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Critical review

The involvement of the sigma-1 receptor in neurodegeneration and neurorestoration



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ABSTRACT

The sigma-1 receptor (Sig-1R) is a single 25 kD polypeptide and a chaperone protein immersed in lipid rafts of the endoplasmic reticulum (ER) where it interacts with mitochondria at the mitochondria-associated ER membrane domain (MAM). Upon activation, the Sig-1R binds to the inositol triphosphate receptor (IP3R), and modulates cellular calcium (Ca^{2+}) homeostasis. Also, the activated Sig-1R modulates plasma membrane receptor and ion channel functions, and may regulate cellular excitability. Further, the Sig-1R promotes trafficking of lipids and proteins essential for neurotransmission, cell growth and motility. Activation of the Sig-1R provides neuroprotection and is neurorestorative in cellular and animal models of neurodegenerative diseases and brain ischaemia. Neuroprotection appears to be due to inhibition of cellular Ca^{2+} toxicity and/or inflammation, and neurorestoration may include balancing aberrant neurotransmission or stimulation of synaptogenesis, thus remodelling brain connectivity. Single nucleotide polymorphisms and mutations of the *SIGMAR1* gene worsen outcome in Alzheimer's disease and myotrophic lateral sclerosis supporting a role of Sig-1R in neurodegenerative disease. The combined neuroprotective and neurorestorative actions of the Sig-1R, provide a broad therapeutic time window of Sig-1R agonists. The Sig-1R is therefore a strong therapeutic target for the development of new treatments for neurodegenerative diseases and stroke.

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1. Introduction

Neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) as well as acute brain injury, such as stroke or traumatic brain injury, are devastating conditions that lead to cell death and loss of critical brain functions (1–5). A major challenge for contemporary clinical neuroscience is to elucidate the mechanisms leading to cell death during these severe conditions and propose novel treatments that may alleviate or ameliorate subsequent brain dysfunctions. The loss of brain function is associated with neuronal degeneration in particular brain areas, but the activity of neurons in the vicinity of degenerated or degenerating cells, such as the peri-infarct tissue

after stroke, can also be depressed (3,6). Currently, new neuroprotective therapies are directed towards preventing degeneration of neurons at risk by abolishing the primary cause of cell death, such as aggregation of misfolded proteins seen in PD, AD or ALS, or by reinstating blood flow following stroke (thrombolysis). Another approach to limit tissue loss and decrease brain dysfunction is by protecting neurons against destructive processes caused by calcium (Ca^{2+}) and glutamate toxicity, oxidative stress or inflammatory processes (5). More recently, it has been demonstrated that it is possible to stimulate recovery or function of neurons not afflicted by disease or injury. This can be accomplished by attenuating dysfunction of neurotransmission, or by simulating brain plasticity thereby remodelling brain connectivity (6). As will be evident in this review, the Sig-1R has been implicated in many of these processes, reflecting its modulatory role in multiple cellular and physiological mechanisms (7,8). Hence, Sig-1R activation is clearly neuroprotective, but can also stimulate recovery of lost function by enhancing repair or plasticity mechanisms in intact healthy neurons of brains afflicted by disease or injury. In this overview we will therefore discuss the sigma-1 receptor (Sig-1R), (i) as a modulator

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of various cell destructive processes, (ii) as a stimulator of brain repair and plasticity, and (iii) as a factor affecting the risk for neurodegenerative diseases and stroke.

2. Neuroprotection by Sig-1R agonists

The Sig-1R is found throughout the body including brain cells: neurons, astrocytes, oligodendrocytes and microglia of the central nervous system (CNS) (9–15) it is bound to the ceramide-enriched microdomain, also called lipid rafts, in complex with the glucose-related protein 78/binding immunoglobulin protein (GRP78/BiP), an endoplasmic reticulum (ER) chaperone of the mitochondria-associated ER membrane (MAM) domain (16). The polypeptide has two transmembrane sequences and the steroid binding domain-like I and II regions (17,18), which also bind cholesterol and other lipids (19) as well as synthetic Sig-1R ligands, such as neurosteroids, antipsychotics, antidepressants and psychostimulants (20). Recently, dimethyl tryptamine has been identified as a potential endogenous ligand for the Sig-1R (21,22).

