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SYNAPTIC PLASTICITY AT THE INTERFACE OF HEALTH AND DISEASE: NEW INSIGHTS ON THE ROLE OF ENDOPLASMIC RETICULUM INTRACELLULAR CALCIUM STORES

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Abstract—Work from the past 40 years has unraveled a wealth of information on the cellular and molecular mechanisms underlying synaptic plasticity and their relevance in physiological brain function. At the same time, it has been recognized that a broad range of neurological diseases may be accompanied by severe alterations in synaptic plasticity, i.e., 'maladaptive synaptic plasticity', which could initiate and sustain the remodeling of neuronal networks under pathological conditions. Nonetheless, our current knowledge on the specific contribution and interaction of distinct forms of synaptic plasticity (including metaplasticity and homeostatic plasticity) in the context of pathological brain states remains limited. This review focuses on recent experimental evidence, which highlights the fundamental role of endoplasmic reticulum-mediated Ca^{2+} signals in modulating the duration, direction, extent and type of synaptic plasticity. We discuss the possibility that intracellular Ca^{2+} stores may regulate synaptic plasticity and hence behavioral and cognitive functions at the interface between physiology and pathology.

Key words: spine apparatus, synaptopodin, synaptic scaling, ischemic LTP (iLTP), repetitive transcranial magnetic stimulation (rTMS).

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Abbreviations: AD, Alzheimer's disease; aPC, activated protein C; CO, cisternal organelle; DHPG, (R,S)-3,5-dihydroxyphenylglycine; ER, endoplasmic reticulum; iLTP, ischemic long-term potentiation; IP3R, Inositol 1,4,5 triphosphate receptors; L-VGCC, L-type voltage-gated Ca^{2+} channels; LPS, lipopolysaccharide; LTP, long-term potentiation; mGluR, metabotropic glutamate receptors; NMDA-R, N-methyl-D-Aspartate receptors; PAR1, protease-activated receptor 1; rTMS, repetitive transcranial magnetic stimulation; RyR, Ryanodine receptors; SA, spine apparatus organelle; SERCA, Sarco(endo)plasmatic reticulum Ca^{2+}-ATPases; SO, subsurface organelle; SOCE, Store-operated Ca^{2+} entry; SP, Synaptopodin; TNFa, tumor necrosis factor alpha.

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INTRODUCTION

The brain is equipped with a complex biological machinery, which provides for the unique ability to cope with and respond to changes in specific internal and external stimuli (McEwen and Morrison, 2013; Schmidt et al., 2013; Kolb and Gibb, 2014; Lucassen et al., 2014). This mechanism is known as *neural plasticity.* It involves a wide range of molecular and cellular processes serving fundamental functions in the central nervous system, such as brain development and circuit formation (Sale et al., 2014; Tottenham, 2014; Vitali and Jabaudon, 2014), learning and memory (Shonesy et al., 2014; Takeuchi et al., 2014; Viola et al., 2014) or aging (Dickstein et al., 2013; van der Zee, 2014).

Synapses are the smallest cellular compartment, at which plasticity takes place. Here, the communication between presynaptic and postsynaptic neurons is shaped by an intricate crosstalk between neurons and other cell types, comprising glial cells, endothelial cells and immune cells (Fig. 1A; Salmina, 2009; Petzold and Murthy, 2011; Kowianski et al., 2013; Welberg, 2014). Although still a matter of intense investigation, it has become clear that *synaptic plasticity* plays an essential role in a variety of physiological processes. During the development of the central nervous system for example the interplay of specific molecular gradients, diverse

adhesion molecules and activity-dependent synaptic changes allows for the establishment of precise structural and functional connectivity between cells (Tongiorgi, 2008; Budnik and Salinas, 2011; Kerschensteiner, 2013). Similarly, during learning, long-term changes of specific synaptic inputs in distributed networks lead to persistent changes in the behavioral patterns, actions and choices, which are often interpreted as the retention of information, i.e., memory formation (Behrens et al., 2005; Sadowski et al., 2011; Buzsaki and Moser, 2013; Carasatorre and Ramirez-Amaya, 2013; Headley and Pare, 2013). Furthermore, the ability of synapses to adjust their capacity to express synaptic plasticity (Abraham and Bear, 1996; Hulme et al., 2013) or their actual strength in a compensatory/homeostatic manner (Turrigiano, 2012; Vitureira et al., 2012; Davis, 2013) has been recognized to play an important role in stabilizing neuronal networks (c.f., Marder and Goaillard, 2006).

