



Review

Characteristics of Sensory Neuron Dysfunction in Amyotrophic Lateral Sclerosis (ALS): Potential for ALS Therapy

Soju Seki ^{*}, Yoshihiro Kitaoka, Sou Kawata, Akira Nishiura, Toshihiro Uchihashi, Shin-ichiro Hiraoka, Yusuke Yokota, Emiko Tanaka Isomura, Mikihiro Kogo and Susumu Tanaka

Department of Oral and Maxillofacial Surgery, Graduate School of Dentistry, Osaka University, 1-8 Yamadaoka, Suita 565-0871, Osaka, Japan

* Correspondence: seki.soju.dent@osaka-u.ac.jp; Tel.: +81-668792936

Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder characterised by the progressive degeneration of motor neurons, resulting in muscle weakness, paralysis, and, ultimately, death. Presently, no effective treatment for ALS has been established. Although motor neuron dysfunction is a hallmark of ALS, emerging evidence suggests that sensory neurons are also involved in the disease. In clinical research, 30% of patients with ALS had sensory symptoms and abnormal sensory nerve conduction studies in the lower extremities. Peroneal nerve biopsies show histological abnormalities in 90% of the patients. Preclinical research has reported several genetic abnormalities in the sensory neurons of animal models of ALS, as well as in motor neurons. Furthermore, the aggregation of misfolded proteins like TAR DNA-binding protein 43 has been reported in sensory neurons. This review aims to provide a comprehensive description of ALS-related sensory neuron dysfunction, focusing on its clinical changes and underlying mechanisms. Sensory neuron abnormalities in ALS are not limited to somatosensory issues; proprioceptive sensory neurons, such as MesV and DRG neurons, have been reported to form networks with motor neurons and may be involved in motor control. Despite receiving limited attention, sensory neuron abnormalities in ALS hold potential for new therapies targeting proprioceptive sensory neurons.

Keywords: amyotrophic lateral sclerosis (ALS); sensory neuron; ALS mouse model; neurodegeneration; dorsal root ganglion (DRG); mesencephalic trigeminal nucleus (MesV)



Citation: Seki, S.; Kitaoka, Y.; Kawata, S.; Nishiura, A.; Uchihashi, T.; Hiraoka, S.-i.; Yokota, Y.; Isomura, E.T.; Kogo, M.; Tanaka, S. Characteristics of Sensory Neuron Dysfunction in Amyotrophic Lateral Sclerosis (ALS): Potential for ALS Therapy. *Biomedicines* **2023**, *11*, 2967. <https://doi.org/10.3390/biomedicines11112967>

Academic Editors: Juan Francisco Vázquez-Costa and Laura Moreno-Martínez

Received: 7 September 2023

Revised: 24 October 2023

Accepted: 29 October 2023

Published: 3 November 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease associated with protein abnormalities and neuritis [1–4]. Genes encoding superoxide dismutase 1 (SOD1), chromosome 9 open reading frame 72 (C9orf72), fused in sarcoma (FUS), TANK-binding kinase 1 (TBK1), and TAR DNA-binding protein (TARDBP) are known causative factors in familial ALS, accounting for 5–10% of patients with ALS [1,5–10]. Most ALS cases are sporadic ALS, and most patients with ALS show intracytoplasmic aggregation of ALS-inducing factors such as SOD1 and TAR DNA-binding protein 43 (TDP-43) in motor neurons, which is increasingly considered a feature of ALS [2,11–15]. The clinical phenotype of ALS includes both upper motor neurons (UMNs) and lower motor neurons (LMNs), but non-motor areas are increasingly found to be involved, leading to non-motor symptoms that include autonomic dysregulation, cognitive impairment, sensory impairment, and frontotemporal dementia (FTD) [15–22]. Clinical and preclinical studies have reported abnormalities in sensory neurons, and further research in this regard is ongoing. Several potential protein biomarkers have also been reported [23–31], but sensory neuronal abnormalities in ALS remain to be elucidated in detail. Proprioceptive sensory neurons not only transmit information from muscle spindles to the brain but also act on motoneurons and are involved in the control of muscle movement. Abnormalities in proprioceptive sensory neurons, such as the dorsal root ganglion (DRG) [8,32–34] and mesencephalic trigeminal

nucleus (MesV) [35,36], were reported early in ALS research and may represent novel targets for ALS treatment.

This review summarises the latest research on sensory neuron abnormalities, with a focus on clinical and preclinical studies. In addition to previous reports [2,16,19], we discuss sensory neuron abnormalities and propose new therapies for ALS, targeting proprioceptive sensory neurons.

2. An Overview of ALS

2.1. Clinical Characteristics of ALS

ALS is a progressive neurodegenerative disorder characterised by motor neuron degeneration in the brain and spinal cord [32,37,38]. It primarily affects voluntary muscles, leading to muscle weakness, atrophy, and eventually, paralysis [27,39–42]. Although the exact cause of ALS is not fully understood, it is believed to be a combination of genetic and environmental factors [43,44]. In some cases, specific genetic mutations that are involved in survival have been identified, including the homeostatic iron regulator (HFE) p.H63D polymorphism, a modifier of the SOD1 gene [45]. However, most cases are sporadic, with no known genetic cause [46]. While ALS is currently incurable, various treatment options are being studied to manage its symptoms and improve the quality of life of individuals with the disease [47–49]. These treatments include medications to manage muscle cramps and spasticity, assistive devices to aid mobility and communication, and multi-disciplinary care involving physical, occupational, and speech therapy. In recent years, the disease paradigm has changed and ALS is increasingly being considered a multi-system disease rather than a motor-neuron-limited disease.

2.2. Motor Neuron Dysfunction in ALS

ALS is characterised by a progressive loss of both UMNs and LMNs [50,51]. UMNs are located in the motor cortex of the brain, whereas LMNs are found in the brainstem and spinal cord. The dysfunction and degeneration of these neurons leads to the characteristic muscle weakness, atrophy, and spasticity seen in ALS [51,52]. The exact mechanisms underlying motor neuron dysfunction in ALS are unclear. However, several key pathological features have been identified. One important protein involved is TDP-43, which forms abnormal aggregates in the cytoplasm of affected neurons and disrupts normal cellular processes [13,53]. Motor neuron dysfunction in ALS is associated with disturbances in the transmission of signals between neurons and muscles. These disturbances result in the failure of motor neurons to adequately stimulate muscle contractions, leading to muscle weakness and the eventual loss of voluntary movement control. The dysfunction and degeneration of motor neurons in ALS are thought to be influenced by various factors, including oxidative stress, mitochondrial dysfunction, impaired protein degradation pathways, glutamate excitotoxicity, and inflammation [54,55]. These factors contribute to the progressive loss of motor neurons and clinical manifestations of ALS.

3. Clinical Research in Patients with ALS

3.1. Clinical Features of Sensory Neuron Dysfunction in ALS

In recent years, growing evidence indicates that sensory neuron dysfunction contributes to the clinical manifestations of ALS and influences disease progression and prognosis [17,56–61] (Table 1). Liu et al. reported that sensory impairments are often mild and there is no significant progression [62]; however, Hammad et al. reported that a third of patients with ALS experience sensory symptoms, with corresponding nerve changes, particularly affecting large, myelinated fibres [56]. Sensory manifestations include paraesthesia, sensory loss, neuropathic pain, and heightened sensitivity to external stimuli [62,63]. Patients may experience these symptoms in various anatomical distributions, including the upper and lower extremities, trunk, and face. The coexistence of sensory symptoms with motor symptoms can significantly impact the overall disease burden and quality of life in patients with ALS [56]. In addition to self-reported symptoms, objective sensory

examination findings support the presence of sensory neuron dysfunction in ALS. Sensory deficits, such as impaired vibration sense, reduced proprioception, and decreased thermal and pain sensation, have been observed in patients with ALS [64–66]. Neurophysiological studies have also demonstrated abnormalities in sensory nerve conduction parameters, including prolonged sensory nerve action potentials and reduced sensory nerve action potential amplitudes [67–72].

Table 1. Major clinical studies supporting sensory involvement in ALS.

Type of Sensory Neuron	Dysfunction	Number of Patients with ALS	References
Median nerve	Attenuation of postsynaptic high-frequency somatosensory evoked potential bursts in patients with ALS with a long duration of the disease.	20	[73]
Sensory system	A total of 14.7% of patients with ALS have damaged sensory systems.	150	[62]
Sensory cortex	Sensory cortex overexcitation is associated with shorter survival in patients with ALS.	145	[71]
Intraepidermal nerve fibres	Decreased intraepidermal nerve fibres density with aggregation of TDP-43 in patients with ALS.	18	[74]
Epidermal nerve fibres	Loss of intraepidermal nerve fibres.	41	[60]
Intraepidermal nerve fibres	Increased axonal expansion rate and negative growth-related proteins in intraepidermal nerve fibres.	32	[58]
Intraepidermal nerve fibres	In 85% of patients with ALS, quantitative sensory testing showed abnormal thermal pain thresholds and skin biopsies showed decreased intraepidermal nerve fibre density.	24	[75]
Ascending sensory fibres	Anatomical damage to ascending sensory fibres in 60% of patients with solitary ALS.	21	[76]
Leg sensory nerve	A total of 27% of patients with ALS had abnormal action potential.	103	[56]
Sensory neuron in sural	Amplitude, and 91% had pathological abnormalities of the leg sensory nerve.	5	[77]
Median, radial, and sural nerves	Sensory neuropathy and axonal degeneration.	19	[67]
Sensory nerves	Asymptomatic decline in sensory nerve function.		
	Early axonal atrophy, increased remyelination, and predominance of smaller fibre diameters.		[78]

ALS, amyotrophic lateral sclerosis; TDP-43, TAR DNA-binding protein 43.

3.2. Peripheral Nerve Abnormalities Observed in Patients with ALS

In recent years, several studies have shed light on the involvement of sensory nerve conduction abnormalities in ALS (Table 1). A study by Heads et al. uncovered noteworthy findings, revealing axonal atrophy, increased remyelination, and abnormalities in small-diameter nerve fibres in patients with ALS [78]. These changes correlate with the duration of the disease [78]. Subsequent investigations further emphasised the significance of sensory nerve conduction abnormalities in ALS. Gregory et al. reported that the potential amplitude of sensory nerve conduction was significantly reduced in 19 patients with ALS compared to healthy control individuals, despite normal nerve conduction velocities [67]. Nolano et al. added more depth to the understanding of ALS-related sensory issues when they examined 41 patients with sporadic ALS and observed a loss of epidermal nerve fibres and Meissner bodies. Interestingly, these findings were associated with a partial reduction in cutaneous vascularity and were correlated with disease progression [60]. Distinguishing between different ALS subtypes, Truini et al. noted that patients with spinal cord-onset ALS exhibited distal small-fibre neuropathy characterised by abnormal heat pain thresholds and decreased epidermal nerve fibre density, in contrast to patients with early-onset ALS [75]. Hammad et al. conducted a study involving 103 patients with ALS that revealed that nearly 30% of these patients exhibited sensory symptoms and abnormalities in leg sensory neuron conduction studies [56]. Peroneal nerve biopsies from these patients showed

histologic abnormalities, including the loss of large-calibre myelinated fibres, axonal loss, and regeneration [77].

Overall, these studies collectively suggest that sensory nerve conduction abnormalities are a notable feature of ALS. Furthermore, recent research on Asian patients with ALS and the identification of abnormal TDP-43 aggregations in skin-derived fibroblasts from patients with sporadic ALS by Riancho et al. support the notion that ALS encompasses a range of neurodegenerative disorders, including sensory neuropathy [79]. Additionally, there is growing interest in the potential utility of distal sensory nerve conduction studies as a diagnostic tool in ALS research.

3.3. Pathological Alterations in Sensory Neurons in Patients with ALS

Sensory peripheral nerve conduction has been a subject of extensive study in the context of ALS. Liu et al. conducted research on 150 patients, employing pathological tests, and detected affected sensory fibres in 22 of these patients, accounting for approximately 14.7% of the cohort [62]. In a retrospective investigation involving 17 patients with ALS who had undergone a peroneal nerve biopsy, a significant finding emerged: more than two-thirds of these patients exhibited substantial axonal loss [80]. Moreover, in a separate study involving 22 patients, Hammad et al. reported histologic abnormalities in 91% of cases. These abnormalities included the loss of myelinated fibres, predominantly those of a large calibre, accompanied by axonal loss and regeneration [56]. In a study by Iglesias et al. on 21 patients with moderate ALS without clinical sensory signs (mean ALS Functional Rating Scale (ALSFRS) score = 39.3 ± 1.0), spinal diffusion tensor imaging reported anatomic damage to ascending sensory fibres in approximately 60% of the patients. They concluded that sensory neuropathy is underestimated in patients with early ALS [76]. Another prospective study, encompassing 32 patients with ALS, analysed both nerve conduction and peroneal nerve biopsies; while nerve conduction did not reveal specific sensory abnormalities, the histological analysis uncovered abnormal axonal swelling in all patients with ALS [58]. Importantly, TDP-43 staining was negative, suggesting failed regeneration in small sensory nerve fibres [58]. However, Ren et al. performed skin biopsies on 18 patients with ALS and reported that TDP-43 deposits were present in cutaneous sensory and autonomic nerves in 33.3% of these patients [74].

