REVIEW

Effect of the Sigma-1 receptor on neurite outgrowth

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Neurite outgrowth is one of the essential processes underlying development and plasticity of the nervous system. Enhancing neurite outgrowth, along with neural protection, is one of the most prominent therapeutic strategies against neuronal degeneration or damage. The sigma-1 receptor (Sig-1R) is a brain-enriched a receptor chaperone expressed in the ER membrane. As Sig-1R is involved in the mode of action of several neurotherapeutic drugs, it is important to elucidate the molecular mechanism of Sig-1R. This would increase our understanding of the pathology of neuronal diseases as well as aid in establishing new approaches for their treatment. In this review, we focus on the findings that Sig-1R contributes to neural protection and neurite outgrowth even in pathological conditions, such as in high glutamate concentration. Although a large part of molecular mechanisms of Sig-1R remains unknown, the interaction of Sig-1R and neurotrophin receptors has been recently reported. Activation of Sig-1R leads to an increase in the secretion of neurotrophin. Meanwhile, Sig-1R enhances neurotrophin receptor-mediated neurite outgrowth upon activation. We discuss the neurite outgrowth effect of Sig-1R, especially in relation to neurotrophin-mediated neurite outgrowth.

Keywords: Sigma-1 receptor, neurite outgrowth, neurotrophin receptor, TrkB

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Introduction

Neurite outgrowth is an essential process to establish the neural wiring in the nervous system. A malfunctioning of this process is associated with the pathology of many neuropsychiatric diseases. The sigma-1 receptor (Sig-1R) is one of the many receptors that have been studied as promising targets for alternative therapeutic treatments. The merit of studying this receptor is the practicality of manipulating its activation. Sig-1R can be easily activated or inactivated by various kinds of synthetic drugs. Moreover, several psychotherapeutic drugs that have been clinically used for the treatment of depression, schizophrenia, and other disorders[1], are known to bind to Sig-1R and have either agonistic or antagonistic effects. Since it is easy to control its activation, the receptor is expected to be a promising target for new approaches to reveal the pathology of, and/or remedy for, neuropsychiatric disorders including depression and Alzheimer's disease [1]. Nevertheless, the precise molecular mechanisms of Sig-1R are still under the investigation. Here, we focus on the role of Sig-1R in neurite outgrowth with an implicated mechanism involving neurotrophin receptors, along with our recent report on Sig-1R and tropomyosin receptor kinase B (TrkB) interactions.

Molecular Profile of Sig-1R

Sig-1R was first identified as a subtype of opioid receptor showing a strong binding to SKF-10047, which lead to opioid effects thus the receptor was named "sigma receptor" for the first letter of SKF-10047 in Greek[2]. Now, the receptor is recognized as a novel receptor chaperone on the ER membrane[3]. The receptor is, however, expressed in various types of organs, such as liver, kidney, heart, and others [4, 5]. Among these organs, the highest expression is detected in the brain[5]. Although expression of Sig-1R was found in various parts of the brain on both the RNA and protein level, the highest signals were detected especially in the granular layer of the olfactory bulb, hypothalamus, specific layers of cortex, and the dorsal horn of the spinal cord [4, 6]. On the cellular level, Sig-1R is highly expressed at the ER-mitochondrion interface, called the mitochondria associated membrane (MAM) [3]. Although Sig-1R is a transmembrane protein that spans the ER membrane twice at the MAM, it is reported to translocate to the plasma membrane upon its activation [3, 7-10]. Furthermore, it has been suggested that the receptor is secreted from cells, as it was detected in the medium of Sig-1R-EYFP-transfected NG108 cell culture [9].

The Effect of Sig-1R on Neurite Outgrowth

Although its molecular profiling is still in progress, Sig-1R is now recognized as a novel ER chaperone regulating Ca^{2+} signaling [3,8]. When Sig-1R is inactivated, it attaches to another molecular chaperone, immunoglobulin heavy chain binding protein (BiP). Upon stimulation, including cellular Ca^{2+} depletion and synthetic agonists, Sig-1R releases BiP and binds to inositol triphosphate (IP_3) receptors. Subsequently, Sig-1R stabilizes the fragile IP_3 receptors. These events lead to Ca^{2+} release from the ER to both the cytosol and mitochondria. This Ca^{2+} influx initiates many molecular transduction pathways, which result in the modulation of cellular activities in many ways, including neurite outgrowth [11-13]. This Sig-1R-induced neurite outgrowth has been shown not only with selective Sig-1R agonists but also with known treatments for neuropsychiatric diseases such as those used in Alzheimer's disease [14]. Similarly, the function of Sig-1R-mediated neurite outgrowth via neurotrophin receptors is discussed in the later section.

Sig-1R-mediated neurite outgrowth has even been confirmed in environments unsuitable for neurons. With increasing the survival rate, the neurite elongation effect has been confirmed in motor neuron and neuron in dorsal root ganglia under excess glutamate environment *in vitro*, that reproduce the glutamate excitotoxicity after spinal cord injury [15, 16]. Sig-1R-mediated axonal elongation in the harsh condition was observed not only *in vitro* studies, but also *in vitro* study using brain injury and stroke mouse models [17, 18]. These effects imply the possibility that activated Sig-1R may contribute to the reformation of degenerated or lost neuronal circuits, even in environments deleterious to neurons.