The neuroprotective actions of the Sig-1R have been reported using various agonists in experimental models of acute brain injury or neurodegeneration. In models of experimental stroke, agonists of the Sig-1R diminish infarct size and improve functional recovery. Using the Sig-1R agonist 4-phenyl-1-(4-phenylbutyl) piperidine (PPBP) administered intravenously starting 15 min prior to the end of ischaemia and then during reperfusion until the study endpoint at 4 h, showed a reduction of infarct volume in a cat model of transient middle cerebral artery occlusion (tMCAO) (23). Importantly, the treatment did not affect cerebral blood flow during reperfusion. Similar results were obtained in rats subjected to 2 h of tMCAO and treated continuously with PPBP for 22 h starting 1 h after occlusion (24) or with (+) pentazocine (25). Furthermore, a reduction of infarct size was also found in rats that were subjected to tMCAO and treated with PRE-084 (5 mg/kg i.p.) at 3 h into reperfusion with evaluation of infarct size at 2 days after permanent MCAO (pMCAO) (26). Rats treated with the Sig-1R agonist dimemorfan starting 15 min before occlusion, and immediately or 2 h after tMCAO, display smaller infarcts than animals treated with vehicle. Importantly, the protective effect could be blocked by concurrent administration of the Sig-1R antagonist BD1047 (27). Interestingly, acute administration of a low dose haloperidol, an antipsychotic drug and Sig-1R antagonist also displayed neuroprotection in ovariectomized rats 24 h after tMCAO (28). Likewise, treatment prior to and at stroke onset with the selective serotonin reuptake inhibitor and Sig-1R agonist fluvoxamine resulted in smaller cortical infarcts and better neurological scores after pMCAO (29). This neuroprotective effect was abolished by concomitant treatment with the antagonist NE-100. Together, these studies show that treatment with Sig-1R agonists during the acute phase after experimental stroke prevent brain tissue demise and enhance recovery of lost neurological functions. In other models of acute brain injury, PRE-084 treatment reduces lesion size in a model of excitotoxic perinatal brain injury (30). Also, daily treatment with PRE-084 enhances survival of motoneurons after root avulsion injury (31).

Neuroprotection by Sig-1R agonists is also achieved in models of neurodegenerative disorders. Administration of PRE-084 for 35 days resulted in significant higher number of tyrosine hydroxylase (TH)-positive neurons in the lesioned dorsolateral striatum and pars compacta of the substantia nigra after a 6-hydroxydopamine (6-OHDA) lesion to the striatum associated with better functional outcome (11). Likewise, in a model of ALS using the SOD1^{G93A} mice, the Sig-1R agonists PRE-084 (32,33) or SA4503 (34) attenuated the gradual loss of motoneurons.

The antidepressant actions of the Sig-1R agonists PRE-084 and (-)MR-22 in beta(25-35)-amyloid peptide-treated mice (35), prompted further neuroprotection studies using these compounds. In a cellular model of AD, beta(25-35)-amyloid peptide-induced neuronal death was significantly inhibited by concomitant treatment with PRE-084 or (-)MR-22. This protective effect could be abolished by co-application of the Sig-1R antagonist NE-100 (36). The protective effect of (-)MR-22 was confirmed in an IgG saporin/amyloid toxicity model (37). Moreover, in the beta(25-35)-amyloid peptide model of AD, administration of the aminotetrahydrofuran derivate ANAVEX-2-73, a mixed muscarinic and Sig-1R agonist, significantly blocked Tau phosphorylation, a hallmark of AD pathology (38). Together, these studies show that Sig-1R activation may antagonize AD brain pathology, which was recently supported by a PET investigation showing a lower binding capacity for Sig-1R in patients with AD compared to age-matched individuals (39).

