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Review

Therapeutic Role of ELOVL in Neurological Diseases

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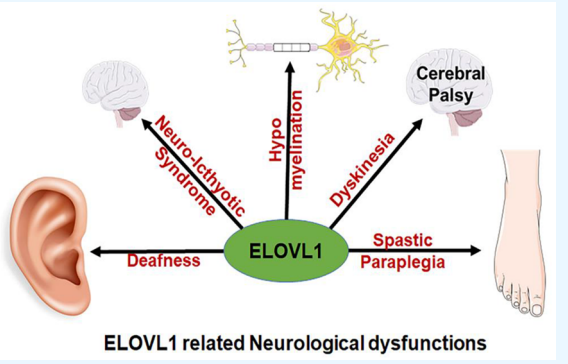
ABSTRACT: Fatty acids play an important role in controlling the energy balance of mammals. De novo lipogenesis also generates a significant amount of lipids that are endogenously produced in addition to their ingestion. Fatty acid elongation beyond 16 carbons (palmitic acid), which can lead to the production of very long chain fatty acids (VLCFA), can be caused by the rate-limiting condensation process. Seven elongases, ELOVL1−7, have been identified in mammals and each has a unique substrate specificity. Researchers have recently developed a keen interest in the elongation of very long chain fatty acids protein 1 (ELOVL1) enzyme as a potential treatment for a variety of diseases. A number of neurological disorders directly or indirectly related to ELOVL1 involve the elongation of monounsaturated (C20:1 and C22:1) and saturated (C18:0-C26:0) acyl-CoAs. VLCFAs and ELOVL1 have a direct impact on the neurological disease. Other neurological symptoms such as ichthyotic keratoderma, spasticity, and hypomyelination have also been linked to the major enzyme (ELOVL1). Recently, ELOVL1 has also been heavily used to treat a number of diseases. The current review focuses on in-depth unique insights regarding the role of ELOVL1 as a therapeutic target and associated neurological disorders.



ELOVL1 related Neurological dysfunctions

1. INTRODUCTION

Long-chain fatty acids (LCFAs, composed of 12C−20C) and very long-chain fatty acids (VLCFAs, more than 20C) are the building blocks of sphingolipids and ceramides as well as eicosanoid (20-carbon polyunsaturated fatty acid (PUFA)) oxidized derivatives produced by the signaling molecule cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (cytP450).These lipids perform a variety of characteristic cellular tasks and are structural elements of biological membranes, where they are vital as permeability barriers of skin, retina, liver, and myelin sheaths of neurons[1,2] Hyperlipidemia, obesity, and atherosclerosis are just a few examples of the numerous metabolic syndromes and disorders that are the direct result of dysregulation of fatty acid metabolism.[3,4] In addition, abnormalities in lipid production and remodeling are associated with more than 100 genetic diseases, including stargardt syndrome and spinocerebellar ataxia.[2,5] Different types of fatty acids are required for normal healthy body function. Mouse knockout studies show the involvement of ELOVL protein (very long chain fatty acid elongation) in insulin resistance and hepatic steatosis,[1,6] and ELOVL7 in particular is associated with cancer, early onset Parkinson's disease, and necroptosis.[7,8] However, not much is known about the chemical processes underlying key steps in ELOVL production of fatty acids and lipids. VLCFAs are further categorized into monounsaturated (MFAs), polyunsaturated (PUFAs), and saturated fatty acids (SFAs). There are four different enzymes that comprise the FA elongase apparatus namely acyl-CoA synthetase, 3-keto-acyl-CoA synthase (Elovl), 3-keto-acyl-CoA reductase, and 3-hydroxy acyl-CoA dehydratase.[9] Seven elongases (ELOVL1−7) have been discovered with characteristic substrate specificity along with distinctive patterns of expression in mammalian tissues, although it is still unclear exactly what their roles are in the pathways of VLCFA elongation.[1] Furthermore, two novel fish elovls were recently identified by Li and colleagues (2020), named *ELOVL8a* and *ELOVL8b*. These ELOVLs were discerned from herbivorous marine teleost rabbitfish (*Siganus canaliculatus*) using genomic surveys and molecular cloning methods.[10] Moreover, ELOVL8 was also identified in zebrafish liver, suggesting its potential role in fatty acid biosynthesis.[11] This knowledge gap is a result of insufficient or imperfect biochemical analyses, a dearth of substrates, and variation in applied research techniques resulting in confounding of

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Table 1. ELOVL Family Members, Their Tissue or Organ Location, and Function