3.4. Abnormalities of the Somatosensory Cortex in Patients with ALS

The concept of somatosensory cortex overexcitation in ALS is intriguing because of its potential impact on the survival of patients with ALS. This hypothesis proposes that somatosensory cortex overexcitation during certain stages of the disease may be a compensatory mechanism used by the sensory cortex in response to reduced motor function [81]. In ALS research, somatosensory evoked potentials (SEPs) have been used to assess sensory signal transduction along central spinal cord pathways. SEPs reveal changes in patients with ALS, with a reported incidence of 50% [73]. Notably, these SEP changes tend to progress relatively slowly, suggesting that, compared to the rapid progression of motor symptoms, sensory deficits may progress at a more gradual pace, despite their common presence at diagnosis [82]. Shimizu et al. reported that larger somatosensory cortex amplitude SEPs correlated with significantly shorter survival times in 145 patients with sporadic ALS. This observation raises the possibility that somatosensory cortex overexcitation may be associated with ALS progression and impacts patient survival [71]. Late SEPs, which reflect cognitive-motor pathways, also show significant reductions in patients with ALS. This observation underscores the multifaceted nature of sensory pathway involvement in ALS [19].

A recent study by Nardone et al. has enhanced our understanding of this phenomenon [73]. The aim of this study was to assess sensory cortical function in 20 consecutive patients with sporadic ALS by evaluating high-frequency SEPs [73]. The results revealed that somatosensory cortex de-repression in patients with ALS becomes more pronounced

after the second year of disease progression, suggesting that changes in somatosensory cortical activity may evolve over and contribute to the course of the disease [73].

More recently, laser evoked potentials (LEPs) have emerged as a new tool to assess central pain signal conduction; studies using LEPs have revealed abnormal latency delays in patients with ALS [83]. These findings suggest the possibility of degeneration in subcortical sensory structures, further highlighting the complex nature of altered sensory pathways in ALS.

In summary, somatosensory cortex hyperexcitability appears to predict shorter survival in patients with ALS. In conclusion, sensory cortical hyperexcitability may reflect a multisystem neurodegenerative disease or represent a compensatory upward control mechanism associated with motor cortical dysfunction.

4. Preclinical Research in ALS

4.1. Pathological Alterations in Sensory Neurons in Patients with ALS

Recent studies have demonstrated that sensory neurons, including those involved in proprioception and nociception, are also impacted in ALS [2,35,72,84]. This broad neuronal involvement may contribute to the diverse clinical manifestations observed in ALS. Pathological alterations in sensory neurons in ALS encompass the degeneration of DRG neurons [34,84], axonal degeneration, demyelination, protein aggregation, mitochondrial dysfunction, gene abnormalities, and glial activation [85,86] (Figure 1). ALS preclinical studies have been conducted using SOD1G93A and TDP-43 A315T transgenic mice and dSOD1G85R and C9orf72 transgenic *Drosophila* (Table 2); for example, in TDP-43A315T and SOD1G93A ALS mice, DRG neurons have slower neurite outgrowth and fewer branches than those in control mice. They are also more sensitive to vincristine treatment, which causes axonal degeneration [84]. In another example, Ringer et al. used SOD1G93A ALS mice and elucidated that the dendritic projection pathology of glutamatergic sensory neurons, restricted to olfactory bulb mitral cells and retinal nodal cells, is responsible for abnormalities in olfaction and vision [87].

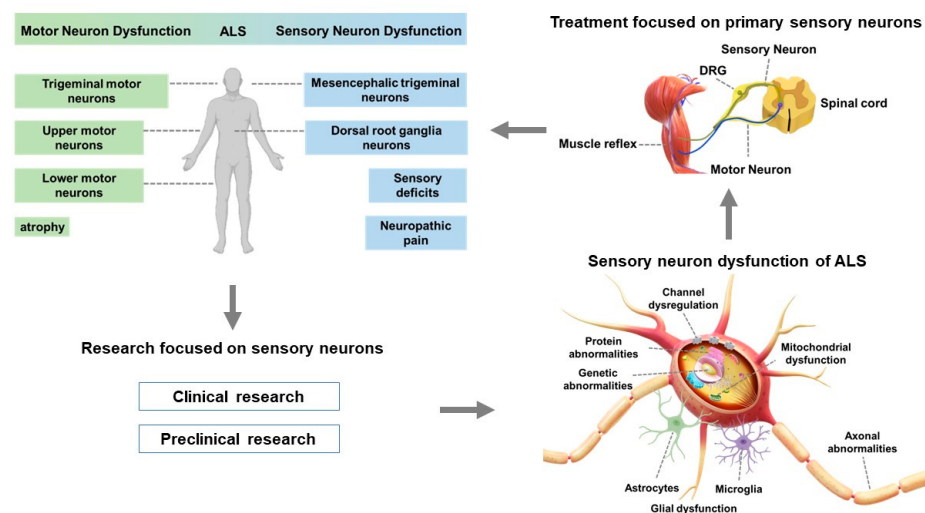


Figure 1. This review focuses on sensory neuron abnormalities in amyotrophic lateral sclerosis (ALS). As various sensory neuron abnormalities have been reported in studies using animal models, this review proposes a novel therapeutic strategy for ALS by correcting the proprioceptive sensory neuron abnormalities in patients with ALS.

Table 2. Characteristics of animal models of ALS with reported abnormalities of sensory neurons.

Animal Model	Animals	Characteristics of the Model	References
SOD1G93A	Mouse	Marked muscle weakness is observed at 15 weeks of age in SOD1G93A transgenic mice with familial ALS	[33]
dSOD1G85R	<i>Drosophila</i>	SOD1G85R knock-in model shows severe motor deficits with apparent degeneration of motor neurons, providing a better understanding of the contribution of multiple cell types in ALS	[72]
C9orf72 ALS	<i>Drosophila</i>	Transgenic <i>Drosophila</i> model overexpressing human TDP-43 shows reduced lifespan, reduced motor activity, increased morphological defects in motor neurons, a loss of neurons, and axonal damage	[88]
TDP-43A315T	Mouse	A315T mutant TDP-43 transgenic mouse model with marked early-onset progressive neurodegeneration resulting in reduced motor performance, spatial memory and de/inhibition, and reduced grip strength due to muscle atrophy	[84]
TDP-43 (TBPH)	<i>Drosophila</i>	Transgenic fly that exhibits an adult locomotor defect and shares many features with human proteins	[89]

C9orf72, chromosome 9 open reading frame 72; TDP-43 (TBPH), TAR DNA-binding protein 43; SOD1, superoxide dismutase 1.

4.2. Degeneration of DRG Neurons

The DRG is a cluster of sensory neurons located along the spinal cord. As the reflex arch circuit is created by dorsal root nerves joining the motor nerves via interneurons within the spinal cord, the innervation of dorsal root nerves is crucial to its construction. Rubio et al. reported the neuronal cell bodies of the DRG and axon terminals of the skin and determined that the number of DRG neurons remained unchanged, although the density of nerve fibres, especially nonpeptidergic fibres, was decreased in the epidermis [78] (Table 3). This finding indicates axonal involvement, particularly distal axonal involvement, as the neuronal cell bodies remained intact [78]. Guo et al. reported that DRG axons are severely damaged in SOD1G93A mice, and although no obvious reduction in the number of DRG neurons is observed, many DRG neurons in SOD1G93A mice have numerous vacuoles. Furthermore, images acquired through transmission electron microscopy reveal mitochondrial swelling in numerous DRG neurons in SOD1G93A mice [90]. The DRG in mice injected with serum from patients with ALS demonstrate decreased Ca currents through high-voltage-activated Ca channels [91]. In a study using ALS model mice (TDP-43A315T and SOD1G93A), TDP-43 and SOD1 were found to directly affect and sensitise DRG neurons to stress [84]. Levels of the stress-related molecules activating transcription factor 3 (ATF3) and protein kinase RNA-like ER kinase (PERK) differed between the two mutants [84]. These findings suggest the direct impact of ALS-related factors on sensory neurons, implying their role in ALS pathogenesis [84]. Furthermore, the DRG in SOD1G93A mice showed axonal stress features and the accumulation of a peripherin splice variant named peripherin 56 [34]. These results suggest a molecular mechanism for the small-fibre pathology found patients with ALS, wherein the dysfunction of DRG neurons mirrors some of the dysfunctions found in motor neurons [33,92]. In addition to neuronal loss, sensory neurons in ALS exhibit axonal degeneration and demyelination [77], owing to the loss of the protective myelin sheath surrounding the axons, resulting in the impaired conduction of sensory neurons. Such axonal abnormalities are characterised by the presence of axonal swellings and varicosities [77].

Table 3. Reports on sensory neuronal abnormalities in animal models of ALS.

Type of Sensory Neuron	Dysfunction	Type of Animals	Genes	References
MesV	Firing abnormality	Mouse	SOD1 G93A	[36]
DRG	Decrease in SGNF density	Mouse	SOD1 G93A	[33]
C4da	TDP-43 accumulation in the cytoplasm via calcium-calpain-A-importin α 3 pathway	Drosophila	C9orf72 ALS	[88]
DRG	SOD1 accumulation in SGCs	Mouse	SOD1 G93A	[8]
MesV	Firing abnormality with sodium channel dysfunction	Mouse	SOD1 G93A	[35]
Non-motor neuron	Neurotrophic BMP pathway	Drosophila	dSOD1G85R	[72]
DRG	Shorter and less complex neurites	Mouse	TDP43 A315TSOD1 G93A	[84]
Long-projection sensory neurons	Defects in MAM signalling	Mouse	TDP43 A315T	[93]
Olfactory bulb and retina	Neuronal vacuolisation in olfaction and vision pathways	Mouse	SOD1 G93A	[87]
DRG	Accumulation of a peripherin splice variant	Mouse	SOD1 G93A	[34]
DRG	Accumulation of misfolded protein	Mouse	dSOD1G85R	[94]
Ia and II proprioceptive nerve	Early disturbances in muscle spindles before motor neuron symptoms	Mouse	TDP43 A315T SOD1 G93A	[95]
C4da	Localised accumulation, predominantly of TDP-43	Drosophila	TDP-43 (TBPH)	[89]
DRG	Mitochondrial abnormalities	Mouse	SOD1 G93A	[90]
DRG	Reduction of high-voltage-activated Ca^{2+} current	Mouse	ICR mice injected with sera from patients with ALS	[91]

BMP, bone morphogenetic protein; C4da, class IV dendritic arborisation; DRG: dorsal root ganglia; MAM, mitochondria-associated membrane; MesV, mesencephalic trigeminal nucleus; SGC, satellite glial cell; SGNF, sweat gland nerve fibre; VNC, ventral nerve cord.

4.3. Characteristic Abnormalities in Mesencephalic Trigeminal Neurons

MesV neurons are proprioceptive sensory neurons that control mastication [35,96]; these directly affect motor neurons through α -amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid and N-methyl-D-aspartate (NMDA) receptors, which are excitatory postsynaptic receptors for neurotransmitters [97,98]. A study using neonatal ALS model mice (SOD1G93A) reported firing inhibition as an electrophysiological feature of the MesV in neonates [35] (Table 3). This inhibition is caused by a decrease in the Na current due to a deficit in the Nav1.6 Na channel, in contrast to the increased Na current observed in motor neurons [99]. Furthermore, the addition of Na channel-derived model currents in the dynamic clamp method improves the firing anomaly characteristics of the MesV. These findings suggest that the abnormalities in the MesV of neonatal ALS model mice may be due to the dysfunction of Na channels [35]. Abnormal firing of the MesV is also observed in adult SOD1G93A mice [36]. Furthermore, abnormalities in masticatory rhythms correlate with weight loss in adult SOD1G93A mice [36]. These findings suggest a novel reflex circuit-specific sensory issue, potentially linked to muscle twitching, which could aid in early diagnosis and treatment strategies for ALS [61,100].