3. Mechanisms of neuroprotection by Sig-1R activation

3.1. Influence of Sig-1R on Ca²⁺ homeostasis

As a consequence of its cellular localization, distribution, and characteristics as a molecular chaperone, the Sig-1R can modulate multiple intracellular pathways and signalling cascades involving Ca²⁺ ions (Figs. 1 and 2). Since Ca²⁺ toxicity plays a pivotal role in cell death after stroke and neurodegenerative diseases, the Sig-1R-mediated effect on Ca²⁺ homeostasis may therefore be of crucial importance for its protective actions on the brain. At the MAM, Sig-1Rs are involved in the regulation of Ca²⁺ mobilization from ER stores. In addition, Sig-1Rs contribute to the stability of inositol trisphosphate receptor (IP3R) channels to ensure proper Ca²⁺ transport between the two organelles (9,17). Furthermore, Sig-1Rs stimulate phospholipase C (PLC) resulting in increased levels of IP3 in the cytoplasm (40) with subsequent release of Ca²⁺ from the ER via activation of IP3R channels (41). Furthermore, the acid sensing ion channel Ia (42,43), voltage sensitive Ca²⁺ channels (44), as well as AMPA and NMDA receptors (45), modulate intracellular Ca²⁺ levels and are regulated by Sig-1Rs. Neuroprotection by Sig-1R agonists could therefore be provided by preventing detrimental elevations of intracellular Ca²⁺-mediated effects by these channels. Under these conditions, activated Sig-1Rs are involved in normalizing intracellular ischaemia- or acidosis-evoked Ca²⁺ overloads (46,47), an effect blocked by selective Sig-1R antagonists BD1047 and BD1063 (46).

3.2. Regulation of nNOS and apoptosis by Sig-1R

In neurons, recruitment and coupling of the Ca²⁺ dependent neuronal nitric oxide (NO) synthase (nNOS) to postsynaptic density protein 95 (PSD95) is inhibited by Sig-1R activation (48,49). Subsequently, a reduction of nNOS in membrane fractions and nNOS association with the NR2 subunit of NMDA receptors has been described (49) resulting in a downregulation of the pro-apoptotic stress-regulated p38 mitogen-activated protein kinase (MAPK) (48).

Upon stress or injury, elevated cytoplasmic Ca²⁺ levels reduce nNOS phosphorylation increasing nNOS activity and leading to NO-induced protein kinase C (PKC)-dependent phosphorylation of NR1 (50). Sig-1Rs also modulate the activity of pleiotropic transcription factors i.e. nuclear factor kappaB, cyclic adenosine monophosphate (cAMP) response element-binding protein and c-fos, which are involved in the regulation of immediate-early genes, cell metabolism and transport processes. These transcription factors can modulate pro- and anti-inflammatory genes as well as cell death and survival genes such as interleukins 8 and 10, *bcl-2* (51) and