Protein	Location	Function	Diseases associated with the protein	Refs
ELOVL1	Mouse stomach, lungs, kidneys, skin, intestine, brown adipose tissue, heart, liver, brain, muscle, and spleen; mildly expressed in the testes	Important for the synthesis of monounsaturated C24:1 and saturated C24:0 sphingolipids via the formation of VLCFAs; indirectly inhibits RPE65	Spinocerebellar ataxia 38 (SCA38), hypomyelination, ichthyotic keratoderma, spasticity, and dysmorphic facial features	24, 75, 76
ELOVL2	Significantly more expressed in the testicles than in the liver; white adipose tissue, the brain, and the kidneys all show weak expression	Production of C24:5(n-6)-to-C30:5(n-6) PUFAs in the testes, which is necessary for healthy spermatogenesis and fertility	Inguinal hernia and autism, and age-related eye diseases such as age-related macular degeneration	47, 77, 78
ELOVL3	Brown adipose tissue, liver, and skin	Enzyme capable of condensing with higher activity toward saturated and unsaturated acyl-CoA substrates as well as C18 acyl-CoAs, especially C18:0 acyl-CoAs. It may aid in the synthesis of saturated and monounsaturated VLCFAs of different chain lengths, which function as lipid mediators and membrane lipid precursors in a number of biological activities	SSCA38	52, 79
ELOVL4	Testes, sperm, meibomian glands, skin, retina, brain, and skin.	Elongates long chain fatty acids (LC-FAs) into very long chain saturated (VLC-SFAs) and polyunsaturated (VLC-PUFAs) fatty acids, which are collectively known as VLC-FAs. This is the rate-limiting step in the process (very long chain fatty acids).	Skin abnormalities, seizures, spinocerebellar ataxia-34 (SCA34), autosomal dominant Stargardt-like macular dystrophy (STGD3)	37, 80, 81
ELOVL5	Weakly expressed in the prostate, lungs, and human brain; highly expressed in the testes and adrenal gland; also expressed in the cerebellum	Elongation of long chain polyunsaturated fatty acids	SCA38	67, 82
ELOVL6	High concentrations in the brain, testicles, liver, white and brown adipose tissue, adrenal glands, and skin	Plays a part in insulin sensitivity and energy metabolism. Saturated and monounsaturated fatty acids with 12, 14, and 16 carbons are lengthened by microsomal enzyme ELOVL6	Idiopathic pulmonary fibrosis, hepatosteatosis and liver injury, SCA38, and occupational dermatitis	71, 83, 84
ELOVL7	Broadly expressed in prostate and skin	Higher activity toward C18 acyl-CoAs, particularly C18:3(n-3) and C18:3(n-6) acyl-CoAs, is observed in ELOVL7 elongation of C16-C20 acyl-CoAs (5)	Prostate and gynecological cancer, early onset Parkinson's disease, SCA34, SCA38, and multiple system atrophy	85, 86

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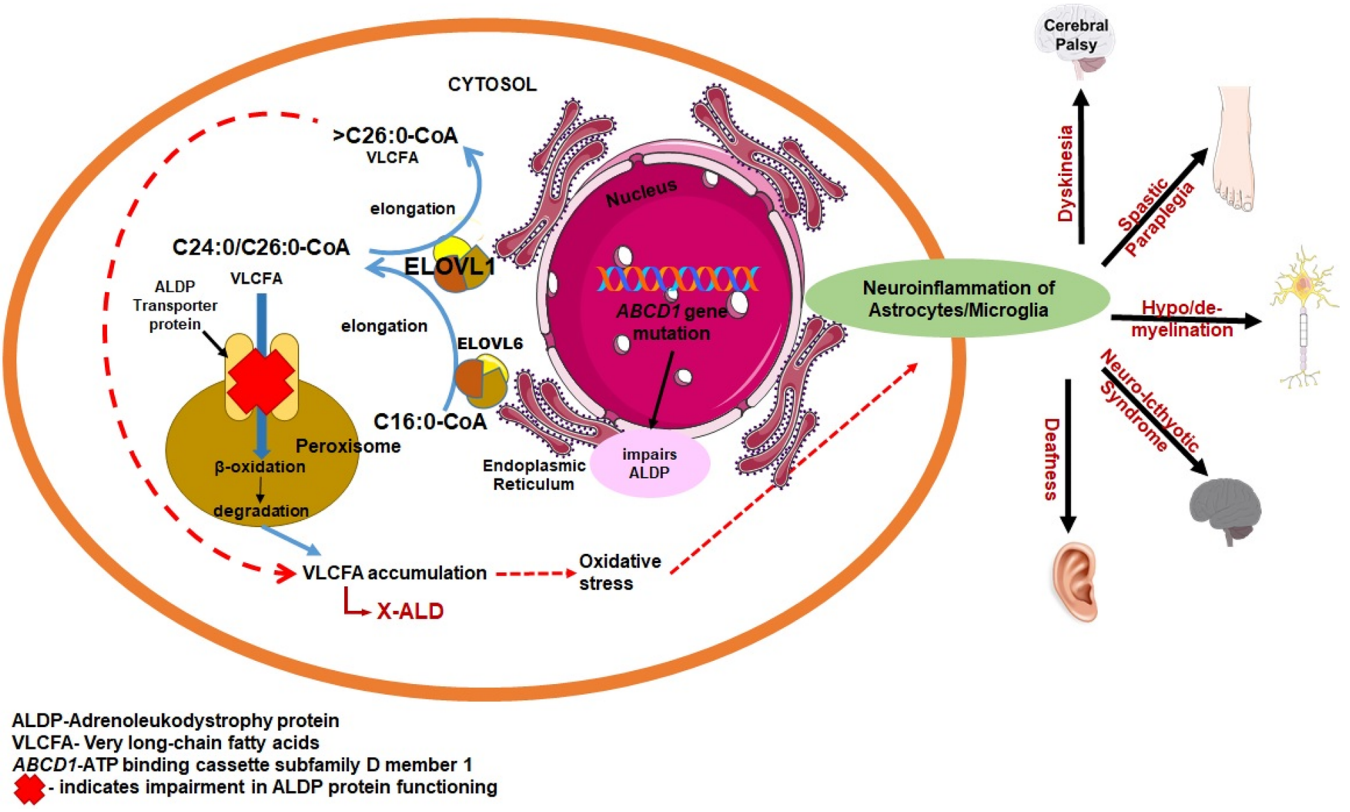