4.4. Protein Aggregates and Mitochondrial Dysfunction

Similar to motor neurons, sensory neurons in ALS display abnormal protein aggregation. Aggregates of misfolded proteins, such as TDP-43, accumulate within the cell body and axons of sensory neurons [94]. Activating bone morphogenetic protein (BMP) signalling in non-motor and motor neurons improves motor function in the early and late disease stages. Non-motor neurons contribute to early ALS-induced motor dysfunction, suggesting potential therapeutic targets for delaying motor neuron degeneration [72]. Furthermore, mitochondrial dysfunction is a common feature in ALS, which leads to impaired energy production and neuronal viability [101,102]. For example, a 2009 study using the SOD1G93A mouse model showed that the axoneme of mild DRG neurons was occupied by vacuoles and swollen mitochondria, with mild degeneration. Histological features of degeneration were seen as early as 60 days of age, after which the degeneration gradually worsened. Thus, the histological abnormalities occurred long before the animals showed

signs of disease. Mitochondrial damage and the caspase-mediated apoptosis of spinal motoneurons have also been shown to play an important role in motoneuron degeneration in hSOD1G93A mice [61,103]. In a study using the *Drosophila* knock-in model of ALS, the reduced number of mobile mitochondria in the axons of multidendritic neurons were found to be most likely due to an inborn defect in the cell organelles themselves, rather than a defect in the axonal transport mechanism [104]. Diseased sensory neurons display specific mitochondrial shape issues and increased synapse mitophagy, which are reversed upon the down-regulation of dynamin-related protein 1 (Drp1). Adjusting oxidative phosphorylation (OXPHOS) subunits also reverse ALS-related mitochondrial defects [104]. Further analysis revealed disruption in the electron transport chain, indicated by genetically encoded redox biosensors. Sensory neurons exhibited compartment-specific abnormalities in mitochondrial morphology, with increased mitophagy at the synaptic regions [90]. Finally, our study on a SOD1-knock-in ALS model revealed compartment-specific mitochondrial abnormalities in sensory neurons, shedding light on their role in ALS and emphasising that mitochondrial transport issues may originate from intrinsic dysfunction rather than trafficking machinery problems [104]. Our work also demonstrated that correcting OXPHOS subunit genes and balancing mitochondrial fission/fusion can restore abnormal morphology to normal levels [104]. These findings pinpoint potential therapeutic targets, advancing our understanding and aiding in ALS treatment (Table 3).

4.5. Glial Involvement

Glial cells, including astrocytes and microglia, play a significant role in ALS pathogenesis. Pereira et al. established a cultured human sensorimotor organoid model and suggested that glial cells may be involved in motor neuron atrophy in ALS [105]. However, the extent to which astrocytes and microglia exert non-cell autonomous effects or even contribute to the capacity of vascular cells for extensive angiogenesis and the blood–brain barrier is unclear [105]. Though glial cells store lipid droplets as an energy reserve, emerging evidence links lipid droplets to neuron–glia metabolic interactions [106]. The high lipid peroxidation levels observed in ALS may serve as a protective detoxification mechanism against oxidative stress in sensory neurons, which is relevant to ALS, given the prevalent lipid metabolism abnormalities in patients with ALS and SOD1 mice. Recent findings also suggest a metabolic shift from glucose to lipids as an energy source in SOD1 mouse ALS models. If this occurs in the DRG of SOD1 mice [107], SGCs might store excess neutral lipids as a neuroprotective strategy to reduce lipotoxicity. Intriguingly, Ruiz-Soto et al. detected lipid droplets within autolysosomes, suggesting a mechanism of lipophagy [8]. Consistent with this finding, Rudnick et al. observed autophagy activation in motor neurons during ALS progression in SOD1G93A mice, and we frequently observed autophagosomes in SGCs from this ALS mouse model [108].

In ALS sensory neurons, satellite glial cells (SGCs) have been examined; SGCs at the DRG showed abnormal SOD1 accumulation, reinforcing the pathogenic role of glial cells in ALS [8]. These changes lead to lysosomal storage issues and occasional degeneration. This finding highlights SGCs as key targets in ALS pathology, underscoring the role of glial cells in motor neuron diseases [8]. In SGCs, impaired lysosomal accumulation due to oxidative stress is observed, suggesting a novel potential mechanism contributing to ALS pathogenesis. SGCs also contribute to the normal function of sensory neurons, highlighting the importance of astroglial cells [8]. Based on the sensory–motor network and prion hypothesis, it is suggested that SGCs may function as a cause of sensory symptoms and influence motor neuron pathogenesis. In ALS spinal cords, reactive astrocytes overexpress γ 1 laminin, particularly around the affected regions [109]. This unique γ 1 laminin distribution indicates that astrocytes may produce γ 1 laminin to aid the survival of neurons in ALS, whereas TDP-43 is lost in the astroglia [109,110]. The multiple ways in which γ 1 laminin and its KDI domain protect neurons neurotrophically and enhance their viability suggest that the overexpression of γ 1 laminin by reactive astrocytes in the ALS spinal cord may be an attempt by the glia to protect neurons and combat ALS pathology. In a study

conducted by Peng et al., these changes do not affect motor neurons or the neuromuscular junction, but the number of mature oligodendrocytes is selectively reduced, implying that the loss of TDP-43 affects oligodendrocyte function [110]. An astroglial TDP-43 deletion in mice causes motor deficits, highlighting its importance in maintaining astrocytic protection for motor function [110]. Glial dysfunction may thus contribute to the degeneration of sensory neurons and the propagation of ALS pathology.

4.6. Excitotoxicity and Calcium Dysregulation

Excitotoxicity and calcium dysregulation are emerging as key contributors to sensory neuron dysfunction, and their hyper-activation can impair LMNs in ALS [100]. In *Drosophila* sensory neurons, the cytosolic calcium-calpain-A-importin pathway was identified as a regulatory mechanism underlying the nucleo-cytoplasmic transport of TDP-43. The calcium-calpain-A-importin $\alpha 3$ pathway is a therapeutic target of ALS [88,111]. Stracher reported that calpain proteolysis, either directly or indirectly, is associated with neurological diseases, such as ischemia, nerve damage, and spinal cord injury [111]. Calpain may be involved, although not directly, in neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease, and ALS [111]. Dysregulated calcium handling and mitochondrial dysfunction have also been shown to collectively disrupt the function of sensory neurons and contribute to their degeneration [88,93,100]. The interaction between the endoplasmic reticulum (ER) and mitochondria significantly impacts neuronal functions; the malfunctioning of the ER-mitochondria interface, the mitochondria-associated ER membrane (MAM), leads to stress, calcium imbalance, and energy disruption. MAM disturbances might initiate axonal degeneration [93], and the MAM is therefore a potential therapeutic target for ALS.

4.7. Oxidative Stress and Protein Homeostasis

Oxidative stress and the generation of reactive oxygen species play an important role in neuronal dysfunction in ALS [14,101,112]. In their 2021 study, Zuo et al. reported that TDP-43 aggregation in neurons of mouse and human origin causes susceptibility to oxidative stress [14]. Aggregated TDP-43 sequesters specific microRNAs (miRNAs) and proteins, increasing the levels of some proteins and functionally depleting others. Many of these functionally disrupted gene products are mitochondrial proteins encoded in the nuclear genome, whose dysregulation causes an overall mitochondrial imbalance and increased oxidative stress. This stress-aggregation cycle may underlie the onset and progression of ALS [14]. Dilliot et al. reported that the J protein DnaJC7 may be regulated in response to cellular stress via the heat shock response [113]. DnaJC7 may be essential under other certain stress conditions, such as oxidative stress, protein misfolding stress, and impaired protein quality control in aging cells, especially in motor neurons [113]. Therefore, an understanding of the mechanisms underlying these processes may provide valuable insights into the maintenance of sensory function in patients with ALS and may help in developing therapeutic strategies for improved clinical outcomes.

Protein homeostasis, or proteostasis, networks are important mechanisms that maintain proper protein folding, degradation, and repair within the cell. A growing body of evidence suggests that the TDP-43-induced reduction of stathmin 2 (STMN2) protein and impaired proteostasis play an important role in ALS pathogenesis [113,114]. In their 2022 study, Krus et al. used STMN2 knockout mice to investigate the possibility that STMN2 deficiency is a cause of ALS; the loss of STMN2 results in the loss of motor neurons and axons, leading to motor behaviour deficits and early sensory neuropathy, which are particularly problematic in ALS [114]. Removing STMN2 in motor neurons causes similar problems. Heterozygous mice mimic the pathophysiology of patients with ALS and exhibit motor-selective neuropathy. Thus, the reduction of STMN2 due to TDP-43 abnormalities likely influences the pathogenesis of ALS [114]. Using a *Drosophila* model with ALS-related mutation in all cells, Held et al. observed motor deficits in both the larval and adult stages [72]. Motor neuron changes could not explain the early-stage locomotion decline [72]. A sensory

feedback issue in proprioceptor neurons, critical for muscle status relay, was identified [72]. Activating BMP signalling in these neurons rescue motor defects, which is indicative of their role in ALS progression [72]. This finding emphasises the significance of non-motor neurons, potential early ALS biomarkers, and novel therapeutic targets [72]. An understanding of how neural circuit dysfunctions contribute to neurodegeneration is crucial for earlier ALS diagnosis and intervention.

4.8. Protein Changes in Sensory Neurons

Studies involving sensory pathways in SOD1 transgenic mice, the most-used mouse model of ALS, have demonstrated pathological changes in the cell bodies of axons of the posterior column, spinal dorsal horn, dorsal root, and DRG neurons [90,115], similar to those observed in Wallerian degeneration. In addition, the abnormal accumulation of SOD1 protein associated with abnormalities in the SOD1 gene in the cell bodies of sensory axons and DRG neurons has been reported [116,117]. Notably, one ALS study also showed increased thickness in certain regions of the retina [118], elucidating a critical role for RAN binding protein 2 (Ranbp2) in signalling between microglia and retinal ganglion cells in the immune response in ALS [119]. Ranbp2 is a protein involved in nucleocytoplasmic transport, and its regulation is impaired in both sporadic and familial ALS [120]. The widespread impairment of the olfactory pathway suggests a common mechanism with classical motor neuron degeneration that goes beyond the pathophysiology of TDP-43. For example, senataxin, a protein associated with dominant juvenile ALS (ALS4) through gain-of-function mechanisms, is most abundantly expressed in the hippocampus and olfactory bulb [16]. TDP-43 has recently been shown to regulate the axonal transport of ribosomal protein mRNA and local translation by ribosomes, which is essential for maintaining axonal morphological integrity [121], and the accumulation of TDP-43 associated with TARDBP gene abnormalities has been reported in case reports [122]. Liao et al. identified eight mutations in the kinesin family member 1A (KIF1A) gene in 10 of 941 patients with ALS; they reported that patients with ALS carrying rare damage variants in KIF1A tend to exhibit sensory deficits and that KIF1A causes hereditary sensory and autonomic neuropathies, which affect sensory neurons [123].

4.9. Role of Cytoskeletal Dysregulation and Neuronal Transport

The dysregulation of the cytoskeleton and neuronal transport is also implicated in ALS pathogenesis [124,125]. Schäfer et al. used progressive motor neuropathy model mice carrying a missense loss-of-function mutation in tubulin-binding cofactor E (TBCE) and showed that sensory neuropathy in ALS is a cytoskeletal defect [85]. Liao et al. investigated the genetic association of the KIF1A gene, which encodes a motor protein involved in the transport of vesicles in neurons, based on the whole-exome sequencing of samples from patients with ALS, and identified rare damage variants in KIF1A associated with the disease [123]. The patients with ALS carrying variants tended to exhibit sensory disturbances [123]. A functional analysis revealed that these variants enhanced the binding of specific vesicles to the KIF1A protein [123]. Additionally, the expression of disease-related KIF1A mutants in cultured neurons resulted in an increased co-localisation of vesicles with the KIF1A motor [123]. These findings highlight the involvement of KIF1A-mediated transport in ALS pathogenesis and suggest its role as an important player in the genetic complexity of ALS. Patients with ALS and model mice exhibit neurofilament accumulation in the cell bodies and axons of motor neurons. Abnormalities in neurofilament transport have also been observed in multiple lines of mutant SOD1 transgenic mice, along with reduced tubulin transport in some cases [126]. Overall, these findings suggest that axonal transport abnormalities contribute to motor neuron pathology in ALS mouse models.

5. Targeting Proprioceptive Sensory Neurons as a Potential Therapy for ALS

5.1. Current ALS Drugs

There are currently no fundamental ALS drugs. The most used is riluzole, which inhibits glutamate release, blocks postsynaptic NMDA and kainic acid-type glutamate receptors, and inhibits membrane potential-dependent sodium channels [127]. The neuro-protective drug riluzole has a modest survival benefit, but has long been the only disease-modifying therapy for ALS [128]. Edaravone (a free radical scavenger) treatment significantly delays disease progression in ALS, with an increasing number of countries approving its use since its initial approval in 2015 [129]. Edaravone has been used to treat acute strokes for almost two decades in Japan; it was approved for the treatment of ALS in Japan and South Korea in 2015; the US Food and Drug Administration (FDA) approved the drug in 2017 and the Chinese National Medical Products Administration approved it in 2019; and it has been used for the treatment of ALS for almost 20 years in Japan and South Korea. In a phase II study, 20 patients with ALS received either 30 or 60 mg of edaravone and a significant reduction in the revised ALSFRS (ALSFRS-R) score was observed during the 6-month treatment period [130]. In a randomised, double-blind phase III trial, significantly smaller reductions in ALSFRS-R scores were also observed compared to the placebo group [131]. However, the exact mechanism of action of edaravone in ALS remains unclear. It demonstrates both neuroprotective effects against oxidative stress and anti-inflammatory effects against activated microglial cells. However, these effects only marginally prolong the life of patients with ALS. Other potential ALS drugs, such as sodium phenylbutyrate and taurursodiol (PB-TURSO), were conditionally approved in Canada in 2022; patients who were randomised to receive PB-TURSO ($n = 87$) had a 47% lower risk of major events compared to the placebo group ($n = 48$), suggesting that early PB-TURSO treatment may significantly slow disease progression and prolong survival in ALS [132]. In April 2023, the FDA approved Tofersen for the treatment of adult patients with ALS associated with a confirmed SOD1 gene mutation [127]. Tofersen is an antisense oligonucleotide that suppresses the production of the harmful SOD1 protein ALS variant by binding to mRNA associated with the SOD1 gene [128]. Finally, the Japan Early-Stage Trial of Ultra-high-Dose Methylcobalamin for ALS (JETALS), a new drug application for a high-dose formulation of methylcobalamin (development code: E0302) for ALS, has been initiated [133]. Although the mechanism of action of methylcobalamin in the pathogenesis of ALS has not been elucidated, results from non-clinical studies suggest its efficacy through neuroprotective and neuroaxonal regeneration effects [133].

