Sporadic amyotrophic lateral sclerosis: integral model of pathogenesis and therapy options

Oleksii Doroshenko (neurobiologist.alex@gmail.com)
Bogomolets National Medical University: Nacional'nij medicnij universitet imeni O O Bohomol'ca
https://orcid.org/0000-0002-8261-9610

Research Article

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Abstract

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive central nervous system degenerative disease, in most cases within 2–3 years inevitably leading to mixed tetraplegia and subsequent death from diaphragmatic paralysis. While for almost half of hereditary cases, mutations are identified as the cause of the disease, the sporadic form of ALS (sALS), due to the polymorphism and complexity of the putative developmental mechanisms raises a lot of questions. To date, there are no sufficiently effective pathogenetic methods for the disease treatment. All the above mentioned makes ALS one of the most relevant and, at the same time, unexplored topics in neurology. In this review, the author combines the most important, in our opinion, currently known factors of sALS pathogenesis, including Coxsackievirus B3 (CVB3) – the infection, TAR DNA binding protein 43 (TDP-43) pathology, human endogenous retrovirus-K (HERV-K) reactivation, RNA-specific editase 1 (ADAR2) dysfunction and oxidative stress (OS) into a unified illustrative model. The author is suggesting a probable sequence of pathogenetic links, based on data regarding the presence of pathophysiological links between them and their ability to cause the typical for sALS histochemical pattern. Simultaneously, the author makes assumptions about the developmental mechanisms for some secondary disorders typical for sALS. In conclusion, in accordance with the derived model, the author conducts a review of possible pharmacological interventions of pathogenetic and etiotropic therapy. The author describes both clinically proven effective drugs, and previously unstudied, but extremely promising compounds that require further testing.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal central nervous system neurodegenerative disease, which is based on a combined lesion of the peripheral motor neurons of the anterior horns of the spinal cord and the upper motor neurons of the precentral gyrus. The incidence of ALS is 2–3 persons per 100,000 per year, with an average life expectancy after diagnosis of about 3 years and death due to diaphragm paralysis [1]. The average age of the disease onset is 65 years [2].

More than 90% of cases are sporadic (sALS), while the rest are known as familial (fALS). To date, about 30 genes are known, mutations in which are associated with ALS [3]. The most significant are mutations in the SOD1, TARDBP, C9orf72, and FUS genes, which in total are responsible for 47.7% of fALS cases and 5.2% of sALS cases [4].

The pathogenesis of ALS, especially sALS, is one of the most difficult issues in neurology. However, while for fALS, in at least half of the cases, the actual cause is known in the form of a specific mutation, for sALS, neither certain causes, nor development mechanisms, nor effective treatments are known, which makes sALS not only one of the most difficult issues in neurology [5], but also, in principle, medicine. Although sALS pathogenesis is considered to be multicomponent [6], various authors regularly propose certain single processes [7, 8] as a self-sufficient cause of the disease. However, separately, none of the processes can fully explain all the signs and disorders typical for sALS, and successful attempts to combine all key processes are absent. Given the insignificant differences between the pathology of sALS

and fALS [9], everything is further complicated by the wide range of mutations in fALS and the lack of data on the mechanisms of their pathological influence. That is, it remains unclear how can the consequence of a wide variety of mutations in fALS result in practically the same clinical and pathogenetic picture, which, in turn, barely differs from the clinical and pathogenetic picture of sALS. Effective pathogenetic treatment regimens for sALS are also lacking, as are etiotropic therapy options.

That is, to date there is no comprehensive model of the sALS pathogenesis, which could combine and tie together all the key factors and mechanisms of the disease development. However, the presence of such a model seems to be an indispensable for a full understanding of this disease, as well as for its effective treatment.

In this article, the author proposes a model for the sALS pathogenesis, which includes all the significant, in the author's opinion, literature data available to date, and an expanded analysis of all mentioned mechanisms of the process. Additionally, the options for pathogenetic therapy in accordance with the key mechanisms of pathogenesis are presented.

