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PLASTICITY OF NEURONAL EXCITABILITY: HEBBIAN RULES BEYOND THE SYNAPSE

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INTRODUCTION

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 post-synaptic potential, EPSP). This process requires the opening of voltage-gated ion channels located in the neuronal membrane upon activation of excitatory synapses. The operational link between the EPSP and the AP is functionally crucial at the scale of a neuron since 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, where 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, Ca^{2+}-, Na^{+}- and K^{+}-permeable voltage-gated channels shape the signal in dendritic spines and shafts of central neurons. These channels either amplify or attenuate the EPSP amplitude and subsequently determine the input-output function. Thus, any activity-dependent long-lasting regulation of their properties or their density will affect the neuronal output and subsequently the spread of information in the brain.

The postulate that modifications in intrinsic excitability could participate in 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^{+} and Ca^{2+} currents (4). Later, Marder and colleagues showed that network activity in the stomatogastric system of crustaceans could regulate ion channels (40). 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 synaptic plasticity. In the last 5 years, a new interest has flourished in the study of the learning rules and expression mechanisms underlying intrinsic plasticity. The search for correlates of learning and memory at the level of cellular excitability has focused on neurons that

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are specifically active during learning. Eye-blink conditioning is well documented in this respect since it involves specific circuits in the cerebellum and hippocampus that have been thoroughly characterized. In conditioned animals, neurons that are active during conditioning exhibit significantly higher excitability than neurons recorded from naive or pseudo-conditioned animals. Cortical, hippocampal and cerebellar neurons of conditioned mammals display increased intrinsic excitability at the somatic (22, 33) or dendritic level (34). In several cases the after-hyperpolarizing (AHP) current was found to be depressed for days. Neuronal excitability might be also enhanced following learning of the watermaze task (31) or following persistent visual stimulations (2). Thus, the mnesic trace may not be exclusively supported by selective changes in synaptic strength and modification of neuronal excitability might be a complementary substrate for information storage in the brain.

Synaptic and intrinsic plasticity in a coherent scheme

Synaptic plasticity represents today a suitable model for persistent storage of information in the brain. In fact, synaptic strength can be indefinitely elevated (long-term potentiation, LTP) or diminished (long-term depression, LTD). Synaptic changes are specific of the stimulated pathway and the huge number of synapse (more than 100 billion synapses) may store the enormous number of facts and events occurring during a mammal's lifetime. Finally, the molecular perturbation of synaptic plasticity may produce learning and memory deficits.

Plasticity of intrinsic excitability cannot be simply considered as an additional level of plasticity that makes understanding of information storage in the brain more complex. Rather, it can be incorporated into a *general framework* in which *synaptic* and *non-synaptic* plasticity interact coherently and harmoniously. Several common features linking the two forms of plasticity must be underlined. First, a functional *synergy* between synaptic plasticity and intrinsic plasticity has been demonstrated. Plasticity in area CA1 of the hippocampus represents a good example. Following induction of LTP with high frequency stimulation, the probability that an EPSP will elicit an action potential is increased (5, 9). This second component has been called EPSP-to-Spike potentiation (*E-S potentiation*) which is complementary to and synergic with LTP (Figure 1A). In the cerebellum, a parallel potentiation in synaptic efficacy and in intrinsic excitability is also observed in granule cells (6).

The reversal of LTP preserves a potential for network plasticity and increases the capacity of memory storage. Bi-directional changes in postsynaptic excitability may also avoid saturation and preserve a larger capacity of information storage. Long-lasting depression of E-S coupling has been observed in parallel to LTD induced by low frequency stimulation (14). In addition, it may reverse E-S potentiation by protocols that induce synaptic depotentiation.

E-S coupling is strongly determined by inhibitory synaptic transmission and E-S plasticity results from both an imbalance between synaptic excitation and inhibition, and a change in intrinsic excitability. E-S potentiation and E-S depression are expressed in the presence of GABAA and GABAB receptor antagonists. The GABA