Figure 1. Role of *ELOVL1* in X-ALD and other neurological diseases.

comparisons. Sequence alignment demonstrates that numerous conserved motifs are necessary for ELOVLs to act as desaturases.

Several members of the ELOVL family, including ELOVL1, -3, -4, -5, and -6, are produced in cells of the central nervous system (CNS), but the extent of this expression varies according to the location of the brain.[12,13] While ELOVL2 is highly expressed in nonmammal brains, ELOVL2 and ELOVL7 are very weakly expressed in mammalian brains.[14] ELOVL4 and ELOVL5 are the most investigated of the ELOVL family members in the human and animal brain.[15] Mutations in human *ELOVL4* or *ELOVL5* genes result in neurological illness.[16] It is interesting to note that in zebrafish, ELOVL4b is highly expressed in the retina,[17] and ELOVL4a expression is reported to occur in the brain,[16,18] where it exclusively catalyzes the production of very long chain saturated fatty acids. Similar patterns of production of both saturated and polyunsaturated very long chain fatty acid in the brain and the retina of teleost fish and mammals have been reported for ELOVL4 isoforms.[19] ELOVL5 is likewise highly expressed in the fish brain, as it is in the mammalian brain.[20]

The importance of ELOVL1 in a variety of neurological illnesses has intrigued researchers of all fatty acid elongases. ELOVL enzymatic protein are widely expressed in every tissue, including the testis, brain, and adrenal gland. Diseases including X-linked adrenoleukodystrophy (X-ALD), neuro-ichthyotic conditions, ichthyotic keratoderma, spasticity, hypomyelination, and others are associated with mutations in the genes encoding elongases particularly ELOVL1.[21−23] Therefore, the present review mainly focuses upon the special function of that one particular fatty acid elongase, ELOVL1, plays in mammals and nonmammals. We also present the latest information about its structure, distribution, and its importance in various neurological disorders along with some of its therapeutic targets.

2. EXPRESSION AND FUNCTION OF ELOVL1

The human body possesses seven elongases (ELOVL1−7) with various tissue expression patterns and specificity toward substrates. Saturated (C20-CoA) and monounsaturated fatty acids (C22-CoA) are necessary for the synthesis of C-24 sphingolipids, and ELOVL1 exhibits high substrate specificity toward these fatty acids.[24] Sphingolipids and ceramide synthase (CERS2) are required for C24 sphingolipid production, which further aids in the regulation of ELOVL1 function. It was suggested in a recent report that ELOVL1 may also be able to use fatty acids with C18 to convert them into fatty acids of C26 chain length. Among the organs that naturally generate ELOVL1 are the lungs, skin, stomach, kidneys, and highly myelinated parts of the CNS (Table 1). The rate-limiting step in the synthesis of VLCFAs is catalyzed by elongase ELOVL1. Ohno et al. successfully cloned mouse *ELOVL1* and demonstrated its involvement in the synthesis of sphingolipids and C26 FAs.[24] According to certain theories, ELOVL1 is the foremost elongase enzyme producing C26:0 in humans. In one study, *ELOVL1* knockdown in fibroblasts obtained from X-ALD affected patients showed diminished C22:0-to-C26:0 elongation with dramatically reduced C26:0 levels. Furthermore, the results of pharmacologically inhibiting ELOVL1 showed the importance of this gene for the formation of C24:0 and C26:0.[25,26] Mutations in ATP binding cassette subfamily D member 1 (*ABCD1*), which encodes the peroxisomal ABC half-transporter (ALDP) protein, cause X-ALD disease, characterized by plasma and tissue accumulation of VLCFAs. The ATP-binding cassette (ABC) transporter

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ALDP, which is encoded by the ABCD1 gene and is a component of the peroxisomal membrane protein, is affected by mutations in the ABCD1 gene. Furthermore, this mutation leads to the impairment of β-oxidation of VLCFA and increases the further elongation of VLCFA by ELOVL1 and accumulation in plasma and tissues. This accumulation results in to X-ALD and other neurological disorders[27,28] Plasma membrane composition, stability, and functionality are known to suffer as a result of VLCFA accumulation in X-ALD (Figure 1).