2. Als Staging

It is commonly known that ALS is characterized by the fact that clinical manifestation is preceded by a long preclinical phase of the disease, which probably begins from the moment of successful effect of the etiological factor in sALS, or the appearance of phenotypical manifestations of a certain mutation in fALS [10].

It has also been proposed to distinguish three periods in the course of the disease, based on the fundamental characteristics of pathological processes in each of the periods [11]. Period A (pre-manifest stage) can be defined as preclinical chronic persistent compensated period, period B (prodromal stage) can be defined as preclinical active decompensating, and period C (clinical stages) as clinically active decompensated [12]

3. Primary Links In Sals Pathogenesis

In the late 1990s, a set of papers started to appear, reporting the isolation of enteroviral RNA closely related to echovirus 7 from the anterior horns of the spinal cord in 88% of patients with confirmed sALS [13], enteroviral RNA closely related to coxsackievirus B3 (CVB3) from the spinal cord in 73% of patients with confirmed sALS [14], enteroviral RNA, closely related to echoviruses, from the anterior horns of the spinal cord in 60% of patients with confirmed sALS [15].

Simultaneously, there were emerging papers in which the fact of RNA detection was questioned, and which reported that enteroviral RNA could not be detected in the spinal motor neurons of patients with confirmed sALS [16, 17].

However, a published protocol for the detection of enteroviral RNA in the spinal cord of patients with ALS [18] suggested possible reasons for the false-negative results in some studies.

In subsequent years, several more papers confirming the enterovirus etiology of sALS were also published [19, 20, 21], including a very recent paper published in 2022 [22].

Naturally, an additional, more thorough study of this issue is needed, however, the data supporting the presence of enteroviral RNA in the spinal cord and spinal motor neurons, particularly, in patients with ALS are too convincing. Thus, it would be a mistake not to consider enteroviruses as a probable link of pathogenesis. In addition, there is a significant theoretical substantiation in favor of this [23, 24]. Even more so, taking into account the well-known ability of another enterovirus, the poliovirus, to cause chronic progredient disorders in spinal motor neurons, resulting in a post-polio syndrome that clinically resembles ALS [25].

In case of sALS, according to the author's view, the most likely enteroviral agents are coxsackie virus B3 (CVB3), enterovirus-71 (EV-71) and echovirus-7 (Echo-7) for the following reasons. CVB-3 has been identified in ALS patients [14] and can initiate a cascade of pathological processes characteristic of sALS [26]. EV-71 is also capable of initiating a cascade of pathological processes characteristic of sALS [27] and has a tropism for motor neurons [28]. Echo-7 was also detected in ALS patients [13, 15]; Regarding the ability of Echo-7 to initiate a cascade of characteristic for sALS processes and tropism for motor neurons there are currently no specific data.

In this regard and given the absence of fundamental differences between these viruses, it seems appropriate to further consider them as a single factor: possible sALS-associated non-polio enteroviruses (PAANPEVs), leaving each of the named representatives with an equal probability of being responsible for the described changes.

A sign that could indirectly confirm the etiological role of PAANPEVs in the development of sALS is, perhaps, the fact that women, on average, are 1.5 times less likely to suffer from certain PAANPEVs-related diseases, such as, for example, CVB3-induced myocarditis [29]. As is known, sALS is also found in women 1.5 times less frequently [30]. A common reason for these two features may be that intestinal replication of many enteroviruses, such as CVB-3, is significantly reduced in women, probably due to the protective effect of estrogens [31].

So far, it remains unclear exactly when and how motor neurons are infected with PAANPEVs. It is possible that infection of the nervous system develops as a consequence of a PAANPEVs-related acute illness suffered in childhood. In particular, structural aberrations of the myocardium found in ALS patients [32] could be the consequence of CVB3-induced myocarditis. However, it is still difficult to draw definite conclusions on this matter.

What are the possible ways in which PAANPEVs could contribute to the progression/initiate ALS? During infection of the nervous system, PAANPEVs, possibly, display tropism for motor neurons, and,

presumably, persist asymptomatically for some time [33]. Subsequently, the expression of PAANPEVs-encoded cysteine proteases A2 and 3C takes place in infected cells, which directly triggers several cascades that are fundamental in the pathological processes of sALS, which take a chronic course as a slow persistent infection [34].