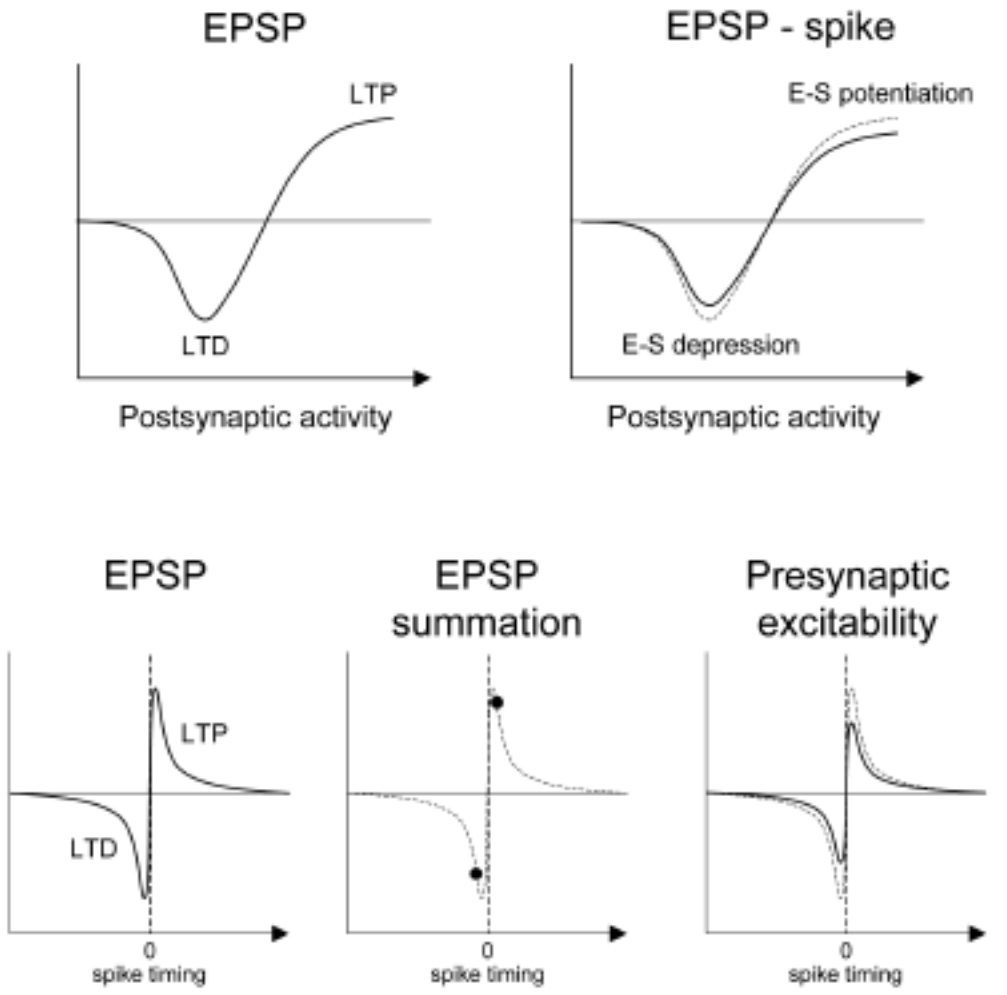

Fig. 1. - *Common learning rules for synaptic and non-synaptic plasticity.*
A. Frequency-dependent LTP and LTD in the area CA1. Left, Bienenstock, Cooper & Munro (BCM) learning rule for synaptic transmission. LTD occurs for weak elevation of synaptic activity whereas LTP results from a larger increase in synaptic activity. Right, EPSP-spike curve follows the BCM curve (adapted from Daoudal et al., 2002).
B. Spike-timing dependent plasticity in hippocampal neurons and beyond. Left panel, learning rule for synaptic transmission (EPSP). LTP is induced when the postsynaptic spike occurs shortly after the EPSP (positive spike timing) whereas LTD occurs when the postsynaptic spike precedes the EPSP (adapted from Debanne et al., 1998 & Bi and Poo, 1998). Central panel, changes in EPSP summation following LTP or LTD induction with STDP protocols (adapted from Wang et al., 2003). Note the gain of summation when LTP is induced and the loss of summation concomitant with LTD. Dashed profile, STDP rule for synaptic transmission. Right panel, changes in excitability of the presynaptic neuron following LTP or LTD induction with STDP protocols (adapted from Ganguly et al., 2000 and Li et al., 2003). The rules for synaptic plasticity (dashed trace) and presynaptic excitability are synergic.

receptor-independent component represents nearly 40% of total E-S plasticity and requires NMDAR activation (14, 37). In single neurons, GABA-receptor independent E-S plasticity is observed without modification of postsynaptic membrane properties recorded at the soma.