While the significance of synaptic plasticity for physiological brain functions appears fairly well established, its role under pathological conditions remains not well understood. In this context, it has been proposed that synaptic plasticity may not only be impaired under disease conditions, but *dysregulated synaptic plasticity* could initiate and even sustain the remodeling of neuronal networks and promote behavioral and cognitive deficits (Nava and Roder, 2011; Ferguson et al., 2012; Leuner and Shors, 2013; Moxon et al., 2014; Papa et al., 2014). This concept of 'maladaptive synaptic plasticity' has been suggested to contribute to the pathogenesis of various neurological diseases such as epilepsy (Swann and Rho, 2014; Winkelmann et al., 2014; Zenonos and Richardson, 2014), ischemic stroke (Calabresi et al., 2003; Di Filippo et al., 2008; Takeuchi and Izumi, 2012) and spinal cord injury (Cirillo et al., 2011; Gwak and Hulsebosch, 2011; Ferguson et al., 2012). It is based on the idea that the threshold for synaptic plasticity events may change and/or plasticity mechanisms may be recruited in a non-specific manner thus influencing the capability of neuronal networks to further modulate, i.e., enhance or diminish plastic properties of specific synapses (Wang and Thompson, 2008; Park and Luo, 2010; Cirillo et al., 2012; Timmermans et al., 2013). Here, we aim at providing a concise review on the role of endoplasmic reticulum (ER-) intracellular Ca^{2+} stores in synaptic plasticity. We put forward the hypothesis that the ER could play a pivotal role in setting the duration, direction, extent and type of synaptic plasticity at the interface of health and disease.

THE ER IS A MULTIFUNCTIONAL ORGANELLE, WHICH CONTROLS DIVERSE PROCESSES RELEVANT FOR SYNAPTIC PLASTICITY

The ER is considerably the largest intracellular organelle consisting of a complex three-dimensional network of endomembranes, which are organized in a set of connected tubules, stacks and cisternae. It extends from the nucleus and soma of neurons into dendrites and axons to reach individual excitatory synapses of dendritic spines (Sala and Segal, 2014) and presynaptic boutons, respectively (Fig. 1B). Hence, the ER is strategically positioned (including loci of inhibitory synapses and voltage-sensitive ion channels) in order to control a set of processes relevant for synaptic plasticity, ranging from local protein synthesis and protein maturation, transport of secretory products and mRNAs, to calcium signaling and homeostasis (Verkhratsky, 2005). Although the functional integration of these diverse ER-properties remains largely unknown, its role as an intracellular source of Ca^{2+}, shaping cytosolic Ca^{2+}-transients through the release and/or uptake of Ca^{2+}, has been recognized to have a fundamental role in synaptic plasticity (Segal and Korkotian, 2014).

ER Ca^{2+} is regulated by four major signaling pathways: (1) Ryanodine receptors (RyR), which serve calcium-induced calcium release that amplifies local cytosolic Ca^{2+}-transients (Rose and Konnerth, 2001; Fill and Copello, 2002; Meissner, 2002; Bouchard et al., 2003) (2) Inositol 1,4,5 triphosphate receptors (IP3R), which are recruited by metabotropic glutamate receptors (mGluR) to release Ca^{2+} from intracellular stores (Bezprozvanny and Ehrlich, 1995; Mikoshiba, 1997; Taylor and Laude, 2002; Ribeiro et al., 2010) (3) Sarco(endo)plasmatic reticulum Ca^{2+}-ATPases (SERCA), which pump Ca^{2+} into the ER thereby reducing and/or shaping the dynamics of cytosolic Ca^{2+} (East, 2000; Shull, 2000; Sweadner and Donnet, 2001; Wuytack et al., 2002) and (4) Store-operated Ca^{2+} entry (SOCE), which is triggered after depletion of ER Ca^{2+} and leads to the influx of extracellular Ca^{2+} (e.g., Putney, 1986; Parekh et al., 1997; Palty et al., 2012).

Although the role of ER Ca^{2+} stores in synaptic plasticity seems well established, research in this field remains challenging, because the interplay of diverse signaling pathways and their precise contribution to structural and functional plasticity of excitatory and inhibitory synapses remains controversial (Segal and Korkotian, 2014). The contribution of ER Ca^{2+} to synaptic plasticity may vary depending on the experimental condition, e.g., brain region and neuronal cell type studied, and may not only depend on neuronal ER, but also involve ER-mediated mechanisms in non-neuronal cell types (c.f., Fig. 1A). In addition, it is important to consider that the ER is a dynamic organelle, which constantly changes its position, entering and leaving individual dendritic spines (Toresson and Grant, 2005; Kucharz et al., 2009; Ng and Toresson, 2008, 2011). Finally, the ER forms a set of specialized organelles composed of stacked smooth ER, which are found in dendritic spines (spine apparatus organelle, SA; Gray, 1959; Spacek, 1985; Spacek and Harris, 1997), in the axon initial segment (cisternal organelle; CO; Palay et al., 1968; Peters et al., 1968; Kosaka, 1980; Somogyi and Hamori, 1976; Rasband, 2010) or in close contact with the somatic and dendritic plasma membrane (subsurface organelle; SO; Rosenbluth, 1962; Takahashi and Wood, 1970; Gallart-Palau et al., 2014), adding additional levels of complexity to this topic (c.f., Fig. 1B).