3.1 Agents of slow motor neuron infection

TAR DNA binding protein 43 (TDP-43) is a DNA/RNA-binding protein involved in transcription, splicing, and maintenance of RNA stability, as well as microRNA biogenesis and nuclear-cytoplasmic transport. In ALS, the TDP-43 structural and functional pathology is the very commonly and regularly identified in motor neurons and glia, occurring in almost 97% of patients. The previously mentioned PAANPEVs proteases interact with TDP-43, leading to disruption of its structure and function [35]. Protease A2 is responsible for the nucleocytoplasmic translocation of TDP-43, as well as for the disruption of nuclear import through the degradation of nucleoporins. Protease 3C cleaves cytoplasmic TDP-43 with the formation of TDP-43-C, which is destroyed in proteasomes, and TDP-43-N, which forms aggregates in stress granules and is also capable of disrupting the function of native TDP-43 when translocating to nucleus [36]. Thus, the nuclear transport dysfunction, the formation of prion-like aggregates in the cytoplasm, as well as the TDP-43 native function disruption itself take place, leading to RNA splicing and transcription pathology, as well as to disruption of miRNA synthesis [37].

At the same time, it has been shown that pathological TDP-43 in ALS is able to reactivate human endogenous retrovirus-K (HERV-K), due to the binding of HERV-K long terminal repeats (LTR) DNA regions [7, 38]. Moreover, it is known that during sALS there is a significant positive correlation between the expression of TDP-43 and HERV-K in motor neurons [39]. Although it is not known for certain how exactly reactivated HERV-K promotes the pathological process development, the selective damage of the upper and lower motor neurons, similar to the damage in ALS has been observed in transgenic mice overexpressing HERV-K [40]. At the same time, treatment of sALS patients with antiretroviral drugs demonstrated a two-fold reduction in the rate of decline in functional parameters within 24 weeks of treatment [41]. The possible mechanism of HERV-K influence could be its ability to cause abnormalities of the nucleolar protein nucleophosmin, also known as NPM1, and, possibly, nucleolin (NCL), and thus lead to nucleolar dysfunction [40, 42]. As it is known, nucleolar dysfunction is one of the most important mechanisms of fALS pathogenesis associated with C9orf72 pathology [43, 44]. The latter further confirms the probable importance of the earlier proposed HERV-K effect in sALS pathogenesis.

It can also be assumed that there is a tight connection between PAANPEVs cysteine proteases and the formation of Bunina bodies in sALS, based on the fact that the main component of Bunina bodies is the cysteine protease inhibitor cystatin C [45]. Another supporting fact is that the concentration of cystatin C in the cerebrospinal fluid in sALS is decreased, and the degree of this decrease directly correlates with the severity of the disease course [46]. Consequently, it is most likely that cystatin C has a protective function in sALS specifically due to its interaction with PAANPEVs proteases. However, for the unknown reason, cystatin C does not fulfill its function and forms aggregates. Cystatin C has also been detected in

inclusion bodies with pathological TDP-43 [47], which possibly occurs due to the interaction of Cyctatin C with PAANPEVs cysteine proteases in the attempt to deactivate them, followed by its aggregation along with TDP-43.

3.2 ADAR2 pathology and excitotoxicity

Excitotoxicity is one of the fundamental mechanisms in the ALS pathogenesis, which has been known for a long time. Structural aberrations and, as a result, excessive permeability to Ca^{2+} of AMPA receptors are of major importance in its development [48]. Such disorders arise due to the RNA-specific editase 1 (ADAR2) dysfunction found in ALS, the main function of which is to edit the GluA2 mRNA. GluA2 is the AMPA receptor subunit that regulates its permeability to Ca^{2+}. In case of ADAR2 pathology, the GluA2 mRNA editing does not occur. As a result, the GluA2 subunit becomes structurally abnormal, and, thus, unable to perform its main function as part of the AMPA receptor – constrain the permeability of this receptor to Ca^{2+} ions. Thus, the AMPA receptor acquires the ability to allow Ca^{2+} freely flow into the neuron's cytoplasm. Consequently, considering that motor neurons in particular show the lowest levels of GluA2 expression, this process underlies their selective damage in sALS [49].