In the hippocampus, LTP and LTD are also induced according to the temporal correlation between pre- and post-synaptic action potentials (7, 16-18). This associative form of plasticity referred as to Spike Timing Dependent Plasticity (STDP) is generalized to a wide range of excitatory synapses and inhibitory synapses (1, 13, 28, 35). STDP shares common induction and expression mechanisms with homosynaptic plasticity that depends on presynaptic stimulation frequency. Again, a functional synergy can be observed between synaptic and non-synaptic changes. First, associative LTP in CA1 pyramidal cells is accompanied by a persistent facilitation of the dendritic summation of subthreshold EPSPs (44, 46; Fig. 1B). Moreover, E-S potentiation is observed following induction of LTP with STDP protocols (10). Reciprocally, associative LTD induced by negative spiking correlation (pre-post) is associated with a reduction of EPSP summation (44; Fig. 1B) and E-S depression (10). Thus, plasticity of postsynaptic excitability in area CA1 follows the learning rules that were initially established for synaptic plasticity (1, 7, 8, 10, 18; Fig. 1A and 1B).

The synergy between synaptic and non-synaptic plasticity also concerns the *presynaptic* element. In connected hippocampal neurons, correlated presynaptic and postsynaptic spiking not only enhances synaptic transmission but also increases the excitability of the presynaptic cell (27; Fig. 1B). The functional consequences of this plasticity may determine 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 neuronal network (15, 38). Thus, enhanced presynaptic excitability may affect the plasticity of upstream synapses made onto the presynaptic cell by facilitating the initiation of back-propagated action potentials. Finally, increased presynaptic excitability may also improve the dynamic properties of the presynaptic axon and may decrease the rate of propagation failures in some axon collaterals (19). Recently, this presynaptic increase in neuronal excitability has been shown to be reversible by protocols that induce associative LTD (30; Fig. 1B). Thus, STDP rule applies to both synaptic efficacy and presynaptic excitability.

Finally, a synergy between intrinsic and synaptic plasticity is also observed in the case of *homeostatic plasticity* (42). This type of plasticity compensates sustained changes in neuronal activity and contributes to maintain the integrity of the organism. For instance, in cultured neurons the deprivation of neuronal activity by bath application of tetrodotoxin scales the excitatory synaptic transmission up (41). In parallel, intrinsic excitability is increased (20, 29). Similar regulation of synaptic transmission and intrinsic excitability has also been reported in the auditory system of deaf mice (43). Conversely, when network activity is increased by pharmacologically blocking GABAA receptors, then excitatory synaptic transmission is decreased (32), intrinsic excitability is depressed and inhibitory synaptic drive is

enhanced (29). Thus, existing data support the simple rule that changes in neuronal excitability follows synaptic changes resulting from homosynaptic, associative and homeostatic plasticity. However, in a few cases, this relation remains unclear (24).

Common induction but different expression

At the mechanistic level, synaptic plasticity and intrinsic plasticity share common induction pathways. The role of *glutamate receptors* such as NMDA and metabotropic glutamate (mGlu) receptors has been underlined in both synaptic and intrinsic plasticity. NMDA receptor activation is required in post-synaptic elevation of intrinsic excitability like E-S potentiation (6, 14) and related potentiation of intrinsic excitability (2). In addition, NMDA receptor is also necessary for E-S depression (14) and for the induction of presynaptic changes in intrinsic plasticity (27, 30). mGlu receptor is the other major actor in the induction of long-term synaptic plasticity in hippocampal and neocortical neurons. Evidence for its contribution to the induction of long-lasting intrinsic plasticity is, however, more recent. Using intracellular recordings from CA1 pyramidal neurons, mGluR stimulation by ACPD, a broad spectrum mGluR agonist, induced a persistent (>20-25 minutes) elevation in neuronal responsiveness (11). In layer V pyramidal neurons of the rat neocortex, a brief synaptic stimulation of mGluR5 induced a long-lasting (>30 min) potentiation of intrinsic excitability measured at the soma (36).

In most cases a postsynaptic calcium elevation is required (2, 12, 27, 36). Downstream of calcium elevation, several protein kinases and phosphatases that play a central role in synaptic plasticity (CaMKII, PKC, PKA) are also involved in the induction of several activity-dependent forms of intrinsic plasticity (12, 27, 44). These kinases and phosphatases have multiple effects on ion channel activity and targeting. In the near future, the entire induction pathway from the receptor to the effector will have to be determined.

If the induction mechanisms of synaptic and non-synaptic plasticity are common, their expression mechanisms however diverge since synaptic receptors are regulated in synaptic plasticity but ion channels are affected in intrinsic plasticity. The study of intrinsic plasticity still remains principally descriptive. However the nature of the ion channels has been characterized in a limited number of cases. Generally, inward currents are up-regulated and outward currents are down-regulated when excitability is increased. A reduction of potassium current accompanied by an up-regulation of the sodium current has been observed in homeostatic plasticity which results from the deprivation of neuronal activity (20). In NMDA-receptor dependent plasticity of intrinsic excitability, several currents are also affected. The presynaptic increase in excitability associated with LTP results from the shift in the activation curve of somatic Na^+ current towards hyperpolarizing values (27). This modification may also account for the lower spike threshold. A similar regulation of the Na^+ current is observed in the postsynaptic cell following induction of LTP with a STDP protocol (45). However, the presynaptic decrease in excitability associated with LTD is due to a lasting regulation of delayed rectifyer K^+ channels (30).