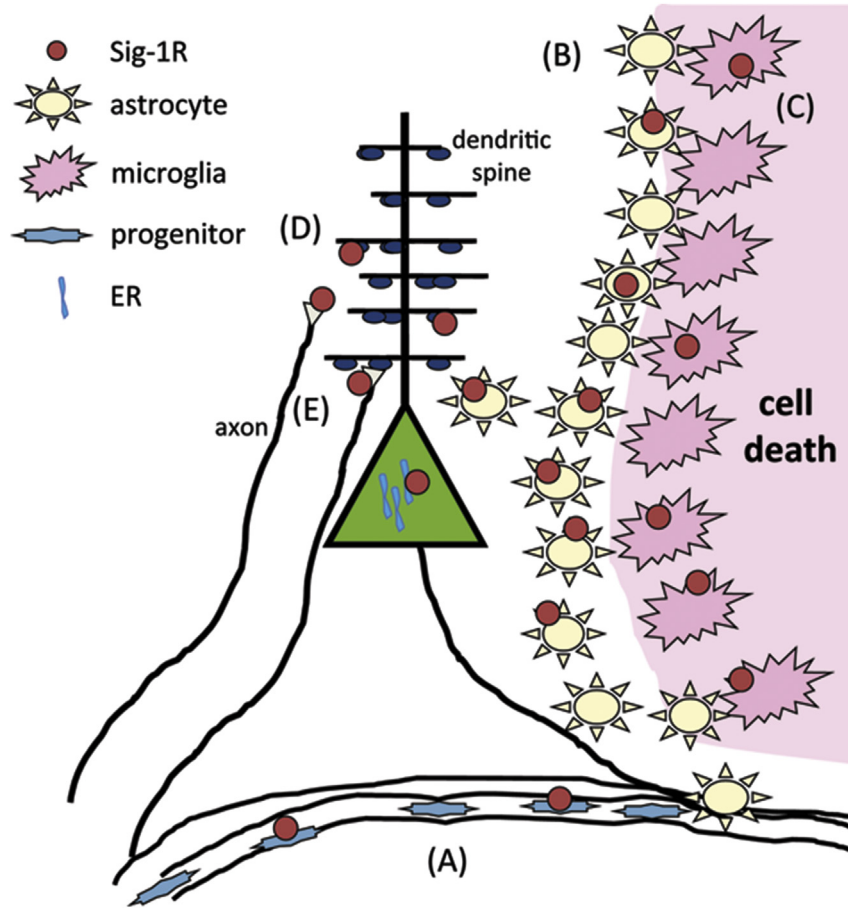


Fig. 1. A schematic picture of the cellular distribution of Sig-1Rs (red dots) relevant for neuroprotection and neurorestoration. Sig-1Rs are found on (A) migrating progenitor cells, (B) reactive astrocytes in the vicinity of surviving and degenerated neurons, (C) microglia cells in glia scar, (D) on neurons, (E) and axonal endings.

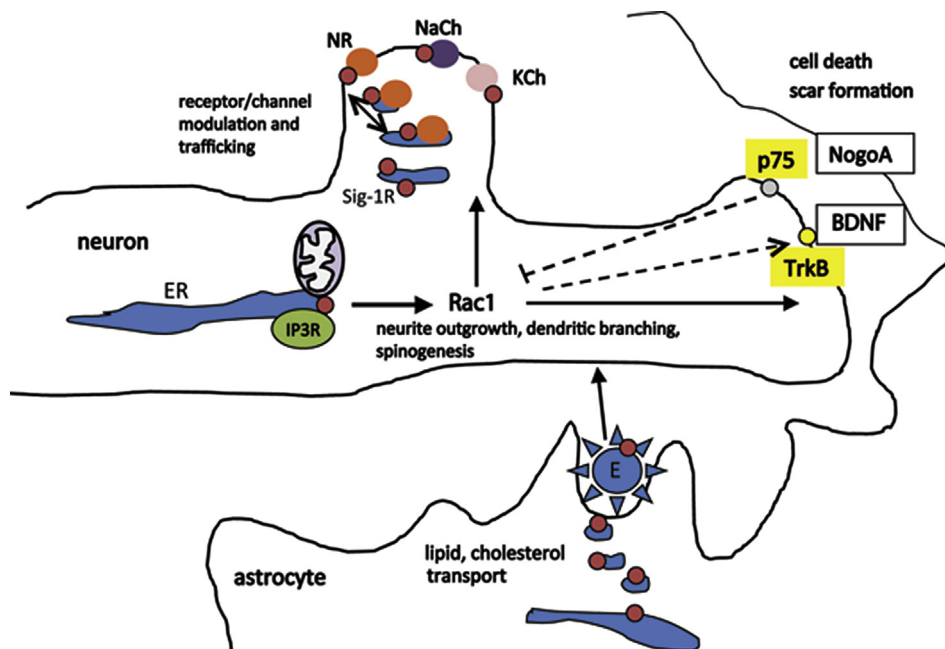


Fig. 2. Hypothetical picture on the involvement of Sig-1Rs (red dots) in cellular processes related to regeneration. Abbreviations: NR, NMDA receptor; NaCh, sodium channel; KCh, potassium channel; IP3R, inositol trisphosphate receptor; E, exosome; BDNF, brain derived neurotrophic factor.

brain derived neurotrophic factor (BDNF) (52). Activation of Sig-1Rs, directly or indirectly via the activation of protein kinase C (53), affects phosphorylation of extracellular-signal-regulated kinases 1/2 resulting in an increase of neurotrophic growth factors i.e. BDNF and glial cell line-derived factor (GDNF) (11).