The cause of ADAR2 dysfunction in ALS is one of the least understood aspects of the disease pathogenesis. Not so long ago, it has been shown that in fALS, mediated by the pathology of C9orf72, among other processes, the ADAR2 synthesis and structural pathology takes place [50], which leads to consequent disorders. The mechanism for the development of ADAR2 dysfunction in sALS, however, remains unknown. Nevertheless, as already mentioned, in fALS mediated by C9orf72 pathology, it is the nucleolar function that is initially impaired, and if ADAR2 pathology subsequently occurs, then it can be assumed that ADAR2 pathology also arises in sALS due to nucleolar dysfunction [51, 52] in this case, caused by the influence of HERV-K. In addition, one of the nucleolar proteins that can be affected by HERV-K is NCL, which is an ADAR-2 associated factor [53], and if its function is impaired, the function of ADAR2 can also be impaired.

The massive influx of Ca^{2+} into motor neurons and a critical increase in its concentration consequently leads to oxidative stress, primarily mediated by mitochondrial dysfunction [54], xanthine oxidase (XO) activation [55], as well as NO synthase activation [56]. An indirect consequence of XO activation is probably an increase in the concentration of purines in the cerebrospinal fluid in sALS [57]. In addition, an increase in Ca^{2+} concentration leads to the activation of calpains, which plays a special role, since calpains themselves can cause TDP-43 pathology [58], and under the existing circumstances, the TDP-43 pathology becomes even more aggravated. Additionally, the massive influx of Ca^{2+} into the cytoplasm causes neuron membrane depolarization, and, as a result, the activation of NMDA, followed by additional influx of Na^{+} and Ca^{2+}, which even further aggravates the state of the cell [59]. The interlink between the mechanisms of pathological process progression in sALS is schematically depicted in Fig. 1.

4. Oxidative Stress – The Culmination Of The Pathological Process In Als

Oxidative stress (OS) is one of the most important and indisputable components of ALS pathogenesis [60]. The underlying mechanism of OS is the cytotoxic effect of a group of mutually potentiated chemical compounds – a variety of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [61].

Mitochondrial dysfunction and respiratory chain disruption arising from exposure to toxic Ca^{2+} concentrations are the key reason for the emergence of the first ROS – the superoxide radical (O_2^-) [62], which, although not highly active, is, however, capable of inducing the subsequent formation of much more cytotoxic ROS under specific conditions, such as inability of antioxidant system to fully neutralize O_2^- due to Ca^{2+} influx [63].

One of the most dangerous ROS is hydrogen peroxide (H_2O_2). The harmfulness of the latter is associated not only with its ability to increase Ca^{2+} influx and inactivate superoxide dismutase (SOD) but also with its ability to easily diffuse through the membrane [64], which is why it is, apparently, the main factor of the rapid ROS and oxidative stress spreading throughout the nervous tissue. The formation of H_2O_2 can occur both due to the increased activity of XO, and because of the direct influence of O_2^-.

Among ROS, the hydroxyl radical (OH.) exhibits the highest activity. The latter can oxidize the SH-groups of enzymes and glutathione [65], thereby reducing the antioxidant potential of the cell; as well as to cause lipid peroxidation (LPO), disrupting the structure of membranes and leading to the formation of aldehydes [66]. In addition, the hydroxyl radical can react with the nuclear DNA bases, causing various mutations and conformational changes. Finally, it can react with mitochondrial DNA bases, enhancing mitochondrial dysfunction. The aldehydes, formed during LPO, can react with proteins amine groups, reducing the cationic charge of protein molecules and causing both an increase in the ability of various proteins to aggregate and the formation of conjugates with glutamate transporters, in particular, EAAT1 and EAAT2. It is also known that a certain RNS, peroxynitrite ($ONOO^-$) can interact with glutamate carrier proteins as well [67], and, apart from that, it can also easily diffuse through the membrane. The modification of glutamate transporter proteins causes the accumulation of the latter in the extracellular space, increasing excitotoxicity.

