsic excitability. This component

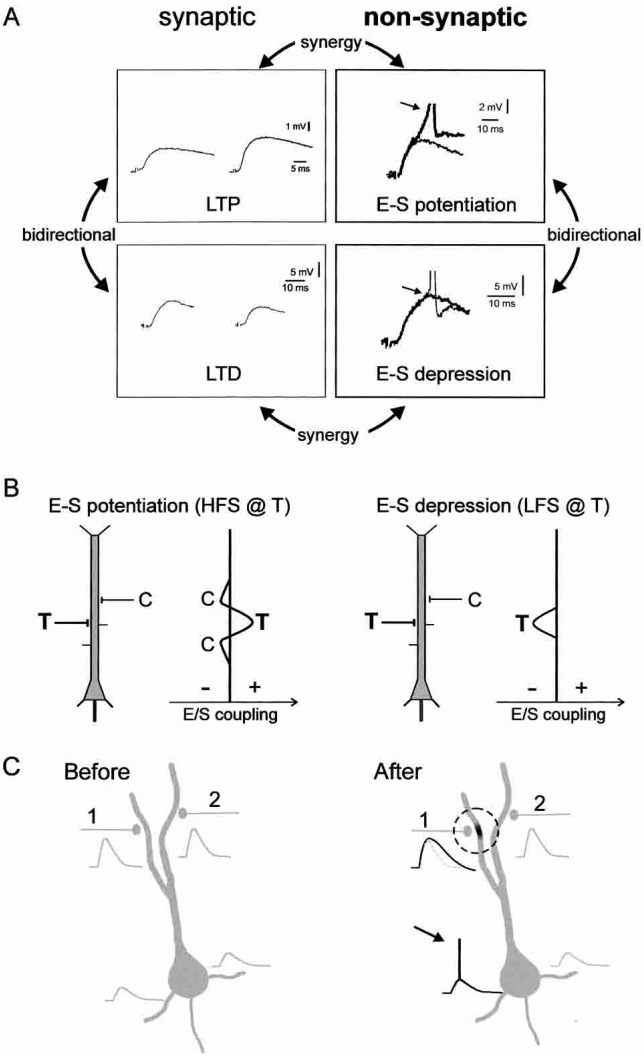

Figure 1 Properties of the $GABA_A$ receptor-independent E-S plasticity in the area CA1. (*A*) E-S potentiation is induced concomitantly to LTP, whereas E-S depression accompanies LTD (adapted from Daoudal et al. 2002). For a given EPSP slope, the probability to generate an action potential (arrow) is enhanced after LTP induction (thick trace, E-S potentiation). Conversely, the firing probability is lowered after low-frequency stimulation (E-S depression). Synaptic plasticity (LTP/LTD) and nonsynaptic plasticity (E-S potentiation/E-S depression) are functionally synergistic. Both synaptic and nonsynaptic plasticity are bidirectional. (*B*) Input specificity of E-S potentiation (adapted from Daoudal et al. 2002). (*Left*) E-S potentiation is observed at the stimulated input (T) and heterosynaptic E-S depression is observed at the control input (C). (*Right*) E-S depression is induced at the stimulated input (T), but not at the control input (C). (*C*) Hypothetical mechanism of selective EPSP-spike potentiation. Two synaptic inputs (1,2) converge on different dendrites of a CA1 pyramidal neuron. In control conditions (*left*), none of the EPSPs is able to generate a spike at the cell body. LTP is induced at input 1. Membrane excitability symbolized by the black area is locally increased in the *left* dendritic branch (broken circle). The EPSP resulting from a synaptic current equivalent to the control current is now prolonged (adapted from Wang et al. 2003; G. Daoudal and D. Debanne, unpubl.). At the soma, this longer EPSP gives rise to an AP (EPSP-spike potentiation), but the EPSP-spike coupling remains unchanged for the other pathway.