The process of E-S coupling relies on integration of EPSPs and recent data indicate that associative LTP in CA1 pyramidal cells is also accompanied by a persistent facilitation of the dendritic summation of subthreshold EPSPs (44). The underlying mechanisms could be common to those responsible for E-S potentiation. Long-lasting down-regulation of *I*h channels and up-regulation of NMDA receptors are thought to be involved in the expression of the enhanced summation of dendritic EPSPs (44). It will be of great important to determine whether these mechanisms also contribute to the expression of E-S potentiation.

Lasting reduction in the sAHP and mAHP is observed in hippocampal (11) and neocortical neurons (36), following pharmacological or synaptic stimulation of mGluRs. In cortical neurons, the potentiation was occluded by apamin and resulted from a long-lasting depression of the Ca^{2+}-dependent K^+ AHP current mediated by SK channels. Interestingly, this potentiation occurred preferentially when the postsynaptic neuron was active during mGluR stimulation, indicating that this potentiation is cell specific. Thus, intrinsic plasticity involves the long-term regulation of several types of voltage-gated or calcium-dependent channels. Further investigations will be required to circumscribe the molecular events underlying the various steps of the expression mechanisms of intrinsic plasticity.

Spatial spread of intrinsic plasticity

The spatial spread of induced changes is a central question in the field of activity-dependent plasticity. Because of its axonal location, the site of spike initiation occupies a strategic location and regulation of ion channels in the axo-somatic axis will produce *global* changes in excitability that may affect all synapses. In contrast, the complex dendritic structure may allow *local* changes in excitability if the modifications in excitability are restricted within a given dendritic area at the post-synapse.

Plasticity of synaptic integration enters within this last category. In fact, E-S potentiation and the enhanced summation of EPSPs accompanying associative LTP are input specific (14, 44; Fig. 2A). Thus, potentiation of neuronal excitability not only shares a common induction pathway with LTP but also respects the input specificity conferred by synaptic plasticity. The GABA receptor-independent component of E-S depotentiation is input specific (14; Figure 2A). Thus, in hippocampal neurons homosynaptic and associative forms of LTP and LTD are associated with local changes in intrinsic excitability that will synergistically regulate the spread of excitation in the network.

Input specificity is however not a general rule and global changes in intrinsic excitability have been reported following synaptic stimulation or post-synaptic depolarizations in cerebellar, hippocampal and neocortical neurons. Use-dependent plasticity of excitability in granule and DCN cells has the potential to broadly affect neuronal throughput (2, 6). In fact, the spike threshold is hyperpolarized in granule cells and DCN neurons, and the probability of spike firing evoked by all excitatory synapses may be enhanced, especially in granule cells that are extremely compact electrotonically. The presynaptic changes in intrinsic excitability associated with

