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Sigma-1 Receptors Fine-Tune the Neuronal Networks

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Abstract

The endoplasmic reticular (ER) protein sigma-1 receptor (Sig-1R) has been implicated in CNS disorders including but not limited to neurodegenerative diseases, depression, amnesia, and substance abuse. Sig-1Rs are particularly enriched in the specific domain where ER membranes make contacts with the mitochondria (MAM). Within that specific domain, Sig-1Rs play significant roles governing calcium signaling and reactive oxygen species homeostasis to maintain proper neuronal functions. Studies showed that the Sig-1R is pivotal to regulate neuroplasticity and neural survival via multiple aspects of mechanism. Numerous reports have been focusing on Sig-1R's regulatory effects in ER stress, mitochondrial function, oxidative stress and protein chaperoning. In this book chapter, we will discuss the emerging role of Sig-1R in balancing the populations of neuron and glia and their implications in CNS diseases.

Keywords

Glia-neuron interplay; Astrocyte; Axon pathfinding; Axon pruning; Sigma-1 receptor

7.1 Introduction

Neurons are functionally polarized cells extended with neurites. Among neurites, axons are distinct from other dendrites due to their specialization in conducting signal propagation and protein transport in the neural circuit. Axonal guidance and pathfinding are precisely governed during neuronal developments. Failures or malfunction in axonal maintenance, regeneration and target recognition have been implied in the pathogenesis of several CNS disorders such as Alzheimer's disease, Parkinson's disease, stroke and spinal cord injuries [1–3].

The axonal pathfinding in the developing nervous system is orchestrated by cytoskeletal element polymerizations as well as the regulation of microtubule-associated proteins and the Rho-GTPases family. In addition, guidance cues and other stimuli such as extracellular

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signaling proteins also contribute to the precision of axonal pathfindings. These factors include growth factors, matrix glycoproteins, and integrin receptors. Emerging evidence indicates that local axonal translation plays important roles in axonal maintenance [4, 5]. Many local translational mechanisms for mitochondrial proteins are responsible for preventing free radical production and oxidative damage and thus may be contributing to axonal health [5–7]. Recent reports also indicated that mitochondrial biogenesis is not limited to the cell body, but also occurs locally in axons [8–10].

7.2 The Role of Sig-1R in Neurogenesis and Axon Guidance

We recently discovered that the sigma-1 receptor (Sig-1R), an ER chaperone protein that resides in the ER and mitochondrial contacting site (also known as MAM) [11], is essential for neurogenesis in dentate gyrus of adult hippocampus [12] and is pivotal to maintain dendritic arborization via the regulation of mitochondrial functions during neuronal development [13]. In addition, axon extensions are regulated by Sig-1R activities [14,15]. In Sig-1R depleted neurons, the growth cones exhibit reduction in size and in Rac GTPase specific GEF Tiam1 intensities. Sig-1R depletion also caused significant reduction in axonal density as well as decreased mitochondrial number and mobility [15]. These findings further support the important notion of Sig-1Rs in maintaining neuronal survival and their implications in many CNS disorders.

In a primary rat hippocampal neuron model, we employed Sig-1R knockdown (KD) using the AAV transduction. Sig-1R deficiency induces non-neuronal cell proliferation as indicated by DAPI staining. Non-neuronal cell proliferation is an early sign of gliosis, and is usually accompanied by astrocytic activation. Axons were visualized by immuostaining with the α-acetylated tubulin. We noticed that the Sig-1R KD neurons exhibited disoriented axon projections (Fig. 7.1). Wild type (WT) hippocampal neurons displayed structurally organized axon networks and connections, while the axons of the KD neurons established abnormal circular routes and displayed a disoriented phenotype. These findings suggest that Sig-1R deficiency may lead to poor arborization of presynaptic axons and fewer synapse formations. Regressive axon growth is essential to coordinate functional axon connections. Axon pruning occurs constantly during axon pathfinding and elongation. Axons may dislocate and mistarget if left without proper pruning. In addition, aberrant axon pathfinding has been associated with neurological diseases [16]. Though Sig-1Rs have been shown to participate in axon elongations [14, 15], surprisingly, Sig-1R antagonists induced aberrant axon elongation in a primary mouse cortical neuron model. 1 μM BD-1063 significantly increased axon elongations in neurons as indicated by phospho neurofilament immunostaining (Fig. 7.2). Similar results were observed using another Sig-1R specific antagonist haloperidol (data not shown). Perhaps it is too early to conclude that inactivation of Sig-1R enhances axonal activities and elongation. Rather, antagonizing Sig-1Rs may disrupt the well-orchestrated mechanisms that are tightly associated with pruning and guidance. This leads to the hypothesis that Sig-1Rs may be involved in axon guidance/pathfinding as well as in axon pruning and facilitate axon targeting to proper functional areas to form functional synapses.