also requires NMDAR activation and is input specific, indicating that the modifications in excitability could be restricted to a given dendritic area (Jester et al. 1995; Daoudal et al. 2002). Although this concept seems, at first glance, in contradiction with the classical view of an axonal location for spike initiation, theoretical studies show that input specificity of E-S potentiation is possible when inputs are spatially segregated on different dendritic branches (Wathey et al. 1992). We reported that E-S potentiation was consistently associated with heterosynaptic E-S depression that could further enhance the input specificity (Daoudal et al. 2002; Fig. 1B). It may result from a nonspecific decrease in excitability of the surrounding dendritic membrane (Fricker and Johnston 2001), but its characterization (spatial spread, mechanisms) will require further studies. Interestingly, the enhanced summation of EPSPs accompanying associative LTP has been shown to be also input specific (Wang et al. 2003). Thus, potentiation of neuronal excitability not only shares a common induction pathway with LTP, but also respects the input specificity conferred by synaptic efficacy. In contrast to other forms of intrinsic plasticity (see in this section 'Plasticity of neuronal excitability in the cerebellum' and 'Long-lasting reduction of AHPs'), the induced change in E-S coupling is not generalized to other synaptic inputs (Fig. 1C). What is the precise degree of input specificity? This question has not yet been fully addressed and would require detailed analysis with a systematic exploration of the spatial spread of E-S plasticity. However, recent results indicate that long-term facilitation in EPSP summation may occur between a potentiated input and a control input separated by ~50 µm, but not when the two inputs are more distant (Wang et al. 2003). These data suggest that input specificity for both synaptic strength and membrane excitability might break down at short distances (Engert and Bonhoeffer 1997).

The expression mechanisms of picrotoxin-resistant E-S potentiation have not been established definitively, although a prolongation of the rising phase of the dendritic EPSP is observed (Hess and Gustafsson 1990; Wang et al. 2003; G. Daoudal and D. Debanne, unpubl.; Fig. 1C). This modification of the EPSP waveform is not mediated by NMDA receptors, but can be replicated by blockade of A-type K^+ channels (Hess and Gustafsson 1990), suggesting that mechanisms that boost the EPSP may be modified. Long-lasting down-regulation of I_h channels and the up-regulation of NMDA receptors is thought to be involved in the expression of the enhanced summation of dendritic EPSPs (Wang et al. 2003). It will be of great importance to determine whether I_h also contributes to the expression of E-S potentiation, and to elucidate the precise role of the NMDA receptor-mediated component. Further investigations will be needed to evaluate the role of protein kinases that are major actors in the induction of LTP as CaMKII and PKC on the I_h current (Cathala and Paupardin-Tristch 1997).

Is There E–S Depression in the Hippocampus?

It is well established today that the reversal of LTP preserves a potential for network plasticity and increases the capacity of memory storage (Wilshaw and Dayan 1990). Long-term synaptic plasticity is bidirectional in the area CA1, and thus, the reversal of E-S potentiation appears of major importance. Again, for the same theoretical considerations, E-S depression and depotentiation might be important to avoid saturation of the system and to increase memory capacity. We have shown recently that synaptic depression is associated with an NMDA receptor-dependent and long-lasting depression of E-S coupling (Daoudal et al. 2002; Fig. 1A). E-S depression is expressed in the presence of $GABA_A$ and $GABA_B$ receptor antagonists. Approximately 40% of E-S depression is still observed in the presence of a $GABA_A$ channel blocker (Daoudal et al. 2002). In single neurons, this GABA-receptor independent E-S depression is observed without modification of postsynaptic passive properties. In addition, it may reverse E-S potentiation by protocols that induce glutamatergic LTD. This GABA receptor-independent component of E-S depotentiation requires the activation of NMDA receptors and is also input spe-

cific (Daoudal et al. 2002), suggesting again that modifications in membrane excitability might be circumscribed within a restricted dendritic area. As with E-S plasticity, the changes in synaptic integration accompanying associative LTP and LTD are also bidirectional and synergistic to the synaptic changes (Wang et al. 2003). However, the input specificity and expression mechanisms of the decrease in dendritic integration associated with LTD have not been yet established.