Additionally, VLCFA has a toxic effect on adrenocortical cells, which lessens their responsiveness to adrenocorticotropic hormone stimulation. Patients with X-ALD may have oxidative stress and brain and adrenal cortical damage as a result of VLCFA accumulation.[29] Lorenzo's oil, a mixture of glyceryl trierucate and glyceryl trioleate, was developed to decrease the amount of saturated VLCFAs in the plasma of X-ALD patients and found to suppress ELOVL1 activity.[30] In addition, *ELOVL1* knockout was found to reduce VLCFAs (C26:0) in X-ALD fibroblasts.[26] The phenotype seen in elovl1 knockout mice, however, illustrates the more fundamental necessity of ELOVL1. Mice lacking the *1* gene die soon after birth due to impaired epidermal permeability barriers.[31] In these *1* knockout mice, both C26 and C24 sphingomyelins had reduced, equal, or greater levels of fatty acid ceramide, while ceramide levels were increased. This finding shows that VLCFAs may, to some extent, be necessary for maintenance and continued functioning of the epidermal permeability barrier.[31] The results of recent studies using goat fetal fibroblasts and bovine mammary epithelial cells indicate that a cellular sensor, rapamycin complex 1, which is a well-known cellular energy sensor that controls protein synthesis, can be targeted in mammals via the regulation of *ELOVL1* expression.[32]

3. NEUROLOGICAL DEFICITS LINKED TO ELOVL1 ALTERATION

A neurological condition with ichthyotic keratoderma, hypomyelination, spasticity, and dysmorphic characteristics is brought on by a dominant *ELOVL1* mutation.[33] Only a small group of Mendelian diseases, which include neurological factors and ichthyosis, can be caused by mutations in genes important for both epidermal and brain functions. The myelin sphingolipids of mice lacking fatty acid elongase *ELOVL1* were observed to have minimized chain length[24] and diminished motor management. Myelin sphingolipids were shown to be more prevalent in VLCFAs with a chain length of >C20.

3.1. Hypomyelination, High-Frequency Deafness, and Spastic Paraplegia. Recently, neurocutaneous conditions such as skin ichthyosis and mutations in the *ELOVL1* gene, which generates fatty acid elongase, were found to be related to a number of neurological disorders, such as spastic paraplegia, hypomyelination, and high-frequency deafness.[34] How *ELOVL1* deficiency impacts the lipid composition and specific pathological disorders in the brain remains unknown. As a model for human *ELOVL1* gene insufficiency, researchers also worked on *ELOVL1* mutant mice. The postnatal survival rate of mice was lower than average, and several died from startle epilepsy. Sphingolipids, for example, galactosylceramides, sphingomyelins, sulfatides, and ceramides, exhibited noticeably shorter acyl chains in the brains of these animals. Galactosylceramide levels, which are essential for the growth and stability of myelin, were also lower in mice. According to electron microscopy studies, the corpus callosum of *ELOVL1* mutant mice showed mild hypomyelination, especially in large-diameter axons. Additionally, an examination of the mice's behavior found that they had poor motor coordination and a diminished ability to be audibly startled in response to strong stimuli.[35] Suggestions regarding the molecular causes of the neurological symptoms experienced by *ELOVL1* mutant patients were made based on results in these studies.

3.2. Neuro-Ichthyotic Syndrome. A broad group of skin disorders known as ichthyoses are characterized by localized or generalized (or both) scaling. Hypohidrosis (diminished sweating), erythroderma, recurrent infections, palmoplantar keratoderma, and erythroderma are other common symptoms. A distinctive feature of ichthyoses is aberrant barrier function, which develops into trans-epidermal water loss and compensatory hyperproliferation. Mutations in more than 50 genes are found to be linked with both syndromic and nonsyndromic ichthyoses; these genes affect keratinocyte proteins (the "bricks"), lipid metabolism, transport (the "mortar"), cell-to-cell junctions, and the transcription and repair of DNA.[36]

In 2018, Kutkowska-Kamierczak et al. reported the first case of a dominant missense mutation in *ELOVL1* that results in ichthyotic keratoderma, dysmorphic, spasticity, and mild hypomyelination features in two kindreds.[33] The formation of saturated and monounsaturated VLCFAs is catalyzed by ELOVL1, which also participates in the elongation of fatty acids. Previously, mice from a strain lacking *ELOVL1* exhibited skin that was wrinkled, shiny, and red, and electron imaging illustrated that the lipid lamellae of the stratum corneum were unprogressive.[37] Thin-layer chromatography showed that the content of C26 fatty acid ceramides was decreased. Kutkowska-Kamierczak et al. hypothesized that the disease may be due to a lack of VLCFAs caused by inactive mutant enzymes. They further stated that the mutation could affect VLCFA levels in the brain and skin significantly more than in fibroblasts or plasma.[33]