3.3. Influence of Sig-1Rs on brain inflammation

Some of the neuroprotective effects mediated by the Sig-1R have been attributed to anti-inflammatory actions of Sig-1R ligands in various disease models. Increased expression and levels of pro-inflammatory cytokines have been found in acute brain injury models, and treatment with PRE-084 or dimemorfan within the first 24 h after stroke onset significantly reduced the level of cytokines (26,27). In contrast to the depressive effects of Sig-1R agonists on inflammation early after injury, no effect on elevated levels of pro-inflammatory cytokines was observed by delayed treatment with SA4503 in rats subjected to tMCAO (15). Likewise, chronic treatment with PRE-084 significantly reduced the number of CD68 positive cells in the affected striatum and substantia nigra in mice subjected to a 6-OHDA lesion (11).

4. Sig-1Rs and tissue repair

4.1. Sig-1R and molecular trafficking

The brain rapidly responds to cell death by proliferation of glial cells, and subsequently by remodelling (plasticity) of synapses and neuronal connections to compensate for lost brain functions (54) (Fig. 1). In this context, gliosis and inflammation, as well as receptor trafficking, spine remodelling and axonal outgrowth, are important recovery-promoting processes where the Sig-1R has been implicated (Fig. 2).

The recovery of brain function after injury depends on recuperation of surviving or healthy neurons afflicted by injury or disease (Fig. 1). Recovery can be accomplished by obliterating factors hampering synaptic transmission such as inflammatory mediators, toxic substances released from dying or dead neurons, or by spontaneous activation of plasticity-promoting processes. The area surrounding the brain infarct after stroke is highly dynamic, involving astrocytes, oligodendrocytes, neuronal progenitor cells, microglia and macrophages in tissue repair. The synergistic action of these cells secures the removal of dead or injured neurons, reutilization of cellular constituents, lipids in particular, and the formation of a "scar" that encapsulates the infarct, preventing the diffusion of toxic substances that may propagate damage and cause further dysfunction of surviving neurons in its vicinity (55). An efficient scar-forming process will allow faster recovery of neurons at risk. Here, the Sig-1R may play an important role by virtue of its regulation of molecular trafficking.

The activated Sig-1R, immersed in lipid rafts, is a vehicle for transport of proteins or lipids to the plasma membrane (8,14,56,57). In neurons this could either involve transport of de novo synthesized proteins from the cell body or promote trafficking in synapses as part of the externalization/internalization process of receptors/channels (58). The translocation of lipid rafts formed in the ER of glia and neurons, also allows the transport of cholesterol and ceramides essential for neuronal function, (10,14). The intracellular trafficking and extracellular release of lipids supported by Sig-1R, may serve to replenish lipids in areas of high turnover such as synapses and/or support growth and proliferation of cells. In this context, it is noteworthy that the Sig-1R also activates gene expression of specific protein mRNAs such as that of the NMDA receptor (58), and processing of various growth factors particularly BDNF (52,59).

The Sig-1R in lipid rafts is upregulated after a hypoxic episode. Trafficking is enhanced in cells activated by a Sig-1R agonist and is depressed by an antagonist (14). After experimental stroke, the Sig-1R is strongly expressed in reactive astrocytes surrounding the infarct and can also be found in the extracellular space. This suggests that Sig-1R may promote the release of exosomes that support the scar-forming and/or plasticity-promoting processes in recuperating neurons (Fig. 1).

Also, Sig-1R agonists could stimulate cell proliferation and migration of progenitor cells. Within hours after stroke, GFAP is expressed in the subventricular zone (60), an important site for cell genesis. Indeed, the Sig-1R is involved in the proliferation of oligodendrocytes (10). Furthermore, in Sig-1R KO animals, neurogenesis in the subventricular zone of the hippocampus is depressed (61).

4.2. Sig-1R and neuronal plasticity

Brain plasticity involves several alternative processes that may act alone or in concert. These processes encompass changes in the activity of receptors and ion channels by covalent modifications, fluctuations in receptor density at spines of active/silent synapses, or formation of new synapses including axonal outgrowth and synaptogenesis (6). Once new connections are established, functional recovery will depend on similar mechanisms as seen during experience-driven plasticity such as memory formation and learning.

As mentioned above, Sig-1R ligands could modulate neurotransmission and, hence, recovery of function after disease and injury (Fig. 2). Normal brain function is the result of a balanced dynamic interplay between excitatory and inhibitory signalling within the microcircuitry in various brain regions. For example, following brain injury, this balance is disturbed with a net increase in GABA-mediated inhibition (62,63). In models of learning, it has been recently reported that Sig-1R stimulation can enhance NMDA receptor trafficking to the plasma membrane (58). This could contribute to recovery of lost function after injury by normalizing the interhemispheric imbalance in excitability.