Homosynaptic LTD and depotentiation in the area CA1 requires NMDAR activation. E-S depotentiation was not induced under NMDAR blockade, suggesting a common induction pathway between synaptic and E-S depotentiation. Calcium entry through NMDAR could therefore represent the first induction signal. Further studies will be required to identify the nature of the ionic conductances that support long-term regulation of dendritic excitability, although those shaping the EPSP (A-type K^+, persistent Na^+, H-type cationic, …) are possible candidates.

Short–Term E–S Plasticity

Very recently, short-term plasticity of E-S coupling has been investigated in several brain areas. Paired-pulse facilitation of the Schaffer collateral-CA1 cell synapse has been found to be associated with a paired-pulse depression of the E-S coupling (Marder and Buonomano 2003). In this short-term E-S depression, the dynamic balance between excitatory and inhibitory transmission was found to be determinantal. However, the role of currents as Ca^{2+}-dependent K^+ channels or voltage-gated K^+ channels that could determine short-term intrinsic plasticity has not been evaluated in this study. In the striatum, paired-pulse synaptic stimulation enhances the E-S coupling (Mahon et al. 2003). This potentiation results from the inactivation of a I_A-like conductance that decreases the spike threshold, allowing firing on subsequent EPSPs.

Plasticity of Neuronal Excitability in the Cerebellum

The cerebellum is a structure in which several examples of activity-dependent plasticity of synaptic strength and intrinsic excitability have been reported (Hansel et al. 2001). As mentioned above, increased neuronal excitability has been observed in the dendrites of Purkinje cells of eye-blink conditioned rabbits (Schreurs et al. 1997). In vitro, the tetanization of glutamatergic inputs from mossy fibers reveals an increase in intrinsic excitability of deep cerebellar nuclei (DCN) neurons (Aizenman and Linden 2000) and granule cells (Armano et al. 2000). In both cases, the activation of NMDAR was found to be required for its induction. However, long-term changes in intrinsic excitability can be induced solely by repeated postsynaptic depolarizations in DCN neurons; the effect is dependent on an elevation of postsynaptic calcium concentration (Aizenman and Linden 2000). It is interesting to note that in granule cells, LTP can be induced in parallel to enhanced postsynaptic excitability, demonstrating again a synergy between synaptic and intrinsic changes. The expression of these forms of intrinsic plasticity was found to be independent of GABAergic inhibition (Aizenman and Linden 2000; Armano et al. 2000). Use-dependent plasticity of neuronal excitability in granule and DCN cells has the potential to broadly affect the neuronal throughput. The spike threshold is reduced in granule cells and DCN neurons, and the probability of spike firing as evoked by every excitatory synapse may be enhanced, especially in granule cells that are extremely compact electrotonically (Fig. 2A). Interestingly, subthreshold EPSPs recorded in DC neurons were prolonged following high-frequency tetanus, but the ionic conductances that are regulated here have not been yet identified.

What are the consequences of intrinsic plasticity for cerebellar function? In cerebellar circuits, plasticity of synaptic excitation and inhibition occurs at five different sites (for review, see Hansel et al. 2001) and intrinsic plasticity has been reported in at least three cell types (Schreurs et al. 1997; Aizenman and Linden 2000; Armano et al. 2000). The search for a memory trace during a relatively simple associative learning such as eyelid conditioning is complicated by the fact that the trace may be stored in multiple cerebellar locations, and that plasticity at one site may result in the induction of plasticity at another site (Hansel et al. 2001). Computational approaches seem particularly well adapted to understand how these different forms of plasticity may interact to form a coherent scheme.