VLCFAs are necessary for the proper functioning of cellular membranes. ELOVL1 is a protein that catalyzes the elongation of monounsaturated and saturated C22−C26 VLCFAs. In a previous work, two study participants were chosen for the investigation based on having the dominant *ELOVL1* mutation. The same patients were separately checked by Kutkowska-Kamierczak et al. for the identical mutation. By sequencing the complete exon, this study's scope expanded to take more biochemical, functional, and therapeutic factors into account. Using LC-MS/MS, the concentrations of ceramide and sphingomyelin were evaluated. ELOVL1 action was assessed based on stable-isotope-labeled (13C) malonyl-CoA elongation. Through the use of RT-qPCR, in situ hybridization, and immunofluorescence, the ELOVL1 expression patterns were investigated. Increased keratinization and epidermal hyper proliferation were observed in ichthyosis patients. Alleviation of peripheral vision and acuity were mostly due to optic atrophy, while spastic paraplegia and central nystagmus were caused by central white matter hypomyelination. The mutation diminished the enzymatic activity of ELOVL1 and decreased the levels of sphingomyelins and C24 ceramides in patient cells. When fibroblasts were loaded with C22:0 VLCFAs, the levels of C24:0 ceramides and sphingomyelin increased.[38] Researchers found that saturated and monounsaturated VLCFAs competitively reduced the production of ceramide and sphingomyelin. A transcriptome study revealed the downregulation of genes involved in

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synaptogenesis, myelination, and neurodevelopment and the upregulation of modules for keratinization and epidermal development. In the 5′ regions of numerous governed genes, consensus PPAR (proliferator-activated receptor) and PPAR-binding motifs were found.[38] Therefore, PPAR-modulating drugs may be used to treat a neuro-ichthyotic disease caused by the dominant *ELOVL1* mutation.

3.3. Hypomyelinating Spastic Dyskinesia and Ichthyosis. Next-generation sequencing technology, which can identify incredibly rare pathogenic gene variants responsible for diseases, was used to identify an autosomal recessive splice-site mutation in the *ELOVL1* gene as the cause of cerebral palsy in two siblings.[39] Thorough molecular analysis of cryptic splicing was carried out using RNA and whole-exome sequencing to study a consanguineous family. Measurements of ceramide were performed with liquid chromatography−tandem mass spectrometry (LC-MS/MS) analysis of the stratum corneum of patient skin. The protein structure of ELOVL1 was computer-modeled. The findings showed that the specific homozygous mutation in the affected siblings was what caused exon skipping.[39] Using LC-MS/MS, a thorough examination of the ceramides in patient stratum corneum indicated considerable condensing of fatty acid moieties and a sharp drop in the quantities of acylceramides. ELOVL1 variants are linked to many disease segregates in an autosomal dominant manner, according to recent studies. Initially, however, researchers presented a different scenario involving autosomal recessive inheritance of ELOVL1.[40] Therefore, it was suggested by these researchers that determining the molecular origins of genetic cerebral palsy and other ultrarare illnesses may be possible by examining the inheritance methods of the gene or genes associated with the disease.

4. ELOVL: ADDITIONAL FAMILY MEMBERS

It is well-known that the main fatty acid products, such as VLC-SFAs and VLC-PUFAs, have different functions and mechanisms of action, which remain unknown despite their clear importance for CNS health and function. Recent research has suggested that some lipid species with both of these kinds of very long acyl chains may play crucial roles, with VLC-SFAs serving as modulators of synaptic transmission and VLC-PUFAs acting as precursors of metabolites associated with homeostatic signaling. A brief description of their location, function, and associated diseases is found in Table 1.

Through meticulous studies of this fatty acid product (VLC-PUFAs), the Bazan laboratory uncovered a novel class of bioactive fatty acids that they termed “elovanoids”.[41] They were shown to be neuroprotective in the retina and to be produced by a particular kind of lipoxygenase. They are the hydroxylated forms of compounds 32:6n-3 and 34:6n-3.[42] In addition, it is known that the primary products of ELOVL4 in the retina are VLC-PUFAs, which are integrated with phosphatidylcholine and are distributed in the outer segmental disc membranes of light-sensitive photoreceptors. Every morning, photoreceptors at the far end of the outer segment shed discs that are phagocytosed and cleaved by the retinal pigment epithelium (RPE). VLC-PUFAs, found in isolated outer segment membranes, act as building blocks for RPE cells to generate oxidized elovanoid derivatives. Elovanoids further facilitate a feedback signal for neuroprotection to counteract excessive oxidative damage, encouraging the photoreceptors to express more pro-survival proteins.[43] Elovanoids have also been found to exhibit protective effects in neurons that were starved of glucose and oxygen and also demonstrated protection against excitotoxicity in in vitro and in vivo ischemic stroke models. Overall, the results showed existence of a distinct lipid-signaling route that supports the maintenance of the health of neuronal cells and is pro-homeostatic and neuroprotective. A new theory holds that VLC-SFAs are decisive for healthy and satisfactory synaptic function and that their absence due to ELOVL4 mutations compromises synaptic transmission and results in synaptopathy. Current studies have demonstrated that these VLC-SFAs are paramount and unique reformers of presynaptic release kinetics in mice homozygous for a 5 bp deletion in STDG3 that renders ELOVL 4 effectively inert.[12,44]