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7.3 Conclusions

Non-neuronal cells are abundant in the central nervous system (CNS) and without doubt participate in axon signaling. Astroglia play important roles and indispensable contributions in many CNS processes including shaping memory formation and recovery from CNS injury. It has been well recognized that the bidirectional astrocyte-neuron communication is part of the axon pruning/pathfinding [17]. A single astrocyte can form synaptic islands by enwrapping a maximum of eight neuron somas and making contact with 300–600 neuronal dendrites [18]. At the synaptic clefts, astrocytes and neurons form the so-called “tripartite synapse” to establish bidirectional communications [19, 20]. Astrocytes can trigger the exocytotic release of gliotransmitters including glutamate, GABA, NMDA receptor co-agonist D-serine and ATP/adenosine, as well as neurotrophic factors [21]. On the other hand, reactive astrocytes can function as the extrinsic inhibition at the lesion site to inhibit axon growth [22, 23]. Sig-1Rs are enriched in astrocytes [24].

Accumulating evidence shows that Sig-1Rs exert regulatory effects on neuropathic pain [25], traumatic brain injury-induced inflammatory responses [26], as well as psychostimulants-induced autophagy [27] and neuroinflammation responses [28] via the astrocytic or microglial activation. Thus, Sig-1Rs may oversee axon guidance/pathfinding via the precise glia-neuron communication networks (Fig. 7.1) as well as govern the functional axon growth via the mechanisms that regulate recessive events (Fig. 7.2). Sig-1R ligands may exert great therapeutic potentials in establishing functional neuronal networks in this regard.

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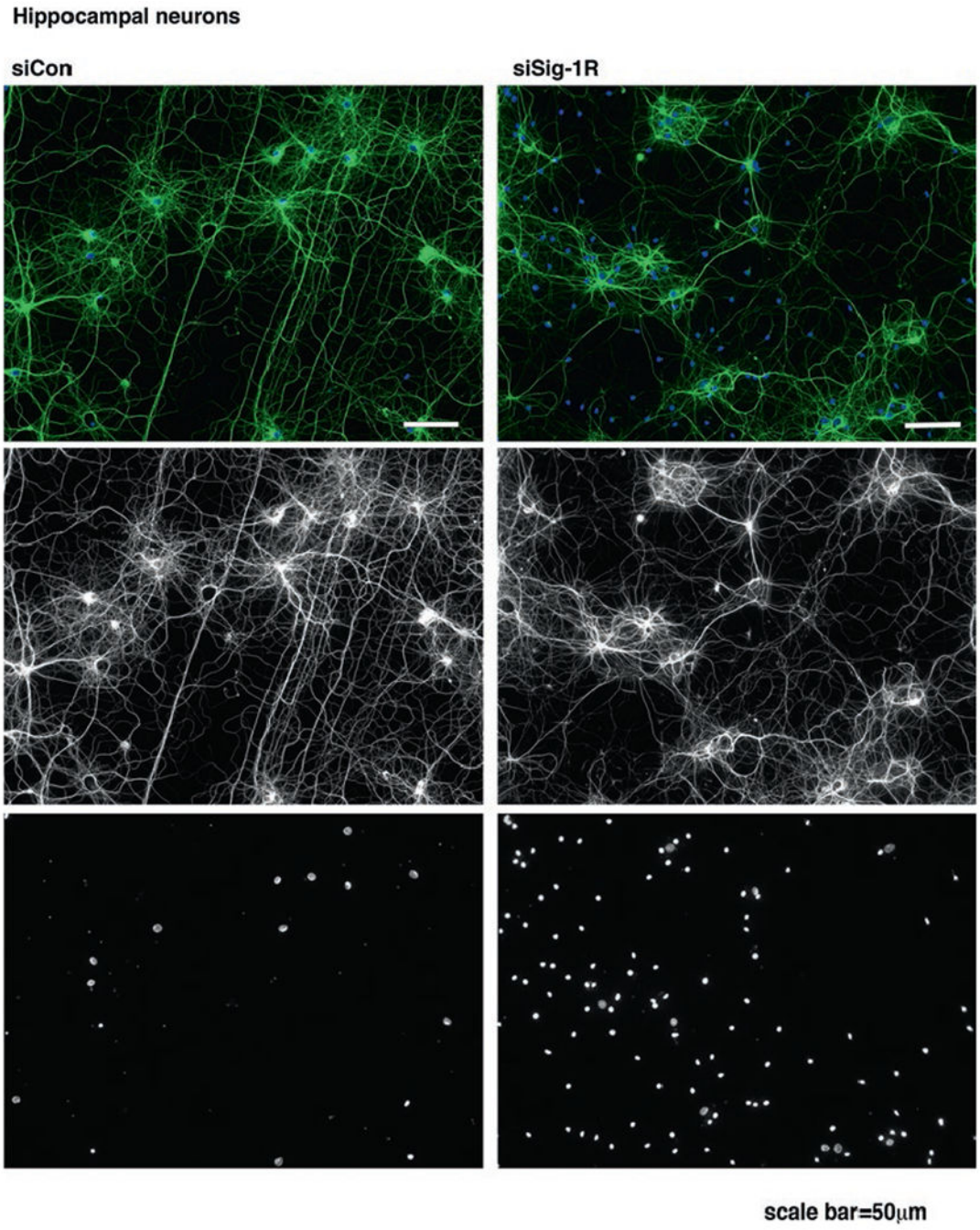

Fig. 7.1. Sig-1R is required to maintain neuronal polarity.