5.2. Addressing DRG Neuron Abnormalities May Treat Motor Neuron Impairments in ALS

Several ALS preclinical studies have reported abnormalities in DRG neurons that precede motor neuron abnormalities [95,116]. Held et al. reported that non-motor neuron dysfunction in animals with early-stage ALS correlates with motor deficits in the absence of motor neuron degeneration, and that the ALS phenotype could be alleviated via the activation of neurotrophic BMP pathways in non-motor neurons using a knock-in SOD1-ALS model [84]. DRG neurons are beginning to attract attention as a therapeutic target for ALS movement disorders in terms of whether intrinsic receptive fibres may play a role in neurodegeneration via glutamatergic excitatory inputs to motor neurons.

The most basic neural circuit of the spinal reflex involving DRG neurons is the stretch reflex arch, which consists of Ia fibres and alpha motor neurons. Ia fibres entering from the dorsal root of the spinal cord make excitatory synaptic connections to alpha motor neurons in the anterior horn of the spinal cord. A lack of afferent input from Ia fibres to spinal gamma motoneurons has been suggested as a mechanism for disease resistance in mouse models of ALS, with some reports suggesting that reduced Ia endoreceptor muscle spindle afferents partially contribute to alpha motoneuron survival [35,134,135], and Guo et al. noted that the cytoplasmic vacuolation of DRG neurons may contribute to motor neuron degeneration in hSOD1G93A mice [90]. Yan et al. noted that calcium modulation led to a decrease in Ca current via HVA Ca channel-targeting abnormalities in a study in

which serum from healthy adults, patients with other neurological diseases, or patients with sporadic ALS was injected into the DRG of mice for 3 days [91]. In DRG neurons, the regulation of calcium homeostasis may be achieved through drug development and interventions that restore or stabilize intracellular calcium levels, which may not only alleviate the sensory deficits associated with ALS, but may also improve motor deficits. In addition, Vaughan et al. reported that the accumulation of misfolded TDP-43 and SOD1 directly affects DRG neurons, resulting in sensitisation to stress; since the degeneration of DRG terminals approximates that seen in motor neurons, future therapies should focus on targeting these proteins [84].

These findings suggest that DRG neurons may be a potential therapeutic target, not only for ameliorating sensory abnormalities in patients with ALS, but also for treating motor impairments in ALS. Whether the normalisation of DRGs in ALS normalises motor neurons, prevents muscle atrophy, and improves motor function is currently unknown, but addressing DRG abnormalities should be considered as a novel strategy for treating ALS.

5.3. Potential for Gene Therapy Targeting TDP-43

Genetic abnormalities are found in DRG as well as in motor neurons in ALS (Table 4). To date, SOD1G93A has received the most attention as an ALS-inducing factor and has been reported in motor neurons in various studies. Preclinical studies have also reported the effects of SOD1G93A in DRGs [8,33,34], and though it is still considered a therapeutic target, TDP-43 accumulation has also recently attracted attention. For example, Vaughan et al. reported that the accumulation of pathological features caused by TDP-43 A315T expression may contribute directly to impaired neurite outgrowth in DRG [84].

Table 4. Genetic abnormalities observed in sensory neurons in ALS.

Genes	Type of Sensory Neuron	Function	References
SOD1	DRG	Encodes an itinerant enzyme that catalyses the conversion of superoxide to hydrogen peroxide and dioxygen.	[117]
KIF1A	DRG	Encodes the kinesin 3 motor that transports presynaptic vesicle precursors and dense core vesicles.	[123]
TARDBP	DRG	Mainly localised in the nucleus and regulates RNA processing.	[122]
FUS	VNC	RNA-binding protein.	[104]

FUS, fused in sarcoma; KIF1A, kinesin family member 1A; TARDBP, TAR DNA-binding protein (TDP-43) gene.

TDP-43 performs several mRNA-related processes in the nucleus, including transcription, splicing, the maintenance of RNA stability, and the processing of miRNAs and long non-coding RNAs [136]. TDP-43 proteinopathy refers to diseases involving TDP-43, including ALS, fronto-temporal lobar degeneration, primary lateral sclerosis, and progressive amyotrophic disease [136]. It has been suggested that TDP-43 plays a pivotal role in the pathogenesis of ALS. TDP-43 is primarily localised to the nucleus, but also relocates to the cytoplasm for some of its functions [137]. In ALS, an increase in cytoplasmic TDP-43 levels is observed, which results in the formation of cytoplasmic inclusion bodies [137,138]. Rumpf et al. reported that autosomal dominant mutations in human valosin-containing protein cause FTD and ALS, a hallmark of which is the formation of TDP-43 aggregates [89]. Park et al. reported that photogenetic stimulation enhanced the nuclear translocation of red fluorescent protein TDP-43 accumulated in the cytoplasm in C4da neurons, a class IV dendritic branch of *Drosophila* larvae, through the action of calcium-dependent regulators and nuclear translocation components [88]. Nagano et al. focused on mRNA transport to neuroaxons, one of the functions of TDP-43 in ALS motoneurons, and identified multiple ribosomal protein mRNAs as target mRNAs transported to axons by TDP-43 [121]. Furthermore, ribosomal proteins are reduced in lesional axonal regions in patients with ALS, and ALS genetic therapy is underway to express ribosomal proteins using adeno-associated virus (AAV) vectors [139]. If a similar decrease occurs in the DRG due to TDP-43 accumula-

tion, gene therapy using AAV vectors expressing ribosomal proteins may be feasible for the DRG in ALS (Figure 2).

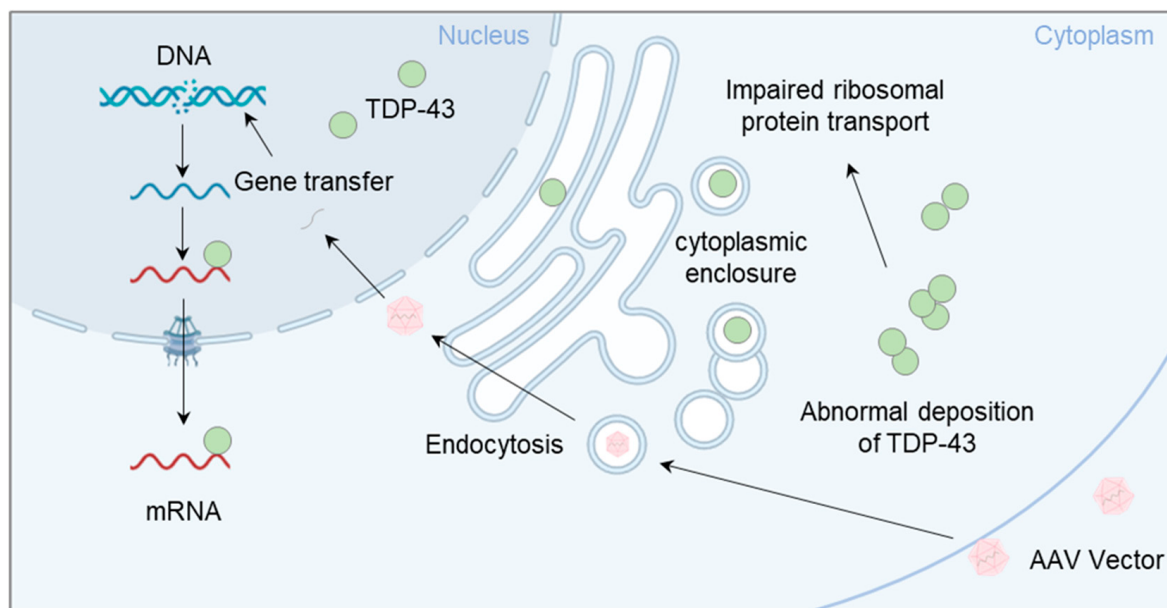


Figure 2. Therapeutic strategies for the cytoplasmic deposition of TDP-43 using AAV vectors. Cytoplasmic deposition of TDP-43 in ALS has been suggested to be due to abnormal RNA metabolism. Attempts to ameliorate TDP-43 cytoplasmic deposition via gene therapy using AAV vectors have been investigated and may be applicable to the treatment of DRGs.

5.4. Treatment Strategies for ALS Masticatory Abnormalities through the MesV

MesV neurons are proprioceptive sensory neurons that are required for mastication that not only transmit intrinsic sensations from muscle spindles in jaw movements to the centre, but also directly act on trigeminal motor neurons to control masticatory movements [35,96–98]. Treatment strategies for mastication disorders in ALS may focus on protecting the survival and function of the MesV, which controls mastication movements [35,36,140–142]. Seki et al. reported excessively inhibited and irregular neuron-firing activity and a significant decrease in the Na current in the MesV in mouse neonates [115]. Notably, MesV abnormalities are more pronounced and definitive than the electrophysiological abnormalities in trigeminal motoneurons in neonatal ALS mice [84]. As SOD1G93A mouse neonate models were used in both studies, it is possible that the abnormalities in the MesV preceded the abnormalities in the trigeminal motoneurons.

Reductions in the Na current reported in ALS model mice are associated with the suppression of MesV activity [35,142]. Moreover, the modelling of Na current inputs to the MesV using dynamic clamps has been reported to improve irregular firing activity [35,142]. Thus, the modification of Na channels can normalise MesV activity. Using fluorescent immunohistochemistry, the reduced Nav1.6 Na current observed in ALS mice was found to be due to the down-regulation of Nav1.6 Na channels on MesV neuronal membranes [35]. Specifically, the development of Na channel modifiers and the identification of factors involved in Na channel dysfunction can be considered. Notably, the abnormality reported in trigeminal motor neurons is overexcitation, the exact opposite of the overinhibition reported in the MesV. Since overexcitation is found in many motor neurons and riluzole, an ALS drug, is an inhibitor of neuronal excitability, the treatment of ALS targeting the MesV should show the opposite effect of the current treatment [128]. Another possible ALS treatment is neuropeptide Y (NPY); Seki et al. reported that the application of NPY shortens the post-hyperpolarisation duration after action potentials in the rat MesV and increases the mean spike frequency during repetitive discharges [139]. In addition, the burst frequency increases in neurons that exhibit rhythmic burst discharges in response to maintained

current injections, and NPY treatment increases the Na current in the MesV [139]. Future studies should investigate whether neuropeptides that act in an excitatory capacity on neurons, such as NPY and Orexin, ameliorate the hypo-excitation of the MesV in ALS and improve MesV function [96]. Whether correcting abnormalities in proprioceptive sensory neurons involved in muscle spindles, such as the MesV, corrects mastication deficits in ALS and helps to treat movement disorders in patients with ALS should also be examined [95] (Figure 3).

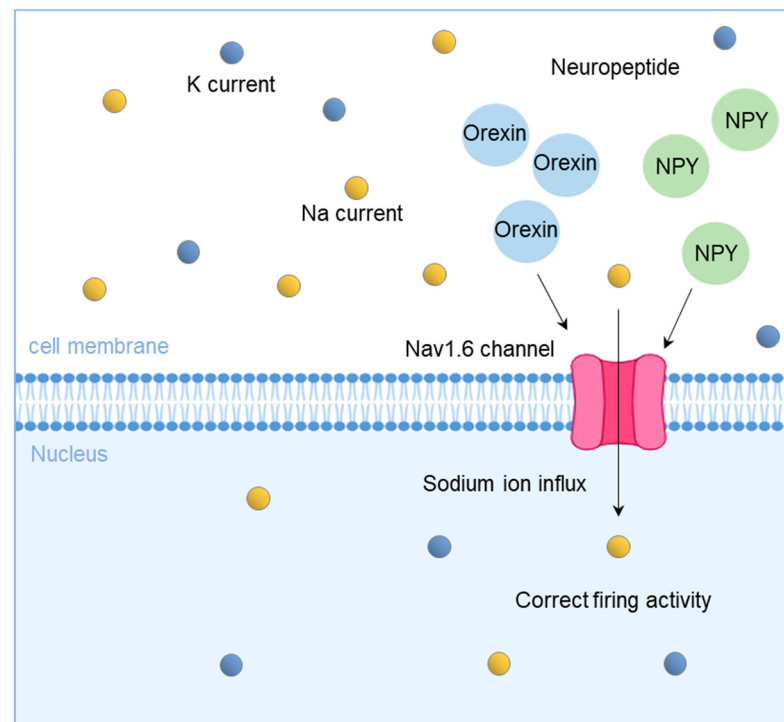


Figure 3. Therapeutic strategies for the correction of sodium ion channels via neuropeptides. Neuropeptides such as orexin and NPY may increase MesV sodium current and improve firing activity in ALS with reduced sodium currents.