Thus, oxidative stress in ALS is an intense, nonspecific, and practically uncontrolled heterogeneous process, with a tendency towards rapid paracrine spreading and the development of “vicious cycles” [68]. Given its rather aggressive rate of development, it can be concluded that the onset of oxidative stress is, apparently, some sort of border between the long-term subclinical inactive course of ALS (period A), and the onset, due to some crucial activating processes, of the active subclinical course (period B), the basis for which is oxidative stress and its consequences. Period C is, consequently, the period, which takes place from the moment the clinical manifestations of ALS emerge. The major ROS and the mechanisms of their formation are shown in Fig. 2.

5. The Unanswered Questions Of Sals Pathogenesis

Despite the completeness and logical consistency of the proposed model, as of date, however, there are still a considerable number of questions regarding the specificities of the aALS pathogenesis, as well as uncertainty regarding the validity of present data on sALS pathogenesis.

If the proposed model is correct, then which representative of the hypothetical PAANPEVs group is the main cause of the development of the disease? Or are all three viruses within the group capable of this? How long can PAANPEVs persist asymptomatically in motor neurons, and under which conditions does putative persistence begin? Is the predominant development of sALS in the elderly associated only with the weakening of antioxidant mechanisms, and what is the reason for the development of casuistic cases of juvenile sALS that is not caused by mutations?

What exactly is the mechanism of interaction between cystatin C and PAANPEVs proteases, and why does cystatin C precipitate into aggregates? Is the effect of HERV-K on the nucleolus function in sALS critical enough and sufficient to cause pathology of ADAR2 synthesis, and, accordingly, to be the cause of the critical influx of Ca^{2+} into motor neurons, which is essential in ALS pathogenesis? Why and how does TDP-43-N ubiquitination proves to be ineffective in sALS, and becomes a part of the pathogenesis of the disease due to resulting depletion of the cellular pool of ubiquitin [69]?

Unfortunately, as of date all these questions remain without unambiguous answers, which hinders a full understanding and effective treatment of the disease.

6. Therapeutic Measures Depending On Links In Als Pathogenesis

6.1. The reduction of oxidative stress

The ALS treatment at the stage of clinical manifestations, due to the insignificant influence of the initiating factors of the disease in this period, as compared to the prevailing significance of oxidative stress, should probably include the use of antioxidants with a wide range of mechanisms of action, affecting as many pathogenetic pathways as possible.

As of today, the main antioxidant, that is FDA approved and used in clinical practice for ALS patients is edaravone, which is a free radical acceptor and has shown significant effectiveness during clinical trials, has demonstrated the ability to slow down the progression of the disease by an average of 35% [70].

Another drug – masitinib is currently in the third phase of clinical trials, has shown the efficacy several years ago. By the means of inhibiting the class III receptor tyrosine kinase (TRK III), it can increase the life expectancy of sALS patients by, on average, 25% [71].

Melatonin exhibits antioxidant properties by activating glutathione peroxidase, inhibiting NO synthase, and reducing mitochondrial dysfunction [72, 73]. In a study involving ALS patients, melatonin was able to improve laboratory parameters, however it didn’t affect the clinical parameters [74].

Alpha-lipoic acid is a cofactor of mitochondrial enzymes and promotes mitochondrial function restoration. During the study with transgenic mice, it has shown a significant effect in the form of improved motor function and increased survival rate [75].

It has also been shown that ginseng extracts facilitate the reduction of Ca^{2+} influx into neurons. In transgenic mice models ginseng effectively reduced the severity of symptoms and increased survival rate as well [76].

Ginkgo biloba extract EGb761 both counteracts the formation of ROS and aldehydes and increases the activity of glutathione peroxidase and catalase. In addition, it activates the antiapoptotic factor Bcl-2 [77]. When tested in transgenic mice models, Ginkgo biloba extract increased survival rate and decreased the loss of motor neurons. However, the effect was present only in males [78].

L-carnitine normalizes mitochondrial function. It has demonstrated the ability to increase survival rate, as well as motor function and to decrease clinical manifestations of ALS in transgenic mice models [79].