Equal density of cultured hippocampal neurons were infected with an AAV vector expressing a short hair-pin RNA (shRNA) sequence for Sig-1R. Ten days after transduction, neurons were immunostained with the axon marker acetylated alpha tubulin (*green*). Depletion of Sig-1R disrupts axon polarity and arborization as axons in the Sig-1R KD groups wrapped around neuronal somas and failed to display proper connections. Though the population of neurons in both control and KD groups is similar, Sig-1R KD cultures may be more susceptible to gliosis as indicated by more non-neuronal DAPI staining (*blue*)

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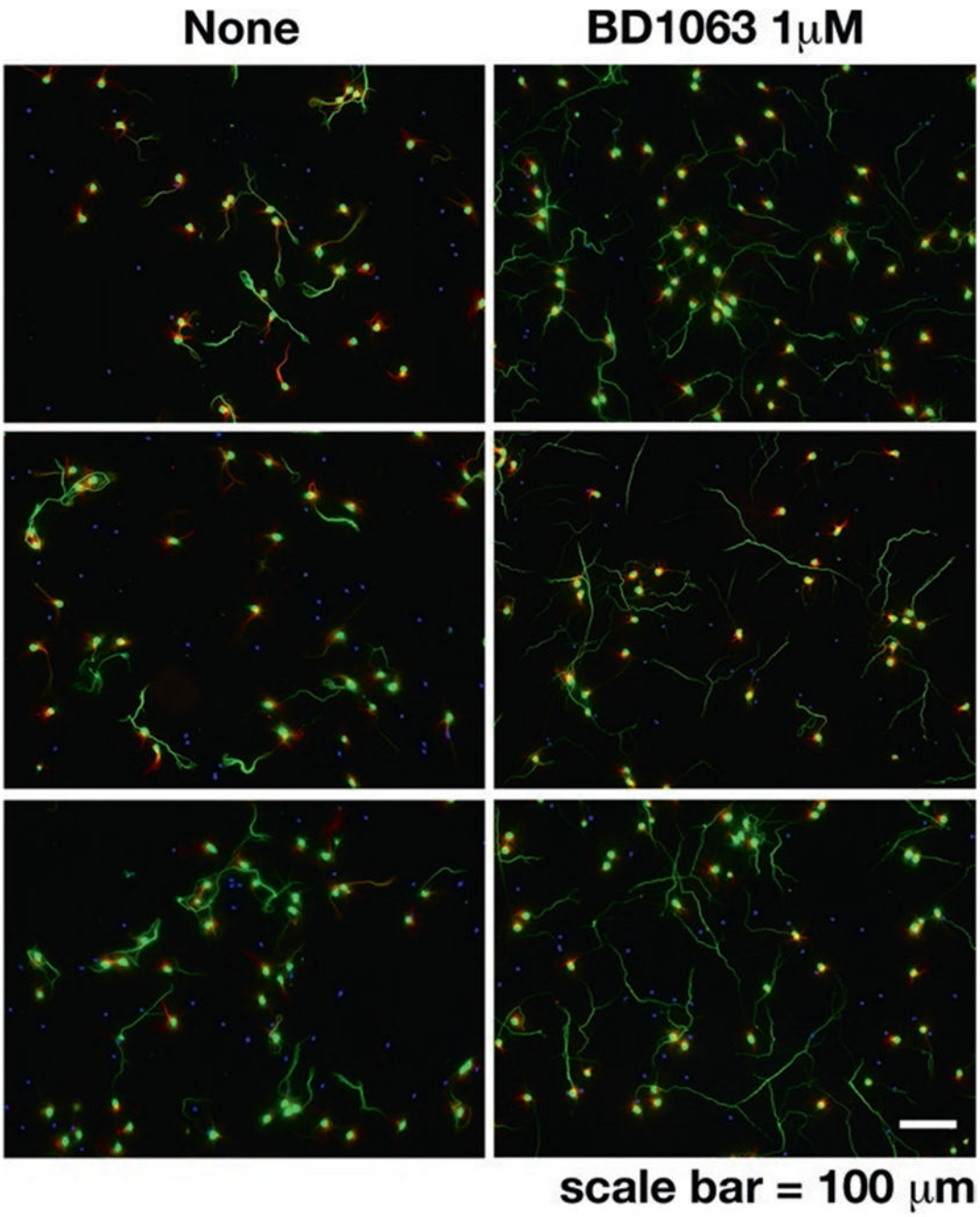

Fig. 7.2. Aberrant axon elongation induced by Sig-1R antagonist.

Primary mouse cortical neurons were treated with the Sig-1R antagonist BD-1063 (1 μM) at days in vitro (DIV) 7. Axon lengths were observed at DIV 10 by immunostaining of phospho neurofilament (pNF-H, SMI 31). Neurons treated with BD-1063 (*right panels*) showed significantly longer axons than the control neurons (*left panels*)