6. Conclusions

In clinical and preclinical studies, emerging evidence suggests that both sensory and motor neurons are involved in the pathogenesis of ALS. Therefore, continued research on both neurons is needed to improve our understanding of the diagnosis, treatment, and pathogenesis of ALS. Primary sensory neurons not only transmit sensory information from muscle spindles, but are also involved in the control of movement, highlighting them as potential therapeutic targets for movement disorders in ALS. Furthermore, as shown in this review, primary sensory neurons such as DRG and MesV neurons may show abnormalities prior to motor neurons in clinical studies. As such, future therapies targeting primary sensory neurons may improve the quality of life of patients with ALS.

Author Contributions: Conceptualization, S.S.; methodology, S.S.; validation, S.S., Y.K., S.K., A.N., T.U., S.-i.H., Y.Y., E.T.I., M.K. and S.T.; investigation, S.S.; writing—original draft preparation, S.S.; writing—review and editing, S.S.; supervision, T.U., S.-i.H., Y.Y., E.T.I., M.K. and S.T.; project administration, S.S. and S.T.; funding acquisition, S.S., M.K. and S.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the JSPS KAKENHI (grant numbers: 21K17088 and 20H03887).

Data Availability Statement: The datasets generated and/or analysed in this study have not been published but are available from the corresponding authors upon reasonable request.

Acknowledgments: The authors would like to thank the members of the Department of Oral and Maxillofacial Surgery, Graduate School of Dentistry, Osaka University.

Conflicts of Interest: The authors declare no competing interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

- Al-Chalabi, A.; Hardiman, O. The Epidemiology of ALS: A Conspiracy of Genes, Environment and Time. *Nat. Rev. Neurol.* **2013**, *9*, 617–628. [\[CrossRef\]](#) [\[PubMed\]](#)
- Riancho, J.; Gonzalo, I.; Ruiz-Soto, M.; Berciano, J. Why Do Motor Neurons Degenerate? Actualization in the Pathogenesis of Amyotrophic Lateral Sclerosis. *Neurología* **2019**, *34*, 27–37. [\[CrossRef\]](#)
- Tanaka, M.; Toldi, J.; Vécsei, L. Exploring the Etiological Links behind Neurodegenerative Diseases: Inflammatory Cytokines and Bioactive Kynurenines. *Int. J. Mol. Sci.* **2020**, *21*, 2431. [\[CrossRef\]](#) [\[PubMed\]](#)
- Tanaka, M.; Szabó, Á.; Spekter, E.; Polyák, H.; Tóth, F.; Vécsei, L. Mitochondrial Impairment: A Common Motif in Neuropsychiatric Presentation? The Link to the Tryptophan–Kynurenine Metabolic System. *Cells* **2022**, *11*, 2607. [\[CrossRef\]](#)
- Bunton-Stasyshyn, R.K.; Saccon, R.A.; Fratta, P.; Fisher, E.M. SOD1 Function and Its Implications for Amyotrophic Lateral Sclerosis Pathology: New and Renascent Themes. *Neuroscientist* **2015**, *21*, 519–529. [\[CrossRef\]](#) [\[PubMed\]](#)
- Hübers, A.; Ludolph, A.C.; Rosenbohm, A.; Pinkhardt, E.H.; Weishaupt, J.H.; Dorst, J. Amyotrophe Lateralsklerose. Eine Multisystemdegeneration. *Nervenarzt* **2016**, *87*, 179–188. [\[CrossRef\]](#)
- Müller, K.; Brenner, D.; Weydt, P.; Meyer, T.; Grehl, T.; Petri, S.; Grosskreutz, J.; Schuster, J.; Volk, A.E.; Borck, G.; et al. Comprehensive Analysis of the Mutation Spectrum in 301 German ALS Families. *J. Neurol. Neurosurg. Psychiatry* **2018**, *89*, 817–827. [\[CrossRef\]](#)
- Ruiz-Soto, M.; Riancho, J.; Tapia, O.; Lafarga, M.; Berciano, M.T. Satellite Glial Cells of the Dorsal Root Ganglion: A New “Guest/Physiopathological Target” in ALS. *Front. Aging Neurosci.* **2020**, *12*, 595751. [\[CrossRef\]](#)
- Yun, Y.; Ha, Y. CRISPR/Cas9-Mediated Gene Correction to Understand ALS. *Int. J. Mol. Sci.* **2020**, *21*, 3801. [\[CrossRef\]](#)
- Taylor, J.P.; Brown, R.H., Jr.; Cleveland, D.W. Decoding ALS: From Genes to Mechanism. *Nature* **2016**, *539*, 197–206. [\[CrossRef\]](#)
- Geser, F.; Martinez-Lage, M.; Robinson, J.; Uryu, K.; Neumann, M.; Brandmeir, N.J.; Xie, S.X.; Kwong, L.K.; Elman, L.; McCluskey, L.; et al. Clinical and Pathological Continuum of Multisystem TDP-43 Proteinopathies. *Arch. Neurol.* **2009**, *66*, 180–189. [\[CrossRef\]](#)
- McCombe, P.A.; Wray, N.R.; Henderson, R.D. Extra-motor Abnormalities in Amyotrophic Lateral Sclerosis: Another Layer of Heterogeneity. *Expert Rev. Neurother.* **2017**, *17*, 561–577. [\[CrossRef\]](#) [\[PubMed\]](#)
- Yu, C.H.; Davidson, S.; Harapas, C.R.; Hilton, J.B.; Mlodzianoski, M.J.; Laohamonthonkul, P.; Louis, C.; Low, R.R.J.; Moecking, J.; De Nardo, D.; et al. TDP-43 Triggers Mitochondrial DNA Release via mPTP to Activate cGAS/STING in ALS. *Cell* **2020**, *183*, 636–649. [\[CrossRef\]](#)
- Zuo, X.; Zhou, J.; Li, Y.; Wu, K.; Chen, Z.; Luo, Z.; Zhang, X.; Liang, Y.; Esteban, M.A.; Zhou, Y.; et al. TDP-43 Aggregation Induced by Oxidative Stress Causes Global Mitochondrial Imbalance in ALS. *Nat. Struct. Mol. Biol.* **2021**, *28*, 132–142. [\[CrossRef\]](#)
- De Marchi, F.; Franjic, T.; Schito, P.; Russo, T.; Nimac, J.; Chami, A.A.; Mele, A.; Vidatic, L.; Kriz, J.; Julien, J.P.; et al. Emerging Trends in the Field of Inflammation and Proteinopathy in ALS/FTD Spectrum Disorder. *Biomedicines* **2023**, *11*, 1599. [\[CrossRef\]](#)
- Tao, Q.Q.; Wei, Q.; Wu, Z.Y. Sensory Nerve Disturbance in Amyotrophic Lateral Sclerosis. *Life Sci.* **2018**, *203*, 242–245. [\[CrossRef\]](#) [\[PubMed\]](#)
- Matamala, J.M.; Howells, J.; Dharmadasa, T.; Huynh, W.; Park, S.B.; Burke, D.; Kiernan, M.C. Excitability of Sensory Axons in Amyotrophic Lateral Sclerosis. *Clin. Neurophysiol.* **2018**, *129*, 1472–1478. [\[CrossRef\]](#) [\[PubMed\]](#)
- de Carvalho, M.; Turkman, A.; Swash, M. Sensory Modulation of Fasciculation Discharge Frequency. *Muscle Nerve* **2019**, *59*, 688–693. [\[CrossRef\]](#) [\[PubMed\]](#)
- Riancho, J.; Paz-Fajardo, L.; López de Munáin, A. Clinical and Preclinical Evidence of Somatosensory Involvement in Amyotrophic Lateral Sclerosis. *Br. J. Pharmacol.* **2021**, *178*, 1257–1268. [\[CrossRef\]](#)
- Riku, Y.; Seilhean, D.; Duyckaerts, C.; Boluda, S.; Iguchi, Y.; Ishigaki, S.; Iwasaki, Y.; Yoshida, M.; Sobue, G.; Katsuno, M. Pathway from TDP-43-Related Pathology to Neuronal Dysfunction in Amyotrophic Lateral Sclerosis and Frontotemporal Lobar Degeneration. *Int. J. Mol. Sci.* **2021**, *22*, 3843. [\[CrossRef\]](#)
- Balendra, R.; Isaacs, A.M. C9orf72-mediated ALS and FTD: Multiple Pathways to Disease. *Nat. Rev. Neurol.* **2018**, *14*, 544–558. [\[CrossRef\]](#) [\[PubMed\]](#)
- McCauley, M.E.; Baloh, R.H. Inflammation in ALS/FTD Pathogenesis. *Acta Neuropathol.* **2019**, *137*, 715–730. [\[CrossRef\]](#)
- Bowser, R.; Turner, M.R.; Shefner, J. Biomarkers in Amyotrophic Lateral Sclerosis: Opportunities and Limitations. *Nat. Rev. Neurol.* **2011**, *7*, 631–638. [\[CrossRef\]](#) [\[PubMed\]](#)
- Krüger, T.; Lautenschläger, J.; Grosskreutz, J.; Rhode, H. Proteome Analysis of Body Fluids for Amyotrophic Lateral Sclerosis Biomarker Discovery. *Proteom. Clin. Appl.* **2013**, *7*, 123–135. [\[CrossRef\]](#)
- Collins, M.A.; An, J.; Hood, B.L.; Conrads, T.P.; Bowser, R.P. Label-Free LC-MS/MS Proteomic analysis of Cerebrospinal Fluid Identifies Protein/Pathway Alterations and Candidate Biomarkers for Amyotrophic Lateral Sclerosis. *J. Proteome Res.* **2015**, *14*, 4486–4501. [\[CrossRef\]](#)