Sig-1R agonists stimulate neurite outgrowth, a central process in the formation of new neuronal connections during brain plasticity (Fig. 2). The Sig-1R is particularly enriched in the neurite growth cone of PC12 cells (64). Stimulating the Sig-1R in PC12 cells with pentazocine or antidepressants enhances neurite outgrowth (65–67), which is prevented by the Sig-1R antagonist NE-100. Likewise, treatment of cortical neurons with SA4503 increases neurite outgrowth which was prevented by Sig-1R knockdown (14). Also, treatment with SA4503 increased spine length and spine head size of hippocampal pyramidal neurons (14). The Sig-1R and growth factors appear to act synergistically; Sig-1R stimulation increases synthesis of growth factors such as BDNF and GDNF (11), and the action of Sig-1R on neurite outgrowth is dependent on growth factors such as nerve growth factor (NGF) or BDNF (31,52,59,68). Dendritic branching is stimulated by Sig-1R activation and is diminished by Sig-1R knockdown (69). The BDNF/TrkB receptor complex-associated intracellular signalling is required for the Sig-1R/BDNF synergistic action and is mediated by the Rac1-GTP complex (69,70). The Rac protein normally acts in concert with Rho and cdc42 to regulate cell shape and motility (71). Activation of the Rac1-GTP pathway could possibly overcome the axonal growth inhibitory action of myelin-associated glycoprotein, Nogo-A and the oligodendrocyte myelin glycoprotein proteins present in the glial scar. These proteins interact with the NogoR-receptor (NgR)/LINGO-1/p75 complex at the neuronal surface and inhibit axonal and neurite outgrowth through the Rho pathway (72).

The relevance of Sig-1R activation in plasticity and repair processes is evident in models of PD where treatment with the Sig-1R agonist PRE-084 increases BDNF and GDNF levels and enhances sprouting of TH-positive cells, which is not evident in Sig-1R KO animals (11). In a model of experimental stroke, treatment with the Sig-1R agonist SA4503 starting 2 days after injury, a time point when the growth of the infarct has subsided, enhances recovery of neurological function. This happens without affecting infarct size, which strongly suggests that Sig-1R activation enhances tissue repair and remodelling (14).

5. Significance of the Sig-1R for disease of the human brain

Observations in the human brain also support a role of Sig-1Rs in cell death and brain dysfunction during neurodegenerative diseases. For example, Sig-1R accumulates in nuclear inclusions of neurons in patients with various neurodegenerative diseases (73) and the levels of the Sig-1R are low in early AD (39). Single nucleotide polymorphisms of the *SIGMAR1* gene (74) are associated with increased risk of AD (75) and individuals with mutations in the Sig-1R carry risk of acquiring ALS (76). The *SIGMAR1* region on chromosome 9p13 displays two important polymorphisms: s1799729 (GC-241-240TT) and rs1800866 (Gln2Pro). rs1800866 is found in the first exon, while rs1799729 is found in the proximal promoter region. In the protein structure of the Sig-1R, rs1800866 is located in the MQWAVGRR motif (77) at the N-terminal part of the protein, which is an ER binding region. Hence, this mutation could affect Sig-1R associated trafficking processes. Indeed, the rs1799729 and rs1800866 have a strong influence in CNS disease (75,78,79), yet, in contrast, in a recent study done with a cohort of stroke patients, we were not able to find any significant association between rs1800866 and rs1799729 in either stroke risk, severity or outcome (80).

6. Conclusion

Various studies have demonstrated that the Sig-1R is involved in maintaining cellular homeostasis and neuronal plasticity in the brain under physiological conditions and protecting the brain against cell loss due to injury or disease. Understanding the signalling cascades regulated by the Sig-1R in acute or delayed neurodegeneration as well as in neuronal plasticity will aid the development of new pharmacological means to improve lost neurological function in acute brain injuries and neurodegenerative disorders.

Competing interests

The authors declare no financial and non-financial competing interests.

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