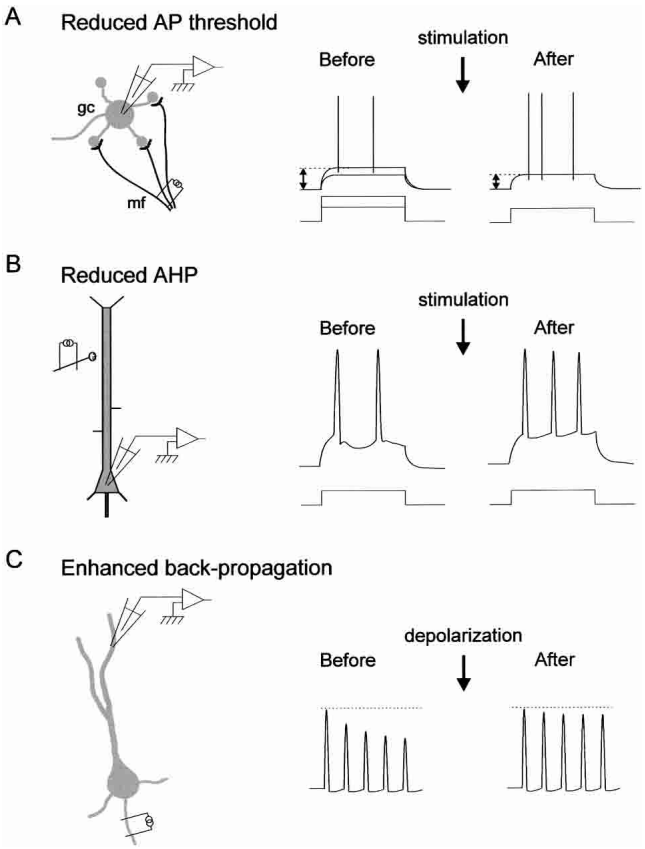

Figure 2 Global changes in intrinsic excitability induced by neuronal activity. (*A*) Reduction of AP threshold in a cerebellar granule cell (gc). (*Left*) Experimental device for monitoring the neuronal excitability at the cell body, before and after stimulation of the mossy-fibers (mf). Before the stimulation, the neuron fires with a large depolarizing pulse, but not with a small pulse. After high-frequency stimulation of the mf, the spike threshold is reduced, and a small current pulse is now able to elicit a burst of APs (adapted from Armano et al. 2000). (*B*) Reduction of the AHP amplitude in a layer V pyramidal neuron. (*Left*) Experimental device to assess the excitability of the neuron before and after stimulation of a glutamatergic input in the apical dendrites. After stimulation of the synaptic input at 10 Hz during 4 min, the AHP is reduced and the same input now elicits three APs (adapted from Sourdet et al. 2003). (*C*) Enhanced back-propagation of APs in the dendrites of CA1 pyramidal neurons. A train of back-propagating APs recorded on the apical dendrite is elicited by antidromic stimulation of the axon. In control condition (Before), a large attenuation of back-propagating APs is observed. After an episode of eight large depolarizing pulses (depolarization) applied to the dendrite, the train of APs displays almost no attenuation (adapted from Tsubokawa et al. 2000).

Long-Lasting Reduction of AHPs

NMDAR is not the only glutamate receptor that participates in the induction of long-lasting plasticity. mGluR is also involved in

the induction of long-term synaptic plasticity in the hippocampus, cortex, and cerebellum, but evidence for its contribution in the induction of long-lasting intrinsic plasticity is more recent. The possible involvement of mGluR in the plasticity of intrinsic excitability was first suggested by the fact that in the area CA1, the application of the broad-spectrum mGluR agonist, ACPD induced not only LTP, but also an increase in EPSP-spike coupling (Breakwell et al. 1995). However, the conclusion was not definitive at this stage, as this E-S potentiation was sensitive to $GABA_A$ receptor antagonists. Using intracellular recordings from CA1 pyramidal neurons, mGluR stimulation by ACPD (for 10 min) was shown to induce a persistent (>20–25 min) elevation in the neuronal responsiveness to a current pulse of constant amplitude (Cohen et al. 1999). Interestingly, the AHP was also found to be depressed 25 min after washout of the agonist. More recently, the type of mGluR was characterized pharmacologically, and both mGluR1 and mGluR5 were found to be involved in the induction of this potentiation (Ireland and Abraham 2002). Although these findings appear very important, it is still unknown whether synaptic activation of these receptors could enhance intrinsic excitability.