26. Chen, Y.; Liu, X.H.; Wu, J.J.; Ren, H.M.; Wang, J.; Ding, Z.T.; Jiang, Y.P. Proteomic Analysis of Cerebrospinal Fluid in Amyotrophic Lateral Sclerosis. *Exp. Ther. Med.* **2016**, *11*, 2095–2106. [[CrossRef](#)] [[PubMed](#)]
27. Vu, L.T.; Bowser, R. Fluid-Based Biomarkers for Amyotrophic Lateral Sclerosis. *Neurotherapeutics* **2017**, *14*, 119–134. [[CrossRef](#)]
28. Barschke, P.; Oeckl, P.; Steinacker, P.; Ludolph, A.; Otto, M. Proteomic Studies in the Discovery of Cerebrospinal Fluid Biomarkers for Amyotrophic Lateral Sclerosis. *Expert Rev. Proteom.* **2017**, *14*, 769–777. [[CrossRef](#)]
29. Thompson, A.G.; Gray, E.; Thézenas, M.L.; Charles, P.D.; Evetts, S.; Hu, M.T.; Talbot, K.; Fischer, R.; Kessler, B.M.; Turner, M.R. Cerebrospinal Fluid Macrophage Biomarkers in Amyotrophic Lateral Sclerosis. *Ann. Neurol.* **2018**, *83*, 258–268. [[CrossRef](#)]
30. Goutman, S.A.; Hardiman, O.; Al-Chalabi, A.; Chiò, A.; Savelieff, M.G.; Kiernan, M.C.; Feldman, E.L. Recent Advances in the Diagnosis and Prognosis of Amyotrophic Lateral Sclerosis. *Lancet Neurol.* **2022**, *21*, 480–493. [[CrossRef](#)]
31. Oh, S.; Jang, Y.; Na, C.H. Discovery of Biomarkers for Amyotrophic Lateral Sclerosis from Human Cerebrospinal Fluid Using Mass-Spectrometry-Based Proteomics. *Biomedicines* **2023**, *11*, 1250. [[CrossRef](#)] [[PubMed](#)]
32. Jerusalem, F.; Pohl, C.; Karitzky, J.; Ries, F. ALS. *Neurology* **1996**, *47* (Suppl. 4), S218–S220. [[CrossRef](#)]
33. Rubio, M.A.; Herrando-Grabulosa, M.; Navarro, X. Sensory Involvement in Amyotrophic Lateral Sclerosis. *Int. J. Mol. Sci.* **2022**, *23*, 15521. [[CrossRef](#)] [[PubMed](#)]
34. Sassone, J.; Taiana, M.; Lombardi, R.; Porretta-Serapiglia, C.; Freschi, M.; Bonanno, S.; Marcuzzo, S.; Caravello, F.; Bendotti, C.; Lauria, G. ALS Mouse Model SOD1G93A Displays Early Pathology of Sensory Small Fibers Associated to Accumulation of a Neurotoxic Splice Variant of Peripherin. *Hum. Mol. Genet.* **2016**, *25*, 1588–1599. [[CrossRef](#)]
35. Seki, S.; Yamamoto, T.; Quinn, K.; Spigelman, I.; Pantazis, A.; Olcese, R.; Wiedau-Pazos, M.; Chandler, S.H.; Venugopal, S. Circuit-Specific Early Impairment of Proprioceptive Sensory Neurons in the SOD1^{G93A} Mouse Model for ALS. *J. Neurosci.* **2019**, *39*, 8798–8815. [[CrossRef](#)] [[PubMed](#)]
36. Kitaoka, Y.; Seki, S.; Kawata, S.; Nishiura, A.; Kawamura, K.; Hiraoka, S.I.; Kogo, M.; Tanaka, S. Analysis of Feeding Behavior Characteristics in the Cu/Zn Superoxide Dismutase 1 (SOD1) SOD1G93A Mice Model for Amyotrophic Lateral Sclerosis (ALS). *Nutrients* **2023**, *15*, 1651. [[CrossRef](#)]
37. Ferrea, S.; Junker, F.; Korth, M.; Gruhn, K.; Grehl, T.; Schmidt-Wilcke, T. Cortical Thinning of Motor and Non-Motor Brain Regions Enables Diagnosis of Amyotrophic Lateral Sclerosis and Supports Distinction Between Upper- and Lower-Motoneuron Phenotypes. *Biomedicines* **2021**, *9*, 1195. [[CrossRef](#)]
38. Raghunathan, R.; Turajane, K.; Wong, L.C. Biomarkers in Neurodegenerative Diseases: Proteomics Spotlight on ALS and Parkinson's disease. *Int. J. Mol. Sci.* **2022**, *23*, 9299. [[CrossRef](#)]
39. Rowland, L.P.; Shneider, N.A. Amyotrophic Lateral Sclerosis. *N. Engl. J. Med.* **2001**, *344*, 1688–1700. [[CrossRef](#)]
40. Mitchell, J.D.; Borasio, G.D. Amyotrophic Lateral Sclerosis. *Lancet* **2007**, *369*, 2031–2041. [[CrossRef](#)]
41. Wijesekera, L.C.; Leigh, P.N. Amyotrophic Lateral Sclerosis. *Orphanet J. Rare Dis.* **2009**, *4*, 3. [[CrossRef](#)] [[PubMed](#)]
42. Kiernan, M.C.; Vucic, S.; Cheah, B.C.; Turner, M.R.; Eisen, A.; Hardiman, O.; Burrell, J.R.; Zoing, M.C. Amyotrophic Lateral Sclerosis. *Lancet* **2011**, *377*, 942–955. [[CrossRef](#)]
43. Akçimen, F.; Lopez, E.R.; Landers, J.E.; Nath, A.; Chiò, A.; Chia, R.; Traynor, B.J. Amyotrophic Lateral Sclerosis: Translating Genetic Discoveries into Therapies. *Nat. Rev. Genet.* **2023**, *24*, 642–658. [[CrossRef](#)] [[PubMed](#)]
44. Ravník Glavač, M.; Mezzavilla, M.; Dolinar, A.; Koritnik, B.; Glavač, D. Aberrantly Expressed Hsa_circ_0060762 and CSE1L as Potential Peripheral Blood Biomarkers for ALS. *Biomedicines* **2023**, *11*, 1316. [[CrossRef](#)]
45. Canosa, A.; Calvo, A.; Mora, G.; Moglia, C.; Brunetti, M.; Barberis, M.; Borghero, G.; Caponnetto, C.; Trojsi, F.; Spataro, R.; et al. The HFE p.H63D (p.His63Asp) Polymorphism Is a Modifier of ALS Outcome in Italian and French Patients with SOD1 Mutations. *Biomedicines* **2023**, *11*, 704. [[CrossRef](#)]
46. Zufiria, M.; Gil-Bea, F.J.; Fernández-Torrón, R.; Poza, J.J.; Muñoz-Blanco, J.L.; Rojas-García, R.; Riancho, J.; López de Munain, A. ALS: A Bucket of Genes, Environment, Metabolism and Unknown Ingredients. *Prog. Neurobiol.* **2016**, *142*, 104–129. [[CrossRef](#)]
47. Zhang, R.; Bracci, P.M.; Azhir, A.; Forrest, B.D.; McGrath, M.S. Macrophage-Targeted Sodium Chlorite (NP001) Slows Progression of Amyotrophic Lateral Sclerosis (ALS) through Regulation of Microbial Translocation. *Biomedicines* **2022**, *10*, 2907. [[CrossRef](#)]
48. Masrori, P.; Van Damme, P. Amyotrophic Lateral Sclerosis: A Clinical Review. *Eur. J. Neurol.* **2020**, *27*, 1918–1929. [[CrossRef](#)] [[PubMed](#)]
49. Wintz, K.; Post, J.; Langen, K.J.; Willbold, D.; Willuweit, A.; Kutzsche, J. Oral Treatment with d-RD2RD2 Impedes Early Disease Mechanisms in SOD1*G93A Transgenic Mice but Does Not Prolong Survival. *Biomedicines* **2023**, *11*, 995. [[CrossRef](#)]
50. van Es, M.A.; Hardiman, O.; Chio, A.; Al-Chalabi, A.; Pasterkamp, R.J.; Veldink, J.H.; van den Berg, L.H. Amyotrophic Lateral Sclerosis. *Lancet* **2017**, *390*, 2084–2098. [[CrossRef](#)]
51. Hardiman, O.; Al-Chalabi, A.; Chio, A.; Corr, E.M.; Logroscino, G.; Robberecht, W.; Shaw, P.J.; Simmons, Z.; van den Berg, L.H. Amyotrophic Lateral Sclerosis. *Nat. Rev. Dis. Prim.* **2017**, *3*, 17071. [[CrossRef](#)]
52. Feldman, E.L.; Goutman, S.A.; Petri, S.; Mazzini, L.; Savelieff, M.G.; Shaw, P.J.; Sobue, G. Amyotrophic Lateral Sclerosis. *Lancet* **2022**, *400*, 1363–1380. [[CrossRef](#)]
53. Ma, X.R.; Prudencio, M.; Koike, Y.; Vatsavayai, S.C.; Kim, G.; Harbinski, F.; Briner, A.; Rodriguez, C.M.; Guo, C.; Akiyama, T.; et al. TDP-43 Represses Cryptic Exon Inclusion in the FTD-ALS Gene UNC13A. *Nature* **2022**, *603*, 124–130. [[CrossRef](#)] [[PubMed](#)]
54. Lu, S.; Hu, J.; Arogundade, O.A.; Goginashvili, A.; Vazquez-Sanchez, S.; Diedrich, J.K.; Gu, J.; Blum, J.; Oung, S.; Ye, Q.; et al. Heat-Shock Chaperone HSPB1 Regulates Cytoplasmic TDP-43 Phase Separation and Liquid-to-Gel Transition. *Nat. Cell. Biol.* **2022**, *24*, 1378–1393. [[CrossRef](#)]

55. Linseman, D.A.; Winter, A.N.; Wilkins, H.M. The 2-Oxoglutarate Carrier Is S-Nitrosylated in the Spinal Cord of G93A Mutant hSOD1 Mice Resulting in Disruption of Mitochondrial Glutathione Transport. *Biomedicines* **2022**, *11*, 61. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Hammad, M.; Silva, A.; Glass, J.; Sladky, J.T.; Benatar, M. Clinical, Electrophysiologic, and Pathologic Evidence for Sensory Abnormalities in ALS. *Neurology* **2007**, *69*, 2236–2242. [\[CrossRef\]](#)
57. Cohen-Adad, J.; El Mendili, M.M.; Morizot-Koutlidis, R.; Lehericy, S.; Meininger, V.; Blanche, S.; Rossignol, S.; Benali, H.; Pradat, P.F. Involvement of Spinal Sensory Pathway in ALS and Specificity of Cord Atrophy to Lower Motor Neuron Degeneration. *Amyotroph. Lateral Scler. Frontotemporal. Degener.* **2013**, *14*, 30–38. [\[CrossRef\]](#)
58. Isak, B.; Pugdahl, K.; Karlsson, P.; Tankisi, H.; Finnerup, N.B.; Furtula, J.; Johnsen, B.; Sunde, N.; Jakobsen, J.; Fuglsang-Frederiksen, A. Quantitative Sensory Testing and Structural Assessment of Sensory Nerve Fibres in Amyotrophic Lateral Sclerosis. *J. Neurol. Sci.* **2017**, *373*, 329–334. [\[CrossRef\]](#) [\[PubMed\]](#)
59. Urso, D.; Zoccollella, S.; Gnoni, V.; Logroscino, G. Amyotrophic Lateral Sclerosis—The Complex Phenotype—From an Epidemiological Perspective: A Focus on Extrapyrimal and Non-Motor Features. *Biomedicines* **2022**, *10*, 2537. [\[CrossRef\]](#)
60. Nolano, M.; Provitera, V.; Manganelli, F.; Iodice, R.; Caporaso, G.; Stancanelli, A.; Marinou, K.; Lanzillo, B.; Santoro, L.; Mora, G. Non-Motor Involvement in Amyotrophic Lateral Sclerosis: New Insight From Nerve and Vessel Analysis in Skin Biopsy. *Neuropathol. Appl. Neurobiol.* **2017**, *43*, 119–132. [\[CrossRef\]](#) [\[PubMed\]](#)
61. Liu, W.; Venugopal, S.; Majid, S.; Ahn, I.S.; Diamante, G.; Hong, J.; Yang, X.; Chandler, S.H. Single-cell RNA-seq Analysis of the Brainstem of Mutant SOD1 Mice Reveals Perturbed Cell Types and Pathways of Amyotrophic Lateral Sclerosis. *Neurobiol. Dis.* **2020**, *141*, 104877. [\[CrossRef\]](#)
62. Liu, J.; Zhang, X.; Ding, X.; Song, M.; Sui, K. Analysis of Clinical and Electrophysiological Characteristics of 150 Patients With Amyotrophic Lateral Sclerosis in China. *Neurol. Sci.* **2019**, *40*, 363–369. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Amoiridis, G.; Tsimoulis, D.; Ameridou, I. Clinical, Electrophysiologic, and Pathologic Evidence for Sensory Abnormalities in ALS. *Neurology* **2008**, *2*, 779. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Mulder, D.W.; Bushek, W.; Spring, E.; Karnes, J.; Dyck, P.J. Motor Neuron Disease (ALS): Evaluation of Detection Thresholds of Cutaneous Sensation. *Neurology* **1983**, *33*, 1625–1627. [\[CrossRef\]](#)
65. Sonkodi, B.; Hortobágyi, T. Amyotrophic Lateral Sclerosis and Delayed Onset Muscle Soreness in Light of the Impaired Blink and Stretch Reflexes—Watch Out for Piezo2. *Open Med.* **2022**, *17*, 397–402. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Chiò, A.; Mora, G.; Lauria, G. Pain in Amyotrophic Lateral Sclerosis. *Lancet Neurol.* **2017**, *16*, 144–157. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Gregory, R.; Mills, K.; Donaghy, M. Progressive Sensory Nerve Dysfunction in Amyotrophic Lateral Sclerosis: A Prospective Clinical and Neurophysiological Study. *J. Neurol.* **1993**, *240*, 309–314. [\[CrossRef\]](#)
68. Pugdahl, K.; Fuglsang-Frederiksen, A.; Johnsen, B.; de Carvalho, M.; Fawcett, P.R.; Labarre-Vila, A.; Liguori, R.; Nix, W.A.; Schofield, I.S. A Prospective Multicentre Study on Sural Nerve Action Potentials in ALS. *Clin. Neurophysiol.* **2008**, *119*, 1106–1110. [\[CrossRef\]](#)
69. Isak, B.; Tankisi, H.; Johnsen, B.; Pugdahl, K.; Torvin MØller, A.; Finnerup, N.B.; Christensen, P.B.; Fuglsang-Frederiksen, A. Involvement of Distal Sensory Nerves in Amyotrophic Lateral Sclerosis. *Muscle Nerve* **2016**, *54*, 1086–1092. [\[CrossRef\]](#)
70. Hama, T.; Hirayama, M.; Hara, T.; Nakamura, T.; Atsuta, N.; Banno, H.; Suzuki, K.; Katsuno, M.; Tanaka, F.; Sobue, G. Discrimination of Spinal and Bulbar Muscular Atrophy from Amyotrophic Lateral Sclerosis Using Sensory Nerve Action Potentials. *Muscle Nerve* **2012**, *45*, 169–174. [\[CrossRef\]](#)
71. Shimizu, T.; Bokuda, K.; Kimura, H.; Kamiyama, T.; Nakayama, Y.; Kawata, A.; Isozaki, E.; Ugawa, Y. Sensory Cortex Hyperexcitability Predicts Short Survival in Amyotrophic Lateral Sclerosis. *Neurology* **2018**, *90*, e1578–e1587. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Held, A.; Major, P.; Sahin, A.; Reenan, R.A.; Lipscombe, D.; Wharton, K.A. Circuit Dysfunction in SOD1-ALS Model First Detected in Sensory Feedback Prior to Motor Neuron Degeneration Is Alleviated by BMP Signaling. *J. Neurosci.* **2019**, *39*, 2347–2364. [\[CrossRef\]](#)
73. Nardone, R.; Golaszewski, S.; Thomschewski, A.; Sebastianelli, L.; Versace, V.; Brigo, F.; Orioli, A.; Saltuari, L.; Höller, Y.; Trinka, E. Disinhibition of Sensory Cortex in Patients with Amyotrophic Lateral Sclerosis. *Neurosci. Lett.* **2020**, *23*, 722. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Ren, Y.; Liu, W.; Li, Y.; Sun, B.; Li, Y.; Yang, F.; Wang, H.; Li, M.; Cui, F.; Huang, X. Cutaneous Somatic and Autonomic Nerve TDP-43 Deposition in Amyotrophic Lateral Sclerosis. *J. Neurol.* **2018**, *265*, 1753–1763. [\[CrossRef\]](#)
75. Truini, A.; Biasiotto, A.; Onesti, E.; Di Stefano, G.; Ceccanti, M.; La Cesa, S.; Pepe, A.; Giordano, C.; Cruccu, G.; Inghilleri, M. Small-fibre Neuropathy Related to Bulbar and Spinal-onset in Patients with ALS. *J. Neurol.* **2015**, *262*, 1014–1018. [\[CrossRef\]](#)
76. Iglesias, C.; Sangari, S.; El Mendili, M.M.; Benali, H.; Marchand-Pauvert, V.; Pradat, P.F. Electrophysiological and Spinal Imaging Evidences for Sensory Dysfunction in Amyotrophic Lateral Sclerosis. *BMJ Open* **2015**, *24*, e007659. [\[CrossRef\]](#)
77. Isaacs, J.D.; Dean, A.F.; Shaw, C.E.; Al-Chalabi, A.; Mills, K.R.; Leigh, P.N. Amyotrophic Lateral Sclerosis with Sensory Neuropathy: Part of a Multisystem Disorder? *J. Neurol. Neurosurg. Psychiatry* **2007**, *78*, 750–753. [\[CrossRef\]](#)
78. Heads, T.; Pollock, M.; Robertson, A.; Sutherland, W.H.; Allpress, S. Sensory Nerve Pathology in Amyotrophic Lateral Sclerosis. *Acta Neuropathol.* **1991**, *82*, 316–320. [\[CrossRef\]](#)
79. Riancho, J.; Castaneda-Vázquez, D.; Gil-Bea, F.; Tapia, O.; Arozamena, J.; Durán-Vián, C.; Sedano, M.J.; Berciano, M.T.; Lopez de Munain, A.; Lafarga, M. ALS-Derived Fibroblasts Exhibit Reduced Proliferation Rate, Cytoplasmic TDP-43 Aggregation and a Higher Susceptibility to DNA Damage. *J. Neurol.* **2020**, *267*, 1291–1299. [\[CrossRef\]](#) [\[PubMed\]](#)
80. Luigetti, M.; Conte, A.; Del Grande, A.; Bisogni, G.; Romano, A.; Sabatelli, M. Sural Nerve Pathology in ALS Patients: A Single-Centre Experience. *Neurol. Sci.* **2012**, *33*, 1095–1099. [\[CrossRef\]](#)

