Neurobiology of Learning and Memory xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Learning to learn – Intrinsic plasticity as a metaplasticity mechanism for memory formation

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Learning
Memory
Metaplasticity
Intrinsic excitability
Aging
Memory modulation
Memory allocation

ABSTRACT

"Use it or lose it" is a popular adage often associated with use-dependent enhancement of cognitive abilities. Much research has focused on understanding exactly how the brain changes as a function of experience. Such experience-dependent plasticity involves both structural and functional alterations that contribute to adaptive behaviors, such as learning and memory, as well as maladaptive behaviors, including anxiety disorders, phobias, and posttraumatic stress disorder. With the advancing age of our population, understanding how use-dependent plasticity changes across the lifespan may also help to promote healthy brain aging. A common misconception is that such experience-dependent plasticity (e.g., associative learning) is synonymous with synaptic plasticity. Other forms of plasticity also play a critical role in shaping adaptive changes within the nervous system, including intrinsic plasticity – a change in the intrinsic excitability of a neuron. Intrinsic plasticity can result from a change in the number, distribution or activity of various ion channels located throughout the neuron. Here, we review evidence that intrinsic plasticity is an important and evolutionarily conserved neural correlate of learning. Intrinsic plasticity acts as a metaplasticity mechanism by lowering the threshold for synaptic changes. Thus, learning-related intrinsic changes can facilitate future synaptic plasticity and learning. Such intrinsic changes can impact the allocation of a memory trace within a brain structure, and when compromised, can contribute to cognitive decline during the aging process. This unique role of intrinsic excitability can provide insight into how memories are formed and, more interestingly, how neurons that participate in a memory trace are selected. Most importantly, modulation of intrinsic excitability can allow for regulation of learning ability – this can prevent or provide treatment for cognitive decline not only in patients with clinical disorders but also in the aging population.

1. Introduction

Neural pathways are plastic and continuously changing in response to internal and external stimuli. These changes can occur at synaptic as well as non-synaptic sites throughout the neuron. The non-synaptic (intrinsic) plasticity can be described as a change in the intrinsic excitability of the neuron and is independent of changes in synaptic transmission. Intrinsic plasticity has been examined in numerous animal models using a wide variety of learning paradigms. Many of these changes are learning-specific and require the same pathways as the substrate of synaptic and behavioral plasticity. Furthermore, intrinsic changes may impact future learning, indicating the involvement of a metaplasticity mechanism. Metaplasticity develops as a result of a series of time-dependent events. That is, an initial priming event first induces physiological or biochemical changes in neurons or synapses that can modulate plasticity induced by a subsequent event (e.g. low- or high-frequency stimulation, or learning, see Abraham & Bear, 1996). In this review, we will briefly examine several forms and basic mechanisms involved in intrinsic plasticity, followed by a discussion of the reciprocal interactions between intrinsic excitability and memory formation. Special emphasis will be placed on recent studies that support the role of intrinsic plasticity in modulation of the strength and allocation of new memories and how this ability is altered during aging. Evidence from these studies will be used to establish intrinsic plasticity as a metaplasticity mechanism that influences memory formation.

1.1. Plasticity: forms and functions

Neural plasticity can serve a multitude of functions (Kim & Linden, 2007). First, plasticity could be *homeostatic* in nature, resulting in restoration of overall firing rates or excitability within

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1074-7427/$ - see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.nlm.2013.07.008

a network (Turrigiano & Nelson, 2004). Second, it could be *mnemonic*, in that it contributes to or forms the basis of the memory trace or engram (Sigurdsson, Doyere, Cain, & LeDoux, 2007). Third, it could serve as a *metaplasticity* mechanism – a higher-order plasticity that affects lower-order synaptic or intrinsic plasticity (Abraham, 2008). Such metaplastic changes could serve to regulate future experience-dependent plasticity and thus impact behavioral plasticity.

In addition to serving many functions, neural plasticity can be achieved in remarkably diverse ways (Marder & Goaillard, 2006). A considerable proportion of these plastic mechanisms affect non-synaptic or intrinsic properties of neurons. Intrinsic plasticity is not only observed following a variety of behavioral paradigms, but it is phylogenetically conserved (see Section 2), which highlights its role in behavioral plasticity. Although synaptic plasticity has received much attention as a mechanism for memory formation (Mayford, Siegelbaum, & Kandel, 2012), it has become increasingly clear that an exclusively synaptic model for memory storage is unlikely and that intrinsic plasticity also plays a critical role in learning and memory (Frick & Johnston, 2005; Song, Detert, Sehgal, & Moyer, 2012; Zhang & Linden, 2003).

Intrinsic plasticity can result from changes in the number or activation of various ion channels. Based on the location of these ion channels, intrinsic plasticity could be local (i.e., limited to a small portion of the dendrite) or global (i.e., somatic, including larger portions of proximal dendrites, thus impacting input from many synapses). Here, we provide a brief description how plasticity of various intrinsic properties affects flow of information within a neuron by following the course of synaptic inputs from the dendrite to the axon terminal.