Neurotrophin Receptors

One of the well-studied molecules for neurite outgrowth is the tropomyosin receptor kinase (Trk) receptor family. This membrane-bound receptor family consists of TrkA, TrkB, and TrkC. Each receptor is activated by its designated neurotrophin, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-4/5 (NT-4/5), and NT-3, respectively. When they are activated, they dimerize, autophosphorylate on their specific tyrosine residues, and then activate their downstream signaling cascades. Eventually, these continuous events give rise to neurite outgrowth, cellular survival, and synaptic plasticity in the cell [19-22]. Because of their crucial roles in neuron, it is easy to imagine that impairment of these receptors would have a major impact on neuronal activities. Down-regulation or defects of these receptors are suspected to be involved in depression [23, 24], and Alzheimer's disease[25].

Sig-1R and Neurotrophin receptors

As both Sig-1R and neurotrophin receptors have similar functions and are suggested to play a role in the pathology of several common psychiatric diseases, an association between these receptors has been reported. First, Sig-1R was suggested to enhance TrkA-induced neurite outgrowth. In addition to the dose-dependent increase of Sig-1R expression in NGF-treated PC12 cells, it was indicated that some widely used antidepressants, such as imipramine, promote NGF-induced neuronal sprouting via Sig-1R[26]. However the molecular mechanism was still remain unknown. Later, employing specific inhibitors of molecules downstream of TrkA, another group identified several transduction pathways that are specifically promoted by Sig-1R activation[27]. Further, there are reports that show donepezil, which is known for the treatment of Alzheimer's disease, and infenprodil, a known therapeutic intervention in post-cerebral ischemia, promote NGF-induced neurite outgrowth via Sig-1R [14, 28]. These imply a possible new remedy for neuronal defects by Sig-1R.

Likewise, the association of Sig-1R and BDNF-induced neurite outgrowth has also been reported. TrkB activity is associated with the effects of antidepressants[29]. Yagasaki et al. showed that antidepressants reinforce BDNF-induced glutamate release through PLC-γ via Sig-1R

activation [30]. This effect of antidepressants was diminished by Sig-1R antagonists and enhanced by Sig-1R overexpression [30]. Then, the activation of Sig-1R by selective agonists solely was found to enhance BDNF expression in the hippocampus[31]. Even though these reports indicate that the relationship between Sig-1R and BDNF is a part of the mode of action of antidepressants, the mechanism of how Sig-1R upregulates BDNF expression was not revealed. Four years after the last report on the connection between BDNF and Sig-1R, Fujimoto et al. reported that SA4503 promotes a post-translational modification, converting pro-BDNF into mature BDNF, and enhances its secretion level in a rat neuroblastoma cell line [32]. This suggests that the chaperone activity of Sig-1R on BDNF plays a role in the molecular mechanism of upregulating BDNF secretion by antidepressants.

Interaction of Sig-1R and TrkB

As described above, several reports indicated a correlation between Sig-1R and neurotrophin receptors. Nevertheless, their direct linkage remained to be explored. We recently reported that Sig-1R physically interacts with TrkB and enhances its activity [33]. In an attempt to focus on Sig-1R and only TrkB among other neurotrophin receptors, cerebellar granule neurons (CGNs), which express predominantly TrkB among neurotrophin receptors, were used in our study. First, we confirmed that stimulation of Sig-1R promoted neurite outgrowth regardless of the presence of BDNF in the environment. Next, since the trk inhibitor, K252a, abrogated this effect, we hypothesized that Sig-1R enhanced TrkB activity in the presence of BDNF. As expected, phosphorylation of TrkB specifically on tyrosine residue at 515 was enhanced when BDNF and the Sig-1R selective agonist, PRE-084, were both present in the CGN primary culture. Then, the physical interaction between Sig-1R and TrkB was shown in both cell lines with Sig-1R and TrkB overexpression, and endogenous Sig-1R and TrkB in CGN. Although the interaction of Sig-1R and several membrane-bound ion channels has been reported before [34-36], we provided evidence for the physical interaction of Sig-1R with neurotrophin receptor and its neurite elongation effect. Our finding revealed at least a first part of the molecular mechanisms of stimulated Sig-1R in neurite outgrowth in the presence of BDNF. Whether this interaction occurs simultaneously with upregulation of BDNF secretion is still unknown. However, revealing mechanisms such as these leads to a better understanding of Sig-1R (Figure 1).

Conclusions

Because of the convenient manipulation of Sig-1R, much attention has been paid to its role in various neuronal diseases as part of the search for new remedies. Remodeling of a lost neuronal circuit is a promising approach against neuronal degeneration and impairment. Activation of Sig-1R results in neurite outgrowth even in unsuitable conditions [15-18]. Moreover, Sig-1R may contribute to the mode of action of several neurotherapeutic drugs by enhancing the neurite outgrowth derived from neurotrophins [14, 26-32]. These findings strongly suggest that Sig-1R may be engaged in the pathology of neuronal damage and impairment, and the mode of action of known therapeutic drugs. Therefore Sig-1R may be one of the most suitable molecules to study for finding new remedies of numbers of neuronal defects. In addition, combining these previous reports with our own report, studying the mechanism underlying the interaction of Sig-1R and neurotrophin receptors in more detail would emphasize the strong connection between Sig-1R and pathogenic mechanisms and/or new treatments for neuronal impairment and degeneration.

A better understanding of the molecular mechanisms of Sig-1R, for instance, knowledge on the binding site of Sig-1R and TrkB or the detailed mechanism of translocation of Sig-1R to the plasma membrane, would lead to more practical applications of this receptor in the future.

Conflict of interest

The authors declare that they have no conflict of interest.

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