81. Hamada, M.; Hanajima, R.; Terao, Y.; Sato, F.; Okano, T.; Yuasa, K.; Furubayashi, T.; Okabe, S.; Arai, N.; Ugawa, Y. Median Nerve Somatosensory Evoked Potentials and Their High-Frequency Oscillations in Amyotrophic Lateral Sclerosis. *Clin. Neurophysiol.* **2007**, *118*, 877–886. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Theys, P.A.; Peeters, E.; Robberecht, W. Evolution of Motor and Sensory Deficits in Amyotrophic Lateral Sclerosis Estimated by Neurophysiological Techniques. *J. Neurol.* **1999**, *246*, 438–442. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Simone, I.L.; Tortelli, R.; Samarelli, V.; D’Errico, E.; Sardaro, M.; Difruscolo, O.; Calabrese, R.; Francesco, V.D.V.; Livrea, P.; de Tommaso, M. Laser Evoked Potentials in Amyotrophic Lateral Sclerosis. *J. Neurol. Sci.* **2010**, *15*, 106–111. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Vaughan, S.K.; Sutherland, N.M.; Zhang, S.; Hatzipetros, T.; Vieira, F.; Valdez, G. The ALS-inducing Factors, TDP43^{A315T} and SOD1^{G93A}, Directly Affect and Sensitize Sensory Neurons to Stress. *Sci. Rep.* **2018**, *8*, 16582. [\[CrossRef\]](#)
85. Schäfer, M.K.; Bellouze, S.; Jacquier, A.; Schaller, S.; Richard, L.; Mathis, S.; Vallat, J.M.; Haase, G. Sensory Neuropathy in Progressive Motor Neuronopathy (pmn) Mice is Associated with Defects in Microtubule Polymerization and Axonal Transport. *Brain Pathol.* **2017**, *27*, 459–471. [\[CrossRef\]](#)
86. Schoeberl, F.; Abicht, A.; Kuepper, C.; Voelk, S.; Sonnenfeld, S.; Tonon, M.; Schaub, A.; Scholz, V.; Kleinle, S.; Erdmann, H.; et al. Sensory Neuropathy Due to RFC1 in a Patient with ALS: More Than a Coincidence? *J. Neurol.* **2022**, *269*, 2774–2777. [\[CrossRef\]](#)
87. Ringer, C.; Weihe, E.; Schütz, B. SOD1G93A Mutant Mice Develop a Neuroinflammation-Independent Dendropathy in Excitatory Neuronal Subsets of the Olfactory Bulb and Retina. *J. Neuropathol. Exp. Neurol.* **2017**, *76*, 769–778. [\[CrossRef\]](#)
88. Park, J.H.; Chung, C.G.; Park, S.S.; Lee, D.; Kim, K.M.; Jeong, Y.; Kim, E.S.; Cho, J.H.; Jeon, Y.M.; Shen, C.J.; et al. Cytosolic Calcium Regulates Cytoplasmic Accumulation of TDP-43 Through Calpain-A and Importin α 3. *eLife* **2020**, *9*, e60132. [\[CrossRef\]](#)
89. Rumpf, S.; Bagley, J.A.; Thompson-Peer, K.L.; Zhu, S.; Gorczyca, D.; Beckstead, R.B.; Jan, L.Y.; Jan, Y.N. Drosophila Valosin-Containing Protein is Required for Dendrite Pruning Through a Regulatory Role in mRNA Metabolism. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 7331–7336. [\[CrossRef\]](#)
90. Guo, Y.S.; Wu, D.X.; Wu, H.R.; Wu, S.Y.; Yang, C.; Li, B.; Bu, H.; Zhang, Y.S.; Li, C.Y. Sensory Involvement in the SOD1-G93A Mouse Model of Amyotrophic Lateral Sclerosis. *Exp. Mol. Med.* **2009**, *41*, 140–150. [\[CrossRef\]](#)
91. Yan, H.D.; Lim, W.; Lee, K.W.; Kim, J. Sera from Amyotrophic Lateral Sclerosis Patients Reduce High-Voltage Activated Ca²⁺ Currents in Mice Dorsal Root Ganglion Neurons. *Neurosci. Lett.* **1997**, *235*, 69–72. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Rubio, M.A.; Herrando-Grabulosa, M.; Vilches, J.J.; Navarro, X. Involvement of Sensory Innervation in the Skin of SOD1(G93A) ALS Mice. *J. Peripher. Nerv. Syst.* **2016**, *21*, 88–95. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Bernard-Marissal, N.; Chrast, R.; Schneider, B.L. Endoplasmic Reticulum and Mitochondria in Diseases of Motor and Sensory Neurons: A Broken Relationship? *Cell Death Dis.* **2018**, *9*, 333. [\[CrossRef\]](#)
94. Ayers, J.I.; Fromholt, S.E.; O’Neal, V.M.; Diamond, J.H.; Borchelt, D.R. Prion-Like Propagation of Mutant SOD1 Misfolding and Motor Neuron Disease Spread Along Neuroanatomical Pathways. *Acta Neuropathol.* **2016**, *131*, 103–114. [\[CrossRef\]](#)
95. Vaughan, S.K.; Kemp, Z.; Hatzipetros, T.; Vieira, F.; Valdez, G. Degeneration of Proprioceptive Sensory Nerve Endings in Mice Harboring Amyotrophic Lateral Sclerosis-Causing Mutations. *J. Comp. Neurol.* **2015**, *523*, 2477–2494. [\[CrossRef\]](#) [\[PubMed\]](#)
96. Tanaka, S.; Seki, S.; Ono, Y.; Enomoto, A.; Kogo, M. Persistent Sodium Conductance Contributes to Orexin-A-mediated Modulation of Membrane Excitability in Neonatal Rat Mesencephalic V Neurons. *Neurosci. Lett.* **2021**, *753*, 135846. [\[CrossRef\]](#)
97. Chandler, S.H. Evidence for Excitatory Amino Acid Transmission Between Mesencephalic Nucleus of V Afferents and Jaw-Closer Motoneurons in the Guinea Pig. *Brain Res.* **1989**, *477*, 252–264. [\[CrossRef\]](#)
98. Trueblood, P.R.; Levine, M.S.; Chandler, S.H. Dual-Component Excitatory Amino Acid-mediated Responses in Trigeminal Motoneurons and their Modulation by Serotonin In Vitro. *J. Neurophysiol.* **1996**, *76*, 2461–2473. [\[CrossRef\]](#)
99. Venugopal, S.; Hsiao, C.F.; Sonoda, T.; Wiedau-Pazos, M.; Chandler, S.H. Homeostatic Dysregulation in Membrane Properties of Masticatory Motoneurons Compared with Oculomotor Neurons in a Mouse Model for Amyotrophic Lateral Sclerosis. *J. Neurosci.* **2015**, *35*, 707–720. [\[CrossRef\]](#)
100. Venugopal, S.; Ghulam-Jhelani, Z.; Ahn, I.S.; Yang, X.; Wiedau, M.; Simmons, D.; Chandler, S.H. Early Deficits in GABA Inhibition Parallels an Increase in L-type Ca²⁺ Currents in the Jaw Motor Neurons of SOD1^{G93A} Mouse Model for ALS. *Neurobiol. Dis.* **2023**, *177*, 105992. [\[CrossRef\]](#)
101. Nakagawa, Y.; Yamada, S. A Novel Hypothesis on Metal Dyshomeostasis and Mitochondrial Dysfunction in Amyotrophic Lateral Sclerosis: Potential Pathogenetic Mechanism and Therapeutic Implications. *Eur. J. Pharmacol.* **2021**, *892*, 173737. [\[CrossRef\]](#) [\[PubMed\]](#)
102. Mehta, A.R.; Gregory, J.M.; Dando, O.; Carter, R.N.; Burr, K.; Nanda, J.; Story, D.; McDade, K.; Smith, C.; Morton, N.M.; et al. Mitochondrial Bioenergetic Deficits in C9orf72 Amyotrophic Lateral Sclerosis Motor Neurons Cause Dysfunctional Axonal Homeostasis. *Acta Neuropathol.* **2021**, *141*, 257–279. [\[CrossRef\]](#)
103. Inoue, H.; Tsukita, K.; Iwasato, T.; Suzuki, Y.; Tomioka, M.; Tateno, M.; Nagao, M.; Kawata, A.; Saido, T.C.; Miura, M.; et al. The Crucial Role of Caspase-9 in the Disease Progression of a Transgenic ALS Mouse Model. *EMBO J.* **2003**, *15*, 6665–6674. [\[CrossRef\]](#)
104. Nemtsova, Y.; Steinert, B.L.; Wharton, K.A. Compartment Specific Mitochondrial Dysfunction in Drosophila Knock-In Model of ALS Reversed by Altered Gene Expression of OXPHOS Subunits and Pro-Fission Factor Drp1. *Mol. Cell. Neurosci.* **2023**, *125*, 103834. [\[CrossRef\]](#)
105. Pereira, J.D.; DuBreuil, D.M.; Devlin, A.C.; Held, A.; Sapir, Y.; Berezovski, E.; Hawrot, J.; Dorfman, K.; Chander, V.; Wainger, B.J. Human Sensorimotor Organoids Derived from Healthy and Amyotrophic Lateral Sclerosis Stem Cells form Neuromuscular Junctions. *Nat. Commun.* **2021**, *12*, 4744. [\[CrossRef\]](#) [\[PubMed\]](#)