Since each ELOVL enzyme has a unique substrate specificity and exhibits a unique pattern of expression in mammalian tissues, they all serve different roles. As a result, faulty ELOVL proteins are connected to a number of diseases in humans. ELOVL2 controls docosahexaenoic acid formation and de novo lipogenesis independently of sterol regulatory element binding protein 1c (SREBP-1c), which in turn commands fat mass growth and lipid storage. The finding that *ELOVL2* mutant mice are resistant to diet-induced weight gain and liver adipose tissue suggests that ELOVL2 is essential for maintaining lipid homeostasis.[45,46]

A molecular link between polyunsaturated fatty acid elongation and visual function was found to be synchronized by ELOVL2 activity, suggesting potential therapeutic approaches for the management of age-related eye illnesses.[47,48] In a study by Garagnani et al., it was discovered that *ELOVL2* methylation could play a role in the aging process through the regulation of different biological pathways. Age-related hypermethylation and *ELOVL2* could act as links between early developmental phases and aging. This involvement of *ELOVL2* could be further investigated in future clinical and forensic research.[49,50] A particular form of ELOVL3 is related to the skin. Studies in mice lacking *ELOVL3* demonstrated that ELOVL3 is necessary for the production of neutral lipids in the skin,[51] wherein these mice had significant water-repelling abnormalities, increased trans-epidermal thin-hair coats, water loss, and hyperplastic pilosebaceous systems. Vitamin D was found to modulate ELOVL3 and the fatty acid composition of subcutaneous adipose tissue.[52] In addition, skin and retina are the primary tissues where ELOVL4 is expressed. The skin permeability barrier, newborn survival, and the generation of VLCFA chains longer than C26 all depend on ELOVL4.[53] In this context, it is intriguing that ELOVL1 and ELOVL4 nonredundantly collaborate in the skin to balance the permeability barrier.

The lack of VLCFAs with chain lengths of C26, which cannot be synthesized by ELOVL4, was reported to cause problems in *ELOVL1* knockout mice.[54] While *ELOVL4* mutant animals show decreased epidermal permeability, it is conceivable that ELOVL1 can produce VLCFAs with chains that are at least as long as C26. However, the levels of VLCFAs with chains longer than C26 were found to be reduced, whereas the levels of C26 VLCFAs were found to be increased in *ELOVL4* knockout mice.[55,56] This suggests that ELOVL1 and ELOVL4 work together as an essential functional relay to produce VLCFAs that are longer than C26 and C26-long VLCFAs, respectively.

The ELOVL family of elongases is highly conserved in eukaryotes, and homologues of the human ELOVL2, ELOVL4, and ELOVL5 have been found and functionally characterized

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in a number of species of teleost fish, including zebrafish, salmon, cobia, and Chu's croaker. In fish, just one ELOVL2 isoform has been discovered. Some fish species, such as Chu's croaker only express ELOVL5 in its single isoform, but other species express two functionally related isoforms (ELOVL5a and b). The functions of ELOVL2 and ELOVL5 are identical to those of their mammalian homologues and are functionally redundant with one another. ELOVL2 elongates C20 and C22 PUFA to C24 PUFA, while *ELOVL5a* and *5b* elongates C18 and C20 PUFA to C22 PUFA.[57] The most broadly distributed and highly expressed member of the ELOVL family in the brain is ELOVL4, according to both in situ hybridization and immunolabeling.[9,57] In addition to zebrafish (*Danio rerio*), Atlantic salmon (*Salmo salar*), Nibe croaker (*Nibea mitsukurii*), and orange-spotted grouper (*Epinephelus coioides*), *ELOVL4* has also been cloned from a number of fish species. Numerous investigations have revealed that *ELOVL4* is essential for the synthesis of fatty acids, and it is generally accepted that this enzyme's purpose is to extend C20 fatty acids to longer-chain fatty acids, even up to C36. *Scatophagus argus ELOVL4* can, however, elongate from 18:3n-6 to 20:3n-6, according to some researchers. It has also been examined that all of the fatty acids such as 18:2n-6, 18:3n-3, 18:3n-6, 20:4n-6, and 20:5n-3 could be elongated by the loach (*Misgurnus anguillicaudatus*) ELOVL4a and ELOVL4b enzymes.[58] According to the literature, ELOVL4 expression differs depending on the tissue and type of cell, which is probably connected to the dysfunctions identified in diseases caused by *ELOVL4* mutations. The bulk of the brain expresses ELOVL4 at high levels, with the cerebellum, cerebral cortex, thalamus, and olfactory bulb particularly standing out[17,57]. The basal ganglia are an exception to this pattern, since they express ELOVL4 only sparingly. ELOVL4 expression is largely neuronal at the cellular level, despite the fact that a small number of ELOVL4-positive cells were discovered in the brain white matter, indicating that they may also be expressed in oligodendrocytes.[59] Sherry et al. (2017) found that glutamatergic and GABAergic neurons, as well as neurons that employ distinct neurotransmitters, express ELOVL4.[59]