Resveratrol, a natural polyphenol capable of exerting a protective effect both through a direct antioxidant effect on reactive oxygen species and through the activation of Sirtuin 1, had a positive effect on the course of ALS in the SOD1 mouse model of ALS, delaying the onset of the disease and slowing down its course [80].

Quercetin, another polyphenol that displays neuroprotective effect through several pathways [81], has also been shown to be effective in mouse models [82, 83].

Curcumin, a polyphenol that can both suppress neuroinflammatory processes and improve mitochondrial function under conditions of oxidative stress [84, 85], in particular, caused by TDP-43 pathology [86, 87], has shown significant efficacy in patients with sALS [88, 89].

Co-enzyme Q10, as a cofactor in ETC and a free radical scavenger [90], led to an increase in lifespan in the SOD1 mouse model of ALS [91] and a decrease in mitochondrial dysfunction in patients with sALS [92].

Epigallocatechin-3-gallate (EGCG), in turn, being able to activate excitatory amino acid transporter 2 (EAAT2) on astrocytes surface, promotes the elimination of glutamate from the synaptic cleft [93]. EGCG has also been shown to improve mitochondrial function under conditions of oxidative stress [94]. When studied in transgenic mice, the EGCG prolonged survival, reduced clinical manifestations of the disease, and also significantly reduced the level of oxidative stress markers [95, 96].

Astaxanthin and lycopene are carotenoids capable of neutralizing reactive oxygen species to a significant extent, providing a pronounced antioxidant effect [97]. A study showed their ability to successfully counteract oxidative stress in a culture of motor neurons [98], while another study suggests that their use can reduce the risk of developing ALS [99, 100].

Bacopa monnieri extract may also be effective in overcoming excitotoxicity and oxidative stress in ALS due to its ability to increase the expression of the GluA2 subunit of the AMPA receptor [101].

Cannabinoids such as tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) have been proven to exhibit a pronounced antioxidant effect by reducing Ca^{2+} levels in neurons [102]. These compounds have shown efficiency in transgenic mouse models, increasing survival rate, reducing weight loss, and slowing down the loss of motor function [103].

Vitamin E affects primarily H_2O_2, O_2- and OH. [104]. Even though vitamin E did not have a noticeable effect on clinical manifestations in ALS [105], many studies have shown that its intake significantly reduced the risk of death from sALS [106, 107, 108].

Creatinine regulates the uptake of glutamate by cells as well as stabilizes mitochondrial membranes. During research, although it showed promising effects in transgenic mice models, it did not appear to be effective during clinical trials [109].

Ceftriaxone acts as an antioxidant by activating EAAT2 on astrocytes. During both the first and second phases of clinical trials ceftriaxone showed extremely promising results, however during the third phase no pronounced effect has been detected [110].

EH301 is a combination of pterostilbene and nicotinamide riboside. Pterostilbene is a polyphenol that has a higher bioavailability than resveratrol, which belongs to the same class (stilbenes) [111] and is capable of both direct antioxidant effect and indirect anti-inflammatory and antioxidant effects [112, 113], primarily due to the activation of SIRT1 [114].

Pterostilbene is also capable of exerting an antiviral effect, including effects against entero- and retroviruses [115]. Nicotinamide riboside is an NAD + precursor that, similar to pterostilbene, can activate sirtuins [116] and, in addition, poly(ADP-ribose) polymerases (PARPs) [117], thus exerting a powerful restorative effect on cellular metabolism [118]. The combination of pterostilbene and nicotinamide riboside in the form of EH301 has been shown to have a significant therapeutic effect, slowing down the progression of the disease and improving clinical parameters [119], while being safe [120].

AMX0035, a combination of sodium phenylbutyrate and tauroursodeoxycholic acid, showed extremely positive results in a double placebo-controlled study, significantly slowing down the progression of the disease [121].

Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, significantly slowed disease progression and increased lifespan in mouse models [122].

In addition, preliminary, clinical efficacy in ALS patients was demonstrated for an anti-inflammatory drug, the phosphodiesterase inhibitor ibudilast, clinical trials for which are currently ongoing [123].