In layer V, pyramidal neurons of the rat somato-sensory cortex, we have shown recently that in the presence of ionotropic receptor antagonists, a brief synaptic stimulation of mGluR (10 Hz for ~4 min) induced a long-lasting (>30 min) potentiation of intrinsic excitability measured at the soma. Following the tetanus, depolarizing current pulses or EPSPs simulated with the dynamic-clamp technique evoked twice as many APs (Sourdet et al. 2003; Fig. 2B). This potentiation was blocked by mGluR5 antagonists. Potentiation could also be induced pharmacologically by the specific mGluR5 agonist CHPG and was found to result from a long-lasting depression of the calcium-dependent K^+ AHP current mediated by SK channels. Interestingly, the potentiation occurred preferentially when the postsynaptic neuron was active during mGluR stimulation. Thus, the associative nature reveals that the mGluR-dependent enhancement of neuronal excitability is cell specific in the cortical network, despite a lack of input specificity (potentiation could be induced by synaptic stimulation, but revealed by current injection in the cell body; Sourdet et al. 2003).

Kainate receptors are also involved in the induction of synaptic plasticity. For instance, LTP at the mossy fiber-CA3 cell synapse requires the activation of kainate receptor (Contractor et al. 2001). Recent data indicate that in CA1 pyramidal cells, kainate receptors including the GluR6 subunit, could induce a long-lasting depression of the slow AHP current, resulting in a long-lasting potentiation of intrinsic excitability (Melyan et al. 2002). This plasticity requires the activation of pertussis toxin-sensitive G proteins and PKC. It will be important to define the physiological conditions in which kainate receptors can be activated synaptically.

Long-lasting plasticity of neuronal excitability mediated by the persistent reduction of AHP currents appears to affect the global excitability of the neuron, as it was generally tested with current pulses injected through the patch-pipette located at the cell body. In particular, one may speculate about the consequences of this plasticity on dendritic excitability. Local dendritic spikes and back-propagation of APs could be facilitated by the down-regulation of AHP currents. The presence of AHP channels in the dendrites support this hypothesis (Sah and Bekkers 1996; Sailer et al. 2002). However, detailed experiments are required, and the precise role of these channels in the long-lasting plasticity of the dendritic function will be one of the main challenges for the coming years in the field of intrinsic plasticity.

Plasticity of Back-Propagating APs in the Dendrites

Long-lasting plasticity of neuronal excitability is not limited to the soma, but also affects the dendrites of hippocampal pyramidal neurons. Activity-dependent plasticity of back-propagating APs was reported for the first time by Tsubokawa et al. (2000). They concluded that large post-synaptic depolarizations induced a long-lasting facilitation of spike train back-propagation in the dendrites of CA1 pyramidal neurons (Fig. 2C). Such postsynaptic depolarization that elicit brief, high-frequency firing causes a long-term increase in intrinsic excitability in DCN neurons (Aizenman and Linden 2000) in visual cortical pyramidal neurons (Cudmore et al. 2001) and in entorhinal cortical neurons (Egorov et al. 2002). The plasticity of dendritic back-propagation was found to be rapidly induced (~1 min) and long-lasting (>25 min). In addition, it was found to require an elevation of the postsynaptic calcium concentration and the activation of CaMKII (Tsubokawa et al. 2000). The precise mechanisms responsible for the decrease in the spike attenuation have not yet been identified, although a long-term down-regulation of voltage-gated K^+ current can be suspected (Hoffman et al. 1997; Hoffman and Johnston 1998; for review, see Schrader et al. 2002; Yuan et al. 2002). In addition, it would be important to know whether this plasticity is related to other changes in intrinsic excitability described above. The phenomenon reported by Tsubokawa and coworkers (2000) is extremely important, because it demonstrates that propagation of the signal back to the dendrite depends on the recent activity in the neuron. It will be important to know whether this plasticity is dendrite specific and whether it can be reversed by some specific regime of activity. It is expected that this long-term modulation may play a role in the subsequent induction of associative synaptic plasticity. For instance, a long-lasting enhancement of back-propagation may enhance the depolarization of the dendrite, and thus promotes LTP induction (see Fig. 4 in Sourdet and Debanne 1999).