Within an area, ELOVL4 expression is cell specific. Only photoreceptor cells in the retina express ELOVL4, according to Agbaga and colleagues (2008), which is congruous with the observation of ELOVL4 mutations in Stargardt's-like macular dystrophy (STGD3) that are implicated in photoreceptor degeneration.[60,61] Granule cells in the cerebellum have exceptionally high levels of ELOVL4, but Purkinje cells have low levels, as do basket and stellate cells. These cell-specific variations in ELOVL4 expression may be related to the signs and development of spinocerebellar ataxia-34 (SCA34), which is brought on by ELOVL4 mutations in humans. According to a previous study,[62] the 5 bp deletion in STGD3 and mutant ELOVL4 allele induce severe, spontaneous epileptiform bursting and seizure activity in mice. The CA3 (caudate amygdala) and CA4 regions of the hippocampus exhibit the highest levels of ELOVL4 expression in neurons, whereas the lowest levels are in the CA1 region and dentate gyrus. The seizure activity seen in recessive human ELOVL4 neuro-ichthyotic disease and this pattern are likewise comparable.[63,64] In mice, the levels of ELOVL4 mRNA expression peak around birth, decline during brain development, and stabilize by postnatal day 30. ELOVL4 expression in the brain is developmentally regulated. The dentate gyrus of the hippocampus subventricular zone and the internal and external granular layers of the cerebellum are examples of regions where ELOVL4 is strongly expressed during periods of neurogenesis, according to studies using antibodies to label the developing mouse brain between embryonic day 18 (E18) and postnatal day 60. It is probable that ELOVL4 and its VLC-FA byproducts are involved in neurogenesis, because ELOVL4 expression in these areas decreases along with neurogenesis.[65]

Arachidonic and docosahexaenoic acids activate SREBP-1c and its target genes, which are associated with the production of fatty acids and triglycerides. Animals lacking *ELOVL5* showed reduced amounts of these fatty acids. *ELOVL5* knockout mice exhibit deficiencies in lipid metabolism, as a result of which they eventually experienced hepatic steatosis.[65,66] Spinocerebellar ataxia was also shown to be connected to the *ELOVL5* mutation in humans.[67,68] *ELOVL5* displays a characteristic expression pattern in the proximal convoluted tubule (PCT) of the pronephros in zebrafish, indicating that this gene may be important for human kidney development and function.[69] It was determined that ELOVL6 is the main earmark of SREBP in the liver.[70] ELOVL6, which elongates C12 to C16, has a considerable impact on both the thermogenic characteristics of brown adipose tissue and the emergence of obesity-induced insulin resistance. Additionally, it is involved in significant regulation of pulmonary fibrosis and nonalcoholic steatohepatitis.[71,72] ELOVL7 was shown to facilitate the extension of saturated long chain fatty acids.[73] Tamura et al. (2009) claimed that SREBP1, which is overexpressed in prostate cancer cells and encourages cancer cell growth, is involved in the mechanism through which the androgen pathway regulates ELOVL7.[73,74] As mentioned above, each elongase has a distinct role, in part due to variances in substrate selectivity and expression in various tissues.

5. ELOVL1 AS A POTENT PHARMACOLOGICAL TARGET

5.1. Lorenzo's Oil. A peroxisomal condition known as X-ALD is brought on by mutations in the *ABCD1* gene, which is essential for the entry of VLCFAs into peroxisomes. The saturated VLCFA level in the plasma of X-ALD patients can be decreased with the use of Lorenzo's oil, a 4:1 blend of glyceryl trioleate and glyceryl trierucate (Figure 2). However, the specific mechanism by which this occurs remains unknown. An experiment was conducted to investigate the biochemical

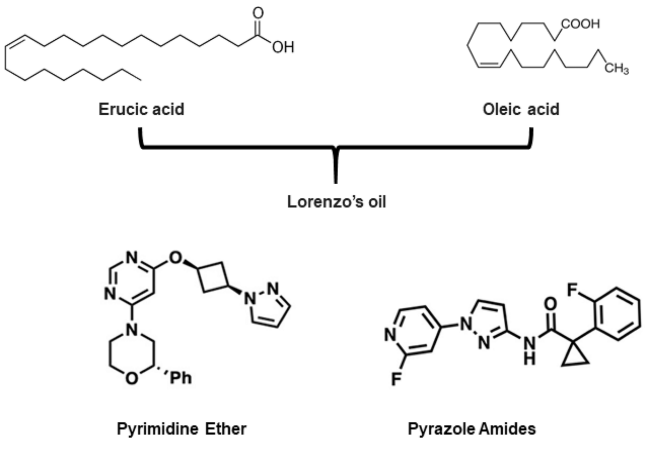

Figure 2. Therapeutic inhibitors of ELOVL1.