At the same time, a phytoestrogen genistein is not only an antioxidant, but also capable of displaying both antiretroviral and anti-enteroviral activity [124, 125]. When tested in transgenic mouse models of ALS, its administration led to a reduction in symptoms and prolongation of survival, however, only in males [126].

To summarize, although some of the listed substances and drugs, which showed a positive effect in animal models and in case of prophylactic use subsequently did not have the same effect on ALS patients, the author is inclined to believe that in ALS only complex measures against oxidative stress is reasonable, with the simultaneous administration of various antioxidants (so-called “mitochondrial cocktail” [127]), which as a group can have a potentiating effect, altogether exhibiting a more pronounced effect than each one of them individually.

6.2. Therapeutic measures against protein aggregation

Arimoclomol is currently the only known drug that can reduce the number of aggregates in ALS, including the ones containing TDP-43. Clinical trials have shown a noticeable efficacy of arimoclomol in patients with ALS [128]. This effect occurs due to an increase in the Hsp70 and Hsp90 proteins expression [129].

6.3. Antiretroviral drugs

Given the fact that HERV-K play one of the crucial roles of in the progression of ALS, effective antiretroviral therapy is an integral part of this disease therapy. Currently, there are data on two clinical trials of antiretroviral drugs for ALS [130], however one of the trials was not performed correctly enough, and the in the second one the drug indinavir was used, which belongs to the class of protease inhibitors that were shown to be ineffective against HERV-K.

The most effective against HERV-K agents are drugs from the nucleoside reverse transcriptase inhibitor (NRTIs) group, such as abacavir, zidovudine, and nevirapine, as well as some of the integrase inhibitors (INSTIs), such as raltegravir and dolutegravir [131]. That is, in a recent clinical study that demonstrated abacavir, lamivudine and dolutegravir use, a significant reduction in disease progression was achieved, as well as a decrease in the level of HERV-K [41].

6.4. Anti-enteroviral therapy

Since PAANPEVs is currently the only factor that could be determined as the initiating factor in the sALS pathogenesis, the therapeutic measures aimed against it should be the basis for the treatment of this disease, especially at the preclinical stage.

Ribavirin is a well-known drug with proven activity in NPEVs-induced (including PAANPEVs) lesions of the CNS [132]. More recently, a paper has been published demonstrating the impressive efficacy of ribavirin in CVB3-induced ALS-like disease in mice, and specifically in case of early administration [22]. These results, as well as the theoretical rationale for the use of ribavirin in sALS, are promising.

In addition, certain lactic acid bacteria, such as *Lactobacillus plantarum* and *Lactobacillus amylovorus*, are also likely to have anti-enteroviral activity [133, 134]. Moreover, it has been shown that in ALS the disturbances in the balance of the intestinal microbiota are present [135].

Conclusions

As it has been shown, to date, there is no direct-acting treatment for sALS, as well as there are no theoretical candidates for this role. Nevertheless, the prospect of sALS treatment, or at least significant slowing down of its progression, still seems possible. Many of the drugs and substances described in this paper are likely to influence the course of sALS. Among such drugs are those that have already shown their effectiveness in clinical trials, for example, AEOL-10150, arimoclomol, and ceftriaxone, as well as the ones that have a convincing theoretical basis and have shown promising results when tested in transgenic mice models or cell culture, but for some reason were not subject to further investigation and clinical trials, such as EGCG, Δ9-THC, L-carnitine, genistein and alpha-lipoic acid. Both antiretroviral and anti-enteroviral drugs deserve special attention, in particular – ribavirin, which, if the proposed model of sALS pathogenesis is correct, can be defined as the first theoretical drug for the etiotropic treatment of sALS. Thus, there is a vital need for its detailed research and clinical trials.

It should also be taken into consideration, that ALS is a disease, the pathogenetic structure of which at the time of the onset of symptoms seems to be extremely heterogeneous and includes the continuing influence of initiating factors such as PAANPEVs infection, TDP-43 pathology, and HERV-K reactivation as well as the numerous consequences of these factors: from oxidative stress to massive cytoplