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Review

Sphingosine-1-Phosphate: Boon and Bane for the Brain

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Abstract
Sphingosine-1-phosphate (S1P), an evolutionary conserved bioactive lipid, is essential for brain development, but might also exert detrimental effects in terminally differentiated post-mitotic neurons. Its concentration in the brain is tightly regulated by specific kinases and phosphatases, and mainly by the S1P degrading enzyme, S1P-lyase (S1PL). The role of S1P in neurons was initially studied in primary cultures by using structural analogues. During the last 3 years generation of a S1PL deficient mouse model substantially promoted our knowledge on the functional role of S1P metabolism in the brain, and its potential relation to neurodegenerative diseases. However, our understanding of the molecular mechanisms that underlie the physiological and pathophysiological actions of S1P in neurons remains rather scarce.

Introduction

Sphingolipids are essential components of lipid bilayers conferring unique structural and signaling functions. Together with cholesterol they are main components of detergent resistant membrane microdomains, called lipid rafts [1]. Membrane dynamics and vesicular trafficking are tightly related to the interconversion of sphingolipids [2].

Complex glycosphingolipids, especially the sialic acid-containing gangliosides are particularly abundant and exhibit characteristic profiles in neuronal cells [3]. Vital functions

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including information flux and transduction occur along neuronal membranes. It is therefore not surprising that impaired sphingolipid metabolism is closely related to various neurological disorders. Metabolic intermediates of these lipids, notably sphingosine, ceramide, and S1P, are bioactive molecules and regulate numerous cellular signalling pathways [4]. S1P can act extracellularly as a ligand for a family of five specific G protein coupled receptors (S1PRs1-5) or inside of cells as a second messenger [5]. In line with the involvement in complex cellular processes, S1P regulates cell survival and differentiation, motility and cytoskeleton dynamics as well as cell specific roles in immunity and angiogenesis [6, 7].

S1P signalling via specific receptors is critical during development. Deficiency in S1PR1 leads to embryonic lethality due to impaired vascular maturation and severe haemorrhage [8]. S1P is, however, not only essential for vascularisation and organ development in the periphery, but also for development of the brain [9]. In addition S1P is an important mediator of nociception [10, 11]. Besides the signalling via specific receptors experimental evidence also suggests receptor-independent functions of S1P in calcium homeostasis [12], cellular growth [13], inhibition of apoptosis [14, 15], histone modifications [16], and nuclear factor-κB signalling [17].

In peripheral tissues, S1P mainly exerts pro-survival and proliferative effects [13]. However, increased S1P levels could also induce death of terminally differentiated post-mitotic neurons [18]. Recent evidence also suggests a role of S1P in Alzheimer's disease (AD) [19-22]. Intriguingly, S1P in murine neurons stimulates beta-site APP cleaving enzyme (BACE1) that catalyzes the rate-limiting step in the formation of the amyloid peptide (Aβ), a major component of the characteristic extracellular plaques in the AD brain [23].

Here we give an overview on experimental data that argue in favour of S1P as a potential molecular link connecting impaired lipid metabolism and neurodegeneration.

S1P metabolism

S1P is a degradation product of ceramide, the central molecule of sphingolipid metabolism (Fig.1). A family of ceramidases, which differ in their pH optimum and subcellular localization, hydrolyses ceramide to sphingosine, which is either phosphorylated to S1P or reutilised for ceramide formation via a salvage pathway [3]. Interestingly, acid ceramidase is a major glycoprotein in human brain and mainly expressed in neurons [24]. Even more interestingly, the expression and activity of this enzyme were found to be elevated in Alzheimer's disease brain and to colocalize with neurofibrillary tangles, suggesting an involvement in neuronal degeneration during the pathogenesis of AD [24]. Sphingosine can be phosphorylated by two sphingosine kinase (SK) isoforms, SK1 and SK2 [25, 26]. The two enzymes differ not only in their kinetic properties and subcellular localizations, but also in their developmental- and tissue-specific expression. While the cytosolic SK1 is activated upon recruitment to the plasma membrane, the constitutively membrane associated SK2 is active in the ER and nucleus. There are contradictory reports on the expression of the two isoforms in the brain. Although SK1 was reported to positively regulate glutamate secretion in embryonic rat hippocampal neurons [27], there are studies with human as well as with rodent brain that identified exclusively SK2, suggesting that this isoform is particularly important in the central nervous system [28, 29]. Two very recent studies, however, highlight the importance of SK1 in AD pathogenesis in human brain [21, 22]. S1P can be dephosphorylated to sphingosine by specific S1P phosphatases (SPP1 and SPP2) and less specific lipid phosphate phosphatases (LPPs) [30]. The interplay of SKs and SPPs allows a fine-tuned regulation of S1P and sphingosine concentrations. In addition, S1P can undergo irreversible cleavage by S1PL (Fig. 1) [31]. S1PL cleaves S1P at the C2-3 carbon bond yielding a long-chain aldehyde and phosphoethanolamine, thus sitting at the junction between sphingolipid and phospholipid metabolism [32]. An N-terminal hydrophobic domain anchors this pyridoxal 5'-phosphate-dependent enzyme to the ER membrane with its active site facing the cytosol. Thus phosphatases enable cells to recycle the sphingoid

scaffold in a ceramide salvage pathway, whereas S1PL activity results in a net reduction of sphingolipid content, representing the only exit point for sphingolipid degradation.

S1P – not always a survival signal

In most cell types S1P and its metabolic precursor ceramide exert antagonistic effects on cell survival. Due to its tissue protective properties S1P emerged primarily as a survival signal whereas ceramide mediates cellular stress and promotes cell death [33, 34]. The observation that S1P can rescue cells from ceramide induced apoptosis [14, 35], led to the ceramide/S1P rheostat model, which assumes that the dynamic balance of intracellular levels of these two bioactive sphingolipids is critical for cellular fate decisions [36]. However, elevated levels of endogenous sphingoid long-chain base phosphates, structurally resembling S1P caused cell death in yeast [37]. In addition, S1P treatment induced apoptosis in mammalian cells including HepG2 [38] and hepatic myofibroblasts [39]. In neuronal cells the grade of differentiation appears to be important for the effect of S1P on cell survival. While S1P stimulates proliferation in neural progenitor cells [40], it induces apoptosis in differentiated hippocampal neurons [41]. As shown in Fig. 1, the metabolism of the two antagonistic bioactive sphingolipids, ceramide and S1P, is closely interconnected. This might hamper the study of their individual signalling function. Accordingly, a recent study in HeLa cells with different pharmacological modulators suggests that not ceramide itself, but rather downstream metabolites of ceramide such as S1P and especially hexadecenal promote cell death [42].

Neurotoxicity of S1P and of structural analogues

Early studies with the synthetic sphingosine analogue *cis*-4-methylsphingosine (cimes) carrying a *cis*- instead of the naturally occuring *trans*- double bond and an additional methyl group on carbon atom C4 [43] showed pro-mitogenic effect of its short-lived physiological counterpart S1P in quiescent Swiss 3T3 fibroblasts [44]. However, it induced apoptosis in terminally differentiated post-mitotic neurons [45]. Cimes is rapidly taken up by cells, but unlike the physiological archetype it was not N-acylated to the respective ceramide. Rather it is exclusively phosphorylated to the corresponding *cis*-4-methylsphingosine-phosphate (cimesP) [46]. In contrast to S1P, cimesP is not cleaved by S1PL, and thus, accumulates in a time-dependent and cell type-specific manner. Consequently, the use of cimes as a synthetic pro-drug that is just phosphorylated to the cleavage resistant S1P-analogue cimesP should enable to differentiate between the potential role of ceramide and S1P in cell fate decisions.

The apoptotic effect of cimesP is mediated by a caspase-dependent and p38 MAPK-triggered pathway and involves an aberrant reactivation of the cell cycle [45]. Interestingly, S1P affected similar pathways, but due to its fast intracellular turn-over in a more transient and less pronounced manner, likely not reaching higher critical concentrations for directing neurons into apoptosis. However, in S1PL-deficient neurons, where degradation of S1P is inhibited (Fig. 1), the levels of accumulated S1P correlated with neuronal apoptosis [18]. Importantly, only S1P generated by SK2 induced neuronal apoptosis, thus highlighting the significance of the subcellular site for the physiological impact of a bioactive compound [18]. SK2 was also reported to be up-regulated in brains of patients with sporadic Alzheimer's disease [23]. While SK1 is highly specific for the phosphorylation of sphingosine, SK2 has broader substrate specificity and also catalyzes phosphorylation of cimes [18]. Accordingly, cimes failed to induce death of SK2-deficient neurons, but was toxic in wild type and SK1-deficient neurons [19]. Notably, the immunosuppressant FTY720 (fingolimod) exerted a similar neurotoxic effect as cimes (Fig. 2). This was not surprising given the fact that FTY720 is a natural sphingosine analogue pro-drug functionally activated by SK2-catalysed phosphorylation [47]. Also phosphorylation of AAL(R), a structural analogue of FTY720 by

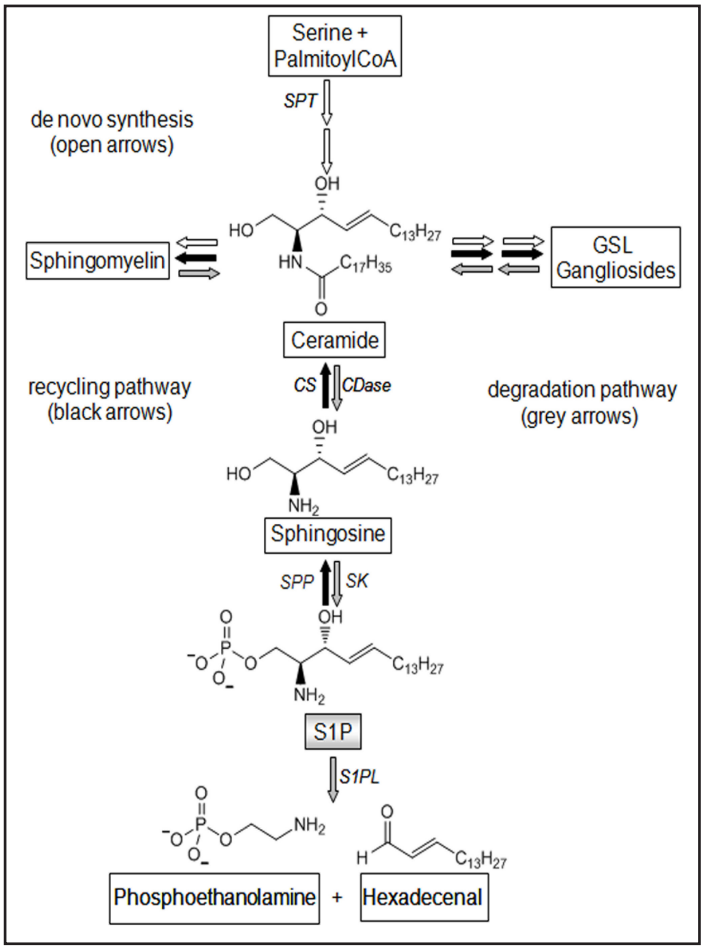


Fig. 1. Scheme of sphingolipid metabolism. Ceramide is formed either *de novo* starting from serine and palmitoylCoA or by hydrolysis of sphingomyelin or glycosphingolipids (GSL) including gangliosides. Alternatively, ceramide can be generated by recycling of its degradation product sphingosine. Ceramide is then further metabolized to more complex sphingolipids including sphingomyelin and GSL from which gangliosides are particularly abundant in neurons. Sphingosine-1-phosphate (S1P) is generated by phosphorylation of sphingosine by sphingosine kinases (SK) of which SK2 isoform predominates in the brain. It is either cleaved by S1PL into common cellular metabolites or dephosphorylated back to sphingosine by S1P-phosphatases (SPP). CS, ceramide synthase; CDase, ceramidases, from which the acid isoform prevails in the brain; SPT, serine palmitoyltransferase.

SK2 was shown to be essential for its potential to induce apoptosis in mouse and human lymphocytes [48]. Similarly, cimes induced apoptosis in B104 neuroblastoma cells [49]. By contrast, direct exposure of mouse embryonic cortical neurons to FTY720-phosphate (1 – 100 pM) protected them against Aβ toxicity [50]. This neuroprotective effect was accompanied by an enhanced expression of brain-derived neurotrophic factor. Obviously, phosphorylated FTY720 in picomolar concentrations is neuroprotective, but when accumulating above a certain threshold - possibly in vulnerable subcellular compartments - might become neurotoxic.

Further studies with S1PL-deficient neurons and with cimes established that downstream neurotoxic signalling of S1P is promoted by the ER-specific proteases caspase-12 and calpain without involvement of mitochondria [19]. The activation of these proteases was dependent on elevated intracellular calcium levels that could result from S1P triggered release from ER stores [51]. Thus, S1P-dependent neurotoxicity involves similar pathways as shown for that triggered by Alzheimer associated Aβ-peptide [19]. Treatment of neurons with extracellular Aβ also activated caspase-12 by disruption of the calcium homeostasis in the ER, independent on membrane- or mitochondria targeted apoptotic signals [52]. Furthermore, Aβ can also induce an aberrant reactivation of cell cycle events and activation of CDK5 [53, 54]. It is important to note that calpain activation has been described in several neuronal pathologies, many of them including also CDK5 deregulation caused by calpain mediated cleavage of the CDK5 regulatory subunit p35 [55, 56]. CDK5 was suggested to link Aβ-peptide containing senile plaques with neurofibrillary tangles composed of hyperphosphorylated tau [57]. Accordingly, S1P-induced neurotoxocity is accompanied by CDK5 activation and hyperphosphorylation of tau [19].

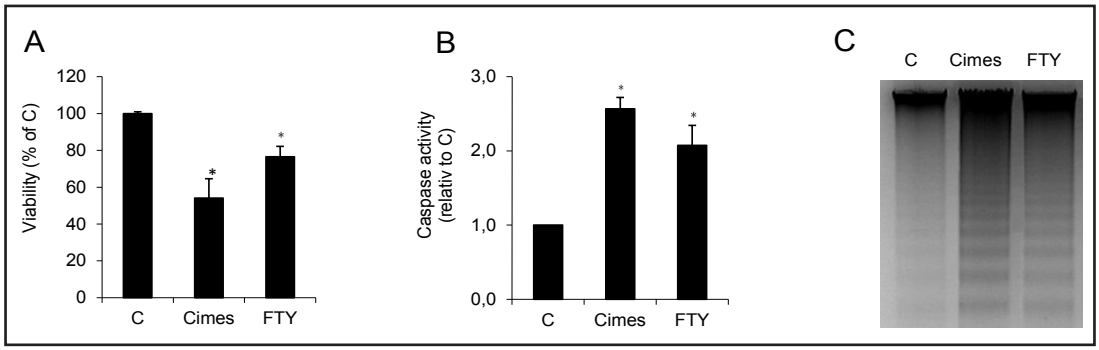
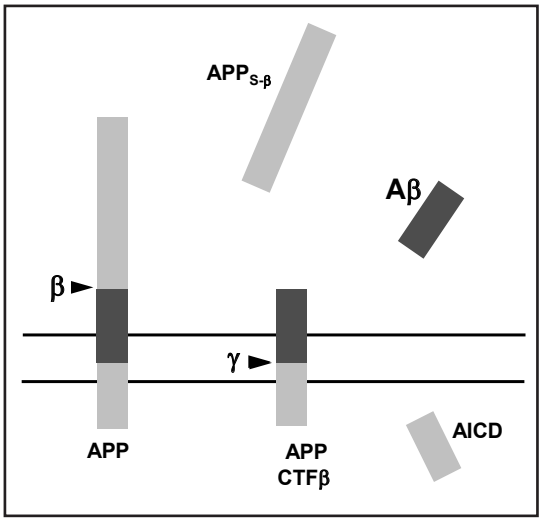


Fig. 2. Fingolimod (FTY720) and cimes induce apoptosis in post-mitotic neurons. Cerebellar neurons were incubated with vehicle (controls, C), or with 10 μM of cimes or fingolimod. After 24 h viability (A), relative effector-caspase activity (B) as well as genomic DNA (C) were assessed as described previously [18]. *significantly different from controls (p<0,05).

Fig. 3. Generation of Aβ by proteolytic processing of the APP. APP is a type I membrane protein with a large ectodomain, a single transmembrane domain, and a small cytoplasmic tail. The Aβ domain starts in the ectodomain and extends into the transmembrane region. Aβ generation is initiated by cleavage of APP in the ectodomain by β-secretase. The resulting C-terminal fragment (CTF) is then processed by γ-secretase within the transmembrane region leading to secretion of Aβ into the extracellular milieu and release of the APP intracellular domain into the cytosol (AICD).



S1P – a potential mediator in the pathogenesis of Alzheimer's disease

Alzheimer's disease is characterized by the progressive accumulation of Aβ in form of extracellular plaques and intraneuronal aggregates of the microtubuli-associated tau protein [58]. Strong evidence from genetics, biochemistry and cell biology supports a critical role of Aβ in the initiation and progression of AD [59, 60]. Aβ derives by proteolytic processing of the amyloid precursor protein (APP), involving proteases called β- and γ-secretase (Fig. 3) [61, 62]. APP and the secretases are integral membrane proteins, and numerous studies have demonstrated a role of cholesterol in the proteolytic processing of APP and the generation of Aβ [63-66]. However, the exact molecular mechanisms and the relevance of cholesterol in AD pathogenesis is still under debate [63-66]. The role of lipid homeostasis in the brain, particularly that of membrane lipids, in AD pathogenesis has been recognized and considered in multitudinous studies [67, 68].

Notably, neuronal membranes contain a highly specific and characteristic pattern of complex sphingolipids. It is therefore not surprising that neuronal function and survival is dependent on the metabolism of these lipids. As depicted above, growing evidence indicates that S1P, a bioactive catabolic intermediate of all sphingolipids might represent a potential link between ganglioside metabolism and neurodegeneration. Neuronal levels of S1P are tightly regulated at very low concentrations in the picomolar range [18, 69]. A direct role of S1P in neuronal Aβ generation has been reported recently [23]. The inhibition of SKs and thus the generation of S1P decreased Aβ production in primary neuronal cultures and in

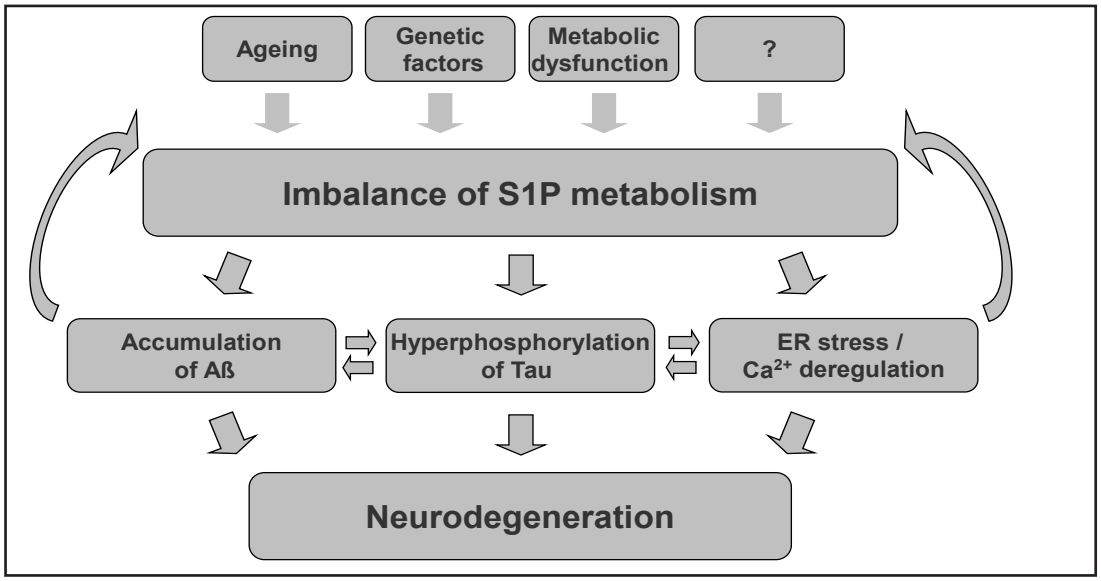


Fig. 4. Hypothetical model for the role of S1P in neurodegeneration. Alterations in S1P levels that might be caused by different factors including ageing, genetics and metabolic changes are associated with hyperphosphorylation of tau, increased generation of Aβ, and deregulation of Ca^{2+} homeostasis eventually leading to neurodegeneration.