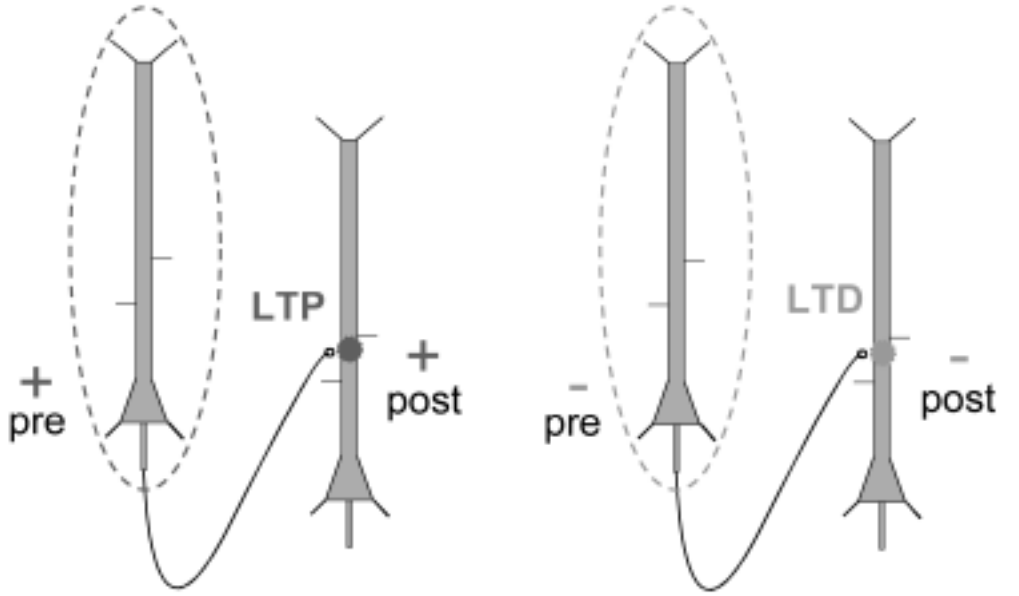

Fig. 2. - *Spatial and temporal changes in neuronal excitability in cortical neurons*.
Spatial spread of plasticity of neuronal excitability induced by synaptic activity. Pre- and postsynaptic excitability is enhanced following LTP induction (left) whereas pre- and postsynaptic excitability is decreased following LTD induction (right). Postsynaptic changes are limited to restricted dendritic areas (red or green spot) but pre-synaptic changes affects the global excitability of the neuron (dashed areas).

LTP/LTD are also likely to be global since excitability changes are measured at the cell body (27, 30).

Long-lasting plasticity of neuronal excitability is not limited to the soma but may also affect the dendrites of hippocampal pyramidal neurons. Activity-dependent plasticity of back-propagating APs was first reported by Tsubokawa and co-workers (39). Dendritic activity induced long-lasting facilitation of spike train backpropagation in the dendrites of CA1 pyramidal neurons. This plasticity was found to be rapidly induced (~1 min) and long-lasting (>25 minutes). In addition, it required an elevation of the postsynaptic calcium concentration and the activation of CaMKII (39). However, the expression mechanisms have not yet been identified. More recently, dendritic excitability has been found to be also up-regulated following induction of hippocampal LTP (26). In this case, the back-propagation is favored because A-type K^+ channel activity is locally depressed. These data demonstrate that propagation of the signal back to the dendrites depends on the recent history of the neuron. It will be important to know whether this plasticity is dendrite-specific and whether specific regimes of activity may reverse the effect.

A global increase in intrinsic excitability might not be a disadvantage on the functional point of view. In the context of working memory, the relative importance of

some events needs to be stored in a non-specific way. Until very recently, the substrate for working memory was though to be based on the persistent activity in reverberating circuits. However, it has been established that in the presence of muscarinic receptor agonist, the post-synaptic firing of layer V neurons of the entorhinal cortex determined subsequent neuronal excitability (23). Post-synaptic activity is maintained for minutes following a large depolarization induced by current injection or by stimulation of EPSPs. This plasticity is graded and is also bi-directional. In fact, post-synaptic hyperpolarizations induced by current pulses or by IPSPs are able to decrease basal excitability. Thus, muscarinic cholinergic actions allow central neurons to behave through a non-synaptic mechanism as analogue memory devices (21, 23, 25). Together with associative network plasticity, these mechanisms could build internal sensory representations.

Long-lasting enhancement of temporal precision

At a glance, a modification in intrinsic excitability can be simply considered as a change in the input-output function. However, several lines of evidence have led to the idea that it is not just the rate of spiking which encodes information in the brain but also the temporal structure of the neuronal discharge. One novel and important question in the field of intrinsic plasticity is to determine whether synaptic activity could modify, on a long-term scale, the temporal parameters of the neuronal firing. This question has been addressed experimentally only recently. For instance, the neuron of the stomato-gastric ganglion (STG) of the lobster slowly convert their firing pattern from tonic to burst-firing when neurons are isolated in culture (40). More specifically, in the rat neocortex, synaptic stimulation of mGluR5 not only enhanced the reliability of the input-output function but also improved the temporal precision of the neuronal discharge (36). In this case, improved firing precision was due to an increase in the trajectory of membrane depolarization before each action potential, as a result of the persistent depression of the SK current (36). It will be important to re-examine whether these changes are generalized to other examples of long-lasting plasticity of intrinsic excitability (47). Long-lasting changes in temporal processing in the brain represent a novel dimension of functional plasticity. The consequences for internal representations and brain coding will have to be determined.

SUMMARY

Activity-dependent synaptic plasticity is classically though to be the cellular substrate for learning and memory. Recent data show that activation of glutamate receptors initiates a long-term modification in pre- or post-synaptic neuronal excitability. Similarly to synaptic plasticity, intrinsic plasticity is bidirectional and input- or cell-specific. In addition to an increase in the reliability of the input-output function, temporal precision of the neuronal discharge is improved. These forms of plasticity not only share common learning rules and induction pathways with the better known

synaptic plasticity but may also contribute in synergy with these synaptic changes to the formation of a coherent mnesic engram.

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