106. Pennetta, G.; Welte, M.A. Emerging Links between Lipid Droplets and Motor Neuron Diseases. *Dev. Cell.* **2018**, *21*, 427–432. [\[CrossRef\]](#)
107. Chaves-Filho, A.B.; Pinto, I.F.D.; Dantas, L.S.; Xavier, A.M.; Inague, A.; Faria, R.L.; Medeiros, M.H.G.; Glezer, I.; Yoshinaga, M.Y.; Miyamoto, S. Alterations in Lipid Metabolism of Spinal Cord Linked to Amyotrophic Lateral Sclerosis. *Sci. Rep.* **2019**, *12*, 11642. [\[CrossRef\]](#) [\[PubMed\]](#)
108. Rudnick, N.D.; Griffey, C.J.; Guarnieri, P.; Gerbino, V.; Wang, X.; Piersaint, J.A.; Tapia, J.C.; Rich, M.M.; Maniatis, T. Distinct Roles for Motor Neuron Autophagy Early and Late in the SOD1G93A Mouse Model of ALS. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E8294–E8303. [\[CrossRef\]](#)
109. Wiksten, M.; Väänänen, A.; Liesi, P. Selective Overexpression of Gamma1 Laminin in Astrocytes in Amyotrophic Lateral Sclerosis Indicates an Involvement in ALS Pathology. *J. Neurosci. Res.* **2007**, *85*, 2045–2058. [\[CrossRef\]](#)
110. Peng, A.Y.T.; Agrawal, I.; Ho, W.Y.; Yen, Y.C.; Pinter, A.J.; Liu, J.; Phua, Q.X.C.; Koh, K.B.; Chang, J.C.; Sanford, E.; et al. Loss of TDP-43 in Astrocytes Leads to Motor Deficits by Triggering A1-like Reactive Phenotype and Trigial Dysfunction. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 29101–29112. [\[CrossRef\]](#)
111. Stracher, A. Calpain Inhibitors as Therapeutic Agents in Nerve and Muscle Degeneration. *Ann. N. Y. Acad. Sci.* **1999**, *884*, 52–59. [\[CrossRef\]](#) [\[PubMed\]](#)
112. Dillio, A.A.; Andary, C.M.; Stoltz, M.; Petropavlovskiy, A.A.; Farhan, S.M.K.; Duennwald, M.L. DnaJC7 in Amyotrophic Lateral Sclerosis. *Int. J. Mol. Sci.* **2022**, *23*, 4076. [\[CrossRef\]](#) [\[PubMed\]](#)
113. Lambert-Smith, I.A.; Saunders, D.N.; Yerbury, J.J. Proteostasis Impairment and ALS. *Prog. Biophys. Mol. Biol.* **2022**, *174*, 3–27. [\[CrossRef\]](#) [\[PubMed\]](#)
114. Krus, K.L.; Strickland, A.; Yamada, Y.; Devault, L.; Schmidt, R.E.; Bloom, A.J.; Milbrandt, J.; DiAntonio, A. Loss of Stathmin-2, a Hallmark of TDP-43-Associated ALS, Causes Motor Neuropathy. *Cell Rep.* **2022**, *39*, 111001. [\[CrossRef\]](#)
115. Fischer, L.R.; Culver, D.G.; Davis, A.A.; Tennant, P.; Wang, M.; Coleman, M.; Asress, S.; Adalbert, R.; Alexander, G.M.; Glass, J.D. The WldS Gene Modestly Prolongs Survival in the SOD1G93A fALS Mouse. *Neurobiol. Dis.* **2005**, *19*, 293–300. [\[CrossRef\]](#)
116. Sábado, J.; Casanovas, A.; Tarabal, O.; Hereu, M.; Piedrafita, L.; Calderó, J.; Esquerda, J.E. Accumulation of Misfolded SOD1 in Dorsal Root Ganglion Degenerating Proprioceptive Sensory Neurons of Transgenic Mice with Amyotrophic Lateral Sclerosis. *Biomed. Res. Int.* **2014**, *2014*, 852163. [\[CrossRef\]](#)
117. Taiana, M.; Sassone, J.; Lauria, G. Mutant SOD1 Accumulation in Sensory Neurons Does Not Associate with Endoplasmic Reticulum Stress Features: Implications for Differential Vulnerability of Sensory and Motor Neurons to SOD1 Toxicity. *Neurosci. Lett.* **2016**, *627*, 107–114. [\[CrossRef\]](#)
118. Rojas, P.; de Hoz, R.; Ramírez, A.I.; Ferreras, A.; Salobrar-Garcia, E.; Muñoz-Blanco, J.L.; Urcelay-Segura, J.L.; Salazar, J.J.; Ramírez, J.M. Changes in Retinal OCT and Their Correlations with Neurological Disability in Early ALS Patients, a Follow-Up Study. *Brain Sci.* **2019**, *9*, 337. [\[CrossRef\]](#)
119. Cho, K.I.; Yoon, D.; Yu, M.; Peachey, N.S.; Ferreira, P.A. Microglial Activation in an Amyotrophic Lateral Sclerosis-Like Model Caused by Ranbp2 Loss and Nucleocytoplasmic Transport Impairment in Retinal Ganglion Neurons. *Cell. Mol. Life. Sci.* **2019**, *76*, 3407–3432. [\[CrossRef\]](#)
120. Ferreira, P.A. The Coming-of-Age of Nucleocytoplasmic Transport in Motor Neuron Disease and Neurodegeneration. *Cell. Mol. Life. Sci.* **2019**, *76*, 2247–2273. [\[CrossRef\]](#)
121. Nagano, S.; Jinno, J.; Abdelhamid, R.F.; Jin, Y.; Shibata, M.; Watanabe, S.; Hirokawa, S.; Nishizawa, M.; Sakimura, K.; Onodera, O.; et al. TDP-43 Transports Ribosomal Protein mRNA to Regulate Axonal Local Translation in Neuronal Axons. *Acta Neuropathol.* **2020**, *140*, 695–713. [\[CrossRef\]](#) [\[PubMed\]](#)
122. Camdessanché, J.P.; Belzil, V.V.; Jousserand, G.; Rouleau, G.A.; Créac'h, C.; Convers, P.; Antoine, J.C. Sensory and Motor Neuronopathy in a Patient with the A382P TDP-43 Mutation. *Orphanet. J. Rare Dis.* **2011**, *6*, 4. [\[CrossRef\]](#) [\[PubMed\]](#)
123. Liao, P.; Yuan, Y.; Liu, Z.; Hou, X.; Li, W.; Wen, J.; Zhang, K.; Jiao, B.; Shen, L.; Jiang, H.; et al. Association of Variants in the KIF1A Gene with Amyotrophic Lateral Sclerosis. *Transl. Neurodegener.* **2022**, *11*, 46. [\[CrossRef\]](#)
124. Hensel, N.; Claus, P. The Actin Cytoskeleton in SMA and ALS: How Does It Contribute to Motoneuron Degeneration? *Neuroscientist* **2018**, *24*, 54–72. [\[CrossRef\]](#)
125. Suzuki, N.; Nishiyama, A.; Warita, H.; Aoki, M. Genetics of Amyotrophic Lateral Sclerosis: Seeking Therapeutic Targets in the Era of Gene Therapy. *J. Hum. Genet.* **2023**, *68*, 131–152. [\[CrossRef\]](#)
126. Farah, C.A.; Nguyen, M.D.; Julien, J.P.; Leclerc, N. Altered Levels and Distribution of Microtubule-Associated Proteins Before Disease Onset in a Mouse Model of Amyotrophic Lateral Sclerosis. *J. Neurochem.* **2003**, *84*, 77–86. [\[CrossRef\]](#) [\[PubMed\]](#)
127. Bensimon, G.; Lacomblez, L.; Meininger, V. A Controlled Trial of Riluzole in Amyotrophic Lateral Sclerosis. ALS/Riluzole Study Group. *N. Engl. J. Med.* **1994**, *330*, 585–591. [\[CrossRef\]](#)
128. Miller, R.G.; Mitchell, J.D.; Moore, D.H. Riluzole for Amyotrophic Lateral Sclerosis (ALS)/Motor Neuron Disease (MND). *Cochrane Database Syst. Rev.* **2012**, *2012*, CD001447. [\[CrossRef\]](#)
129. Rothstein, J.D. Edaravone: A New Drug Approved for ALS. *Cell* **2017**, *171*, 725. [\[CrossRef\]](#)
130. Yoshino, H.; Kimura, A. Investigation of the Therapeutic Effects of Edaravone, a Free Radical Scavenger, on Amyotrophic Lateral Sclerosis (Phase II Study). *Amyotroph. Lateral. Scler.* **2006**, *7*, 241–245. [\[CrossRef\]](#)

131. Sever, B.; Ciftci, H.; DeMirci, H.; Sever, H.; Ocak, F.; Yulug, B.; Tateishi, H.; Tateishi, T.; Otsuka, M.; Fujita, M.; et al. Comprehensive Research on Past and Future Therapeutic Strategies Devoted to Treatment of Amyotrophic Lateral Sclerosis. *Int. J. Mol. Sci.* **2022**, *23*, 2400. [[CrossRef](#)] [[PubMed](#)]
132. Fels, J.A.; Dash, J.; Leslie, K.; Manfredi, G.; Kawamata, H. Effects of PB-TURSO on the Transcriptional and Metabolic Landscape of Sporadic ALS Fibroblasts. *Ann. Clin. Transl. Neurol.* **2022**, *9*, 1551–1564. [[CrossRef](#)]
133. Oki, R.; Izumi, Y.; Fujita, K.; Miyamoto, R.; Nodera, H.; Sato, Y.; Sakaguchi, S.; Nokihara, H.; Kanai, K.; Tsunemi, T.; et al. Japan Early-Stage Trial of Ultrahigh-Dose Methylcobalamin for ALS (JETALS) Collaborators. Efficacy and Safety of Ultrahigh-Dose Methylcobalamin in Early-Stage Amyotrophic Lateral Sclerosis: A Randomized Clinical Trial. *JAMA Neurol.* **2022**, *79*, 575–583. [[CrossRef](#)] [[PubMed](#)]
134. Schneider, C.A.; Rasband, W.S.; Eliceiri, K.W. NIH Image to ImageJ: 25 Years of Image Analysis. *Nat. Methods.* **2012**, *9*, 671–675. [[CrossRef](#)]
135. Brownstone, R.M.; Lancelin, C. Escape from Homeostasis: Spinal Microcircuits and Progression of Amyotrophic Lateral Sclerosis. *J. Neurophysiol.* **2018**, *119*, 1782–1794. [[CrossRef](#)] [[PubMed](#)]
136. Prasad, A.; Bharathi, V.; Sivalingam, V.; Girdhar, A.; Patel, B.K. Molecular Mechanisms of TDP-43 Misfolding and Pathology in Amyotrophic Lateral Sclerosis. *Front. Mol. Neurosci.* **2019**, *12*, 25. [[CrossRef](#)]
137. Ayala, Y.M.; De Conti, L.; Avendaño-Vázquez, S.E.; Dhir, A.; Romano, M.; D'Ambrogio, A.; Tollervey, J.; Ule, J.; Baralle, M.; Buratti, E.; et al. TDP-43 Regulates its mRNA Levels Through a Negative Feedback Loop. *EMBO J.* **2011**, *30*, 277–288. [[CrossRef](#)]
138. Neumann, M.; Mackenzie, I.R.; Cairns, N.J.; Boyer, P.J.; Markesbery, W.R.; Smith, C.D.; Taylor, J.P.; Kretzshmar, H.A.; Kimonis, V.E.; Forman, M.S. TDP-43 in the Ubiquitin Pathology of Frontotemporal Dementia with VCP Gene Mutations. *J. Neuropathol. Exp. Neurol.* **2007**, *66*, 152–157. [[CrossRef](#)]
139. Hasegawa, K.; Yasuda, T.; Shiraishi, C.; Fujiwara, K.; Przedborski, S.; Mochizuki, H.; Yoshikawa, K. Promotion of Mitochondrial Biogenesis by Necdin Protects Neurons Against Mitochondrial Insults. *Nat. Commun.* **2016**, *7*, 10943. [[CrossRef](#)]
140. Seki, S.; Tanaka, S.; Yamada, S.; Tsuji, T.; Enomoto, A.; Ono, Y.; Chandler, S.H.; Kogo, M. Neuropeptide Y Modulates Membrane Excitability in Neonatal Rat Mesencephalic V Neurons. *J. Neurosci. Res.* **2020**, *98*, 921–935. [[CrossRef](#)] [[PubMed](#)]
141. Komuro, A.; Morimoto, T.; Iwata, K.; Inoue, T.; Masuda, Y.; Kato, T.; Hidaka, O. Putative Feed-Forward Control of Jaw-Closing Muscle Activity During Rhythmic Jaw Movements in the Anesthetized Rabbit. *J. Neurophysiol.* **2001**, *86*, 2834–2844. [[CrossRef](#)] [[PubMed](#)]
142. Venugopal, S.; Seki, S.; Terman, D.H.; Pantazis, A.; Olcese, R.; Wiedau-Pazos, M.; Chandler, S.H. Resurgent Na⁺ Current Offers Noise Modulation in Bursting Neurons. *PLoS Comput. Biol.* **2019**, *15*, e1007154. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.