brains of mice. Further, it has been shown that S1P stimulates the β-secretase BACE1 by direct interaction with the enzyme [23]. Interestingly, primary cultured neurons of S1PL-deficient mice revealed a striking correlation of elevated S1P concentration and neuronal death. The S1P-induced neurotoxicity was found to be mediated by a calcium/calpain/CDK5 promoted mechanism. Moreover, S1PL deficiency also induced hyperphosphorylation of tau [19]. In addition, S1PL knock-out cells showed strong accumulation of APP and potentially amyloidogenic APP C-terminal fragments, which was associated with impaired lysosomal degradation [70]. Besides, we also observed increased generation of Aβ in S1PL-deficient cells [70]. Together, the combined data from pharmacologic and genetic models suggest that S1P could modulate both Aβ generation and toxicity. Of interest, in the central nervous system S1P levels were found to be highest in spinal cord and brainstem, moderate in cerebellum and lowest in cortex [71]. The distribution of S1P correlated positively with S1PL expression, suggesting an up-regulation of this enzyme in areas with high S1P levels [72]. Apparently, brain regions most susceptible to neurodegeneration have low S1P content. Based on our finding that neurons with most abundant S1PL expression are those that degenerate first in S1PL-deficient brains [19], and on the fact that S1PL is the major regulator of S1P levels [73], one could speculate that brain regions with lowest S1P content are those with most abundant S1PL activity, and are therefore particularly sensitive to an impaired degradation of S1P by S1PL. Thus, alterations in the levels of S1P, sphingosine and probably other lipids caused by different factors, could affect the metabolism of both characteristic proteins in AD, Aβ and tau (Fig. 4). Notably, the effect of S1PL deficiency on sphingolipid metabolism in neurons and cholesterol levels in the brain was rather slight when compared with that in liver and serum [69, 73]. Thus, no significant changes of the content of ceramide, sphingomyelin and of glycosphingolipids in neurons could be detected [69]. This might be explained by the substantially decreased *de novo* formation of sphingolipids and a concurrent increase in the recycling pathway in these neurons [69].

Two very recent reports also highlight the importance of S1P in AD pathology, but suggest that rather a reduction than an increase of S1P in the brain is associated with neurodegeneration [21, 22]. Interestingly, the region-specific decline of the S1P/sphingosine ratio in the hippocampus and temporal cortex during the course of AD pathogenesis was

correlated primarily with a loss of SK1 activity [21]. In addition, expression of SK1 was reduced whereas that of S1PL was increased in the entorhinal cortex in human AD brains suggesting a negative correlation of Aβ deposits and S1P content in AD relevant brain regions [22].

Concordantly, FTY720 reduced Aβ release in cultured neurons, apparently independent of known downstream signaling pathways of S1PRs [74]. FTY720 was also found to attenuate Aβ-induced cognitive impairment and neuronal damage in the hippocampus of rats [75]. The neuroprotective effect of FTY720 was associated with altered gene transcription of mitogen activated protein kinases (MAPKs) and some inflammatory markers [76]. Thus, FTY720 might not only affect Aβ generation, but also the neruoinflammatory process during the pathogenesis of AD.

Conclusions and Outlook

The inhibition of S1P degradation tightly correlates with neuronal death *in vitro* and *in vivo*. Interestingly, S1PL deficiency also induces hyperphosphorylation of tau [19], and altered metabolism of APP resulting in increased generation of Aβ [70]. Thus, a genetic model of impaired S1P metabolism reveals certain disease specific alterations of the two major proteins involved in AD. This raises intriguing questions on the pathophysiological role of S1P metabolism during AD pathogenesis: Could age-dependent alterations in S1P/sphingosine metabolism trigger or at least modulate pathological pathways leading to the accumulation of Aβ, hyperphosphorylation of tau and ultimately cell death in AD? Could S1P and related metabolites and enzymes be further explored for AD therapy, prevention or biomarker identification? A recent study reports on reduced expression of SK1 and enhanced expression of S1PL suggesting a deregulated S1P signalling in AD brains [22]. Thus, it will be important to further dissect the molecular mechanisms that underlie the different effects of S1P metabolism in AD pathogenesis.

Disclosure Statement

The authors declare no conflict of interest in writing this article.

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