Does regulation of dendritic AP back-propagation occur during behavior? It has been reported recently that the attenuation of spike amplitude recorded extracellularly in rat hippocampus is reduced with experience in an environment (Quirk et al. 2001). Interestingly, this activity-dependent modulation of spike attenuation requires the activation of NMDAR and is environment specific. These results provide an important step in linking in vivo studies to in vitro data, and suggest that the mechanisms of plasticity engaged during behavior may be sufficient to modulate biophysical and integrative properties of hippocampal cells.

Long-Term Plasticity of Presynaptic Excitability

Developmental Regulations

Synaptic activity determines the development of excitability in presynaptic neurons. At the developing neuromuscular junction of *Xenopus*, the blockade of postsynaptic nicotinic receptors by α-bungarotoxin (α-BgTx) broadened action potentials and decreased repetitive firing of presynaptic motorneurons (Nick and Ribera 2000). Thus, neurons that belong to physically connected neuromuscular junctions with inactive synapses behave as immature neurons that have not yet established a functional connection with myocytes; the spike threshold is more depolarized, and the refractory period is longer. This delayed maturation of presynaptic excitability results from an abnormally low level of a retrograde messenger released by the postsynaptic element. The neurotrophin NT3 that is normally up-regulated by postsynaptic depolarization prevents the effects of α-BgTx (Nick and Ribera 2000). The blockade of synaptic transmission down-regulates inward rectifying K^+ current, and shifts the activation curve of Na^+ current toward depolarized values. Thus, this example shows that a decrease in postsynaptic activity during development down-regulates presynaptic excitability. It would be important to know whether this presynaptic plasticity is also observed at central synapses when synaptic activity is reduced physiologically.

Activity–Dependent Long–Term Plasticity of Presynaptic Excitability in Mature Systems

One of the first examples of activity-dependent regulation of presynaptic excitability reported in the literature was observed at glutamatergic axons of the area CA3. The repetitive stimulation of Schaffer collateral axons at 2 Hz leads to a long-lasting lowering of the antidromic activation threshold (McNaughton et al. 1994). This effect requires the activation of NMDAR and nitric-oxide synthase. This presynaptic potentiation depends on the temperature; it is observed reliably at 22°C, but is not detectable at a more physiological temperature (32°C). Thus, although these findings point to a substrate for a presynaptic change in LTP, this form of activity-dependent plasticity of presynaptic excitability may not be expressed in physiological conditions.

Crustacean neuromuscular junctions display a long-term facilitation of synaptic transmission following sustained intense activity of the motor neuron. This form of long-lasting plasticity is rather unusual in that its locus is entirely presynaptic (however, see Briggs et al. 1985 for an example of presynaptic LTP in the superior cervical ganglion). The mechanism involved in the persistent increase is not clear, but considerable evidence supports a role for adenosine 3′,5′-monophosphate (cAMP). This presynaptic LTP is mediated by a long-lasting up-regulation of I_h channels (Beaumont and Zucker 2000; Beaumont et al. 2002). Are nonsynaptic mechanisms peculiar to the neuromuscular junction of the crayfish? For years, it has been well established that mossy-fiber LTP in the area CA3 results from a change in the presynaptic release of glutamate that also depends on the cAMP pathway. Recently, this increase in neurotransmitter release was proposed to result from a long-lasting up-regulation of the H-type current at the nerve terminal (Mellor et al. 2002). However, the I_h blockers used in this study also reduce synaptic transmission presynaptically, and the occlusion of LTP by I_h channel blockers might be simply due to the nonspecific action of these drugs (Chevaleyre and Castillo 2002). Thus, although attractive, the idea that long-lasting regulation of I_h channels in the presynaptic axon could determine the functional coupling between excitable cells appears to be valid only for the neuromuscular junction of the crayfish.