Intrinsic plasticity (dendritic or somatic) has been linked to modulation of synaptic plasticity and *vice versa*. Modulation of dendritic intrinsic excitability can regulate the throughput of synaptic transmission in various ways (see Fig. 1). First, it can have consequences for the dendritic integration processes that influence degradation of synaptic signals (see Fig. 1, Panel 2; also see Spruston, 2008, for an excellent review of how dendritic properties can affect synaptic integration in pyramidal neurons). For example, in hippocampal CA1 pyramidal neurons, repetitive firing activates the slow afterhyperpolarization current (sI_{AHP}, see Section 1.2 for a description of the AHP, Hotson & Prince, 1980; Lancaster & Adams, 1986; Storm, 1989), which hyperpolarizes the somatic and proximal dendritic membrane potential (Sah & Bekkers, 1996). Interestingly, activation of the sI_{AHP} reduces the amplitude of EPSPs arising from stimulation of the apical dendritic tree (Sah & Bekkers, 1996). Furthermore, inhibition of the sI_{AHP} reduces the threshold for LTP induction in CA1 neurons (Cohen, Coussens, Raymond, & Abraham, 1999; Sah & Bekkers, 1996). Thus, the sI_{AHP} can act as an adjustable gain control mechanism, influencing the ability of synaptic signals from dendrites to reach the soma. Similar effects have been observed in the amygdala as well as the medial prefrontal cortex following modulation of the sI_{AHP} (Faber, Delaney, & Sah, 2005; Power, Bocklisch, Curby, & Sah, 2011; Zaitsev & Anwyl, 2012). Thus, intrinsic plasticity can alter the integration of synaptic inputs, which in turn impacts action potential generation, and neuronal output.

Better transmission of synaptic inputs to the soma is evident as an enhanced ability of an EPSP to generate an action potential (AP), referred to as EPSP-to-spike (ES) coupling or ES potentiation (Bliss & Lomo, 1973). As shown in Fig. 1, Panel 3, ES coupling can undergo bidirectional plasticity following induction of long-term potentiation or depotentiation (Daoudal, Hanada, & Debanne, 2002). Furthermore, environmental enrichment can also enhance ES coupling (Malik & Chattarji, 2012). Although ES plasticity can result from changes in the balance between inhibitory and excitatory synaptic drive, changes in neuronal intrinsic excitability also contribute to ES plasticity (see Daoudal & Debanne, 2003, for review). Thus, intrinsic plasticity in the form of changes in the active properties of dendrites can shape synaptic signals significantly, and thus impact ES coupling.

Once the synaptic inputs reach the soma, various intrinsic factors can contribute to AP initiation, including modulation of AP threshold or local membrane potential. In addition to the all-or-none firing of an AP, efficient relay of neuronal information may require repetitive AP firing (see Fig. 1, Panel 4). For example, in working memory tasks such persistent neuronal firing is critical for maintaining representations across time, and reduced excitability in the form of greater spike frequency adaptation may limit working memory performance (Durstewitz, Seamans, & Sejnowski, 2000).

Single AP characteristics also contribute to neuronal excitability (see Fig. 1, Panel 5). AP amplitude and half-width are plastic intrinsic properties (Varela, Wang, Christianson, Maier, & Cooper, 2012) that can influence the duration and extent of Ca^{2+} influx at the presynaptic terminal (Deng et al., 2013). In addition, when a neuron fires an action potential, the AP can backpropagate into portions of the dendritic tree, which can be influenced by changes in local dendritic excitability (see Fig. 1, Panel 6; Frick, Magee, & Johnston, 2004). Such backpropagating APs (bAPs) are associated with Ca^{2+} influx into the dendritic compartments (Larkum, Zhu, & Sakmann, 1999) and are important for LTP induction (Sjostrom & Hausser, 2006). Moreover, LTP induction enhances local dendritic excitability through modulation of A-type K^+ channels and results in an input-specific increase in bAP amplitude (Frick et al., 2004). Thus, APs and bAPs represent yet another example of how intrinsic neuronal excitability is closely associated with synaptic throughput and plasticity in the brain.

1.2. Mechanisms of intrinsic plasticity: change beyond the synapse

While many neuronal components are involved in intrinsic plasticity (see Section 1.1), the current review largely focuses on plasticity of the afterhyperpolarization (AHP) and spike frequency adaptation (as discussed in Section 2). The AHP is a hyperpolarizing current that follows a burst of action potentials and limits action potential firing (Hotson & Prince, 1980). Spike frequency adaptation refers to the process by which the instantaneous firing of a neuron gradually slows over time in response to sustained excitation (e.g. see Madison & Nicoll, 1984). In CA1 neurons, spike frequency adaptation is heavily influenced by the AHP (although other currents are also involved). When the AHP is small, spike frequency adaptation is also reduced, meaning that a sustained depolarization can now evoke more action potentials.

The AHP is influenced by several underlying currents mediated by Ca^{2+}-activated K^+ channels. There are several phases of the AHP, including fast, medium, and slow AHP (for an excellent review see Storm, 1990). These are evoked as a result of action potential-elicited K^+ currents, including: (1) a voltage- and Ca^{2+}-dependent current (I_C); (2) a voltage-dependent, muscarine-sensitive current (I_M); (3) a Ca^{2+}-dependent and apamin-sensitive current (I_{AHP}); and (4) a Ca^{2+}-dependent apamin-insensitive current (sI_{AHP}; Gasparini & DiFrancesco, 1999; Sah, 1996; Stocker, Krause, & Pedarzani, 1999; Storm, 1989). The fast AHP is modulated by changes in I_C; the medium AHP is modulated by changes in I_C, I_M, and the apamin-sensitive I_{AHP}; the slow AHP is modulated by changes in the apamin-insensitive sI_{AHP} (Gasparini & DiFrancesco, 1999; Sah, 1996; Stocker et al., 1999; Storm, 1989). Although learning-related modulation is possible for all three phases of the AHP (e.g. see Matthews, Linardakis, & Disterhoft, 2009; Matthews, Weible, Shah, & Disterhoft, 2008; Santini, Quirk, & Porter, 2008 for learning-realted changes in fast AHP), the current review will focus mostly on learning-related changes in the medium and slow AHP for two reasons:

Please cite this article in press as: Sehgal, M., et al. Learning to learn – Intrinsic plasticity as a metaplasticity mechanism for memory formation. *Neurobiology of Learning and Memory* (2013), http://dx.doi.org/10.1016/j.nlm.2013.07.008