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properties of Lorenzo's oil activity toward ELOVL-1, the essential enzyme involved in the synthesis of saturated and monounsaturated VLCFAs. An FA ratio of 4:1 between oleic and erucic acids in Lorenzo's oil demonstrated the biggest impact on ELOVL1. Following investigation, the kinetics of this inhibition were found to be mixed rather than competitive. Treatment with the 4:1 mixture increased the amount of sphingomyelin (SM) with monounsaturated VLCFA while decreasing the amount of SM with saturated VLCFA in the cells, most likely as a result of erucic acid being incorporated into the FA elongation cycle.[30,87] These results indicate that inhibition of ELOVL1 may be one possible mechanism behind the effects of Lorenzo's oil.

5.2. Pyrimidine-Ether-Based and Pyrazole Amides as Inhibitors of ELOVL1. The primary goal should be the identification of ELOVL1 small-molecule inhibitors that might penetrate the blood−brain barrier and potentially be used to treat adrenoleukodystrophy (ALD) by reducing the concentrations of VLCFAs in the CNS. The impact of ELOVL1 inhibitors on VLCFA levels in *ABCD1* KO mice prompted researchers to look into a number of chemical compounds with a variety of structural properties that suggested they might match or even outperform the results observed with pyrazole amide (Figure 2). The researchers investigated a series of thiazole amides that eventually led to a highly potent, CNS penetrant with favorable in vivo pharmacokinetics using a substrate reduction approach based on the inhibition of ELOVL1 enzyme. The compound inhibits ELOVL1 in ALD patient fibroblasts, lymphocytes, and microglia by lowering C26:0 VLCFA production as well as decreased C26:0 VLCFA concentrations in mice models of ALD to levels close to wild type in the blood and up to 65% in the brain. Inhibiting ELOVL1 and targeting pyrazole amides as inhibitor could be a successful method for restoring normal VLCFA levels in ALD models.

In an another experiment, a total of 130 analogues were synthesized and tested to fully investigate this vector by conducting a high-throughput radiometric screen, and it was discovered that piperidine analogue 4 provided a breakthrough in efficacy. It decreases C26:0 VLCFA production in fibroblasts and lymphocytes from ALD patients. The compound's biochemical and cellular activity was found to be further elevated when the pyridine core was switched with a pyrimidine ring using HEK293, an immortalized human embryonic kidney cell line.[88]

It was shown that in order to avoid cerebral adrenoleukodystrophy, delay the beginning of the disease, or diminish its severity and development in adrenomyeloneuropathy patients, a 50−75% reduction in C26:0 VLCFAs may be necessary.[89] The researchers reported the identification of powerful, brain-penetrant pyrazole amides (Figure 2) that block VLCFA synthesis in vitro in a variety of cell types, including ALD patient cells, and in vivo in the blood and brain of an ALD-prone mouse model.[90]

5.3. Saturated Lipids Assist in Inducing Cell Death (In Vitro/In Vivo) by Neurotoxic Reactive Astrocytes. In an in vitro and in vivo model of acute axonal injury, the astrocyte-specific ablation of the saturated lipid production enzyme ELOVL1 decreases toxicity caused by astrocytes. Recently, it was investigated that elongation of longer chain, fully saturated lipids (C16:0), which are more prevalent in reactive astrocytes and ACM (conditioned medium from adult reactive astrocyte cultures), could also be facilitated by the metabolic enzyme ELOVL1 (the similar enzymes ELOVL3 and ELOVL7 are expressed at low levels in astrocytes). To create an *ELOVL1* conditional knockout (cKO) mouse model that is specific to astrocytes, mice of an *ELOVL1*flox/flox line were crossed with those of a Gfap-Cre line. The lipidomes of latent and active astrocytes from wild-type and *ELOVL1* cKO mice were examined after cell separation. As expected, the astrocytes with *ELOVL1* knockout had decreased concentration of long chain saturated free fatty acids.[91] In comparison with reactive ACM from wild-type mice, reactive ACM from *ELOVL1* cKO mice caused significantly less injury to oligodendrocytes in vitro. This reactive ACM was toxic to oligodendrocytes after being concentrated 10 times, but wild-type reactive ACM was substantially more harmful. These findings imply that the *ELOVL1* cKO mutation decreases the generation of these harmful lipids, which mediates the risky behavior of reactive astrocytes.

6. CONCLUSION

Recent studies have elucidated novel functional roles for ELOVL1 and its VLC-FA products throughout the CNS, including the retina and brain, in both healthy and diseased contexts. VLC-PUFAs are of vital importance to the CNS as they cater as the basis for compounds with recently recognized roles in homeostatic signaling and the regulation of neuronal survival. Recent research has established that VLC-SFAs are necessary for synaptic transmission and that disruption of VLC-SFA synthesis results to seizures and neurodegeneration in both ELOVL1-deficient humans and ELOVL1 mutant models. A better understanding of the metabolism of VLC-SFA and VLC-PUFA and their effects in the CNS could facilitate the development of new therapeutic strategies for the treatment of epilepsy and neurodegenerative diseases.

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