Presynaptic changes in intrinsic excitability might also be observed following induction of LTP. In hippocampal neurons, LTP induced by synchronized pairing depends on NMDAR activation and is mediated by postsynaptic mechanisms (Sourdet and Debanne 1999; Bi and Poo 2001). It has been established by Ganguly et al. (2000) that correlated presynaptic and postsynaptic spiking in pairs of hippocampal cells not only induces LTP of synaptic transmission, but also increases the excitability of the presynaptic cell. This presynaptic plasticity of neuronal excitability is rapidly expressed (<2 min) and is long-lasting (>30 min). Its induction requires NMDAR activation, postsynaptic calcium elevation, and activation of PKC. The expression mechanisms have been studied at the soma of the presynaptic neurons and involve a shift in the activation curve of Na^+ current toward hyperpolarizing values that may account for the lower spike threshold (Ganguly et al. 2000). In addition, the sodium current exhibits an improved recovery from inactivation following correlated pre- and postsynaptic activity. The functional consequences of this plasticity are fundamental for the dynamics of the network. First, the increased frequency of presynaptic firing following correlated spiking activity may facilitate the induction of bursting-like behavior and will enhance the reliability of signal transmission in the brain. Together with the post-synaptic E-S potentiation, the presynaptic increase in intrinsic excitability may form privileged activity pathways in small neural networks (Fig. 3). In addition, enhancement of presynaptic neuronal excitability may affect the plasticity of upstream synapses made onto the presynaptic cell by facilitating the initiation of back-propagated action potentials (Tao et al. 2000). Finally, this increased presynaptic excitability may improve the dynamics of the presynaptic axon. It may not only decrease the rate of propagation failures in some axonal, but also diminish the short-term depression that depends on Na^+-channel inactivation (Brody and Yue 2000; He et al. 2002). In further studies, it will be particularly important to know whether this presynaptic increase in neuronal excitability affects all presynaptic partners equally and whether it is reversible by protocols that induce associative LTD (Debanne et al. 1996, 1998; Bi and Poo 2001).

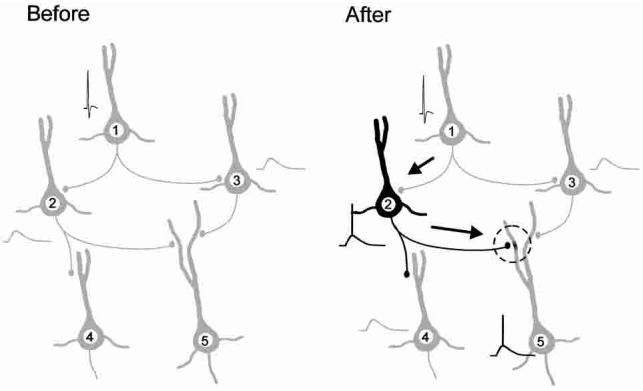

Figure 3 Specific spread of excitation in a network following pre- and post-synaptic increase in intrinsic excitability accompanying LTP. Before LTP induction (*left*), the spread of excitation from the neuron 1 is limited to its monosynaptic targets (neurons 2 and 3) because EPSPs in 2 and 3 are subthreshold. Pre- and postsynaptic changes in intrinsic excitability occur after LTP of the synapse between 2 and 5 (After). First, the excitability in the dendrite of neuron 5 is locally increased (postsynaptic, see also Fig. 1C). In addition, the spike threshold in 2 is decreased, indicating a global increase in excitability (presynaptic, adapted from Ganguly et al. 2000). As a result, when the neuron 1 generates an AP, the EPSP in 2 is now suprathreshold. Subsequently, the neuron 5 fires because of the conjunction of the synaptic potentiation and the increase in postsynaptic excitability. Thus, a specific pathway of activity appears between neurons 1, 2, and 5 (arrows). In contrast, no change in the spread of excitation occurs in the other pathways, and neurons 3 and 4 remain silent.

Synaptic and Intrinsic Plasticity: Toward Common Learning Rules?

The ultimate goal of this review is to define a general framework in which synaptic and nonsynaptic plasticity could interact coherently and harmoniously. Several common features linking the two forms of plasticity must be underlined.

At the phenomenological level, several lines of evidence argue for a functional synergy between synaptic plasticity and intrinsic plasticity. E-S plasticity in the CA1 area of the hippocampus is a particularly good example. E-S potentiation is observed when LTP is induced homosynaptically (Bliss and Lømo 1973; Abraham et al. 1987; Daoudal et al. 2002) or associatively (Jester et al. 1995; Wang et al. 2003). Reciprocally, E-S depression is concomitant with synaptic depression or depotentiation (Daoudal et al. 2002; Wang et al. 2003). Thus, E-S plasticity in the area CA1 follows the Bienenstock Cooper Munro curve that was described initially for synaptic plasticity (Bienenstock et al. 1982; Daoudal et al. 2002; Wang et al. 2003). A parallel potentiation in synaptic efficacy and in intrinsic excitability is also observed in granule cells of the cerebellum following high-frequency stimulation of glutamatergic inputs (Armano et al. 2000). However, as in synaptic plasticity (Abbott and Nelson 2000), this rule seems to be opposite for the Purkinje cell, which is a GABAergic neuron.

Enhanced dendritic excitability is concomitantly observed with LTD (Schreurs et al. 1997). Thus, excitatory synaptic plasticity is associated with synergistic modifications in intrinsic excitability at the postsynaptic site of glutamatergic neurons. However, the synergy between synaptic and nonsynaptic plasticity also concerns the presynaptic element. It has been shown that in parallel to LTP induced by synchronous pre- and postsynaptic discharge, an increase in excitability was induced in the presynaptic neuron (Ganguly et al. 2000). This plasticity could participate in the formation of retrograde activity pathways in the brain (Tao et al. 2000). Finally, homeostatic changes appear to affect synergistically excitatory synapses and intrinsic excitability (Desai et al. 1999a,b; Burrone et al. 2002). However, this synergy is not observed in the developing optic tectum of the *Xenopus* tadpole. Visual stimulation decreases AMPA receptor-mediated synaptic drive (Aizenman et al. 2002) but enhances intrinsic excitability (Aizenman et al. 2003).

At the mechanistic level, synaptic plasticity and intrinsic plasticity share common induction and expression pathways. We have previously underlined the role of glutamate receptors such as NMDAR, mGluR, and kainate receptors in both synaptic and intrinsic plasticity. It is also important to note that the depression of the AHP current seen as a cellular correlate of eye-blink conditioning (Disterhoft et al. 1986; Coulter et al. 1989; Moyer et al. 1996; Saar et al. 1998) is also reported following stimulation of mGluR (Cohen et al. 1999; Ireland and Abraham 2002; Sourdet et al. 2003) and kainate receptors (Melyan et al. 2002). If the activation of a synaptic receptor was not involved directly in the induction of the plasticity, postsynaptic depolarization was a determining factor, and calcium elevation was necessary in most examples (Aizenman and Linden 2000; Ganguly et al. 2000; Tsubokawa et al. 2000). Downstream of calcium elevation, several protein kinases and phosphatases that play a central role in synaptic plasticity (Lisman 1994; CaMKII, PKC, PKA) are also involved in the induction of several activity-dependent forms of intrinsic plasticity (Ganguly et al. 2000; Tsubokawa et al. 2000; Wang et al. 2003). These kinases and phosphatases are also known to have various activity on Na^+ channels, Ca^{2+} channels, K^+ channels, and cationic I_h channels (Cathala and Paupardin-Tritsch 1997; Herzig and Neumann 2000; Cantrell and Catterall 2001; Schrader et al. 2002). In addition, they may regulate targeting and recycling of many ion channels at the plasma membrane (Dargent et al. 1995; Tanemoto et al. 2002; Hu et al. 2003). In the near future, the entire induction pathway from the receptor to the effector will have to be determined. Unification of learning rules including the cellular and molecular mechanisms will need conjugated efforts of neuroscientists from complementary fields of expertise. In particular, neuro-computation will be of great help to establish integrated models of synaptic and nonsynaptic plasticity in realistic neuronal networks.

In conclusion, intrinsic plasticity has been identified as a cellular correlate of learning in various brain areas including the hippocampus, the neocortex, and the cerebellum, and further studies might reveal its existence in other brain regions. It determines the short-term and long-term dynamics of neuronal activity. Long-term intrinsic plasticity shares common features with the better-known synaptic plasticity. The learning rules that have been defined during these last 30 yr for synaptic plasticity will be useful guidelines for neuroscientists to integrate this novel dimension into an integrated scheme of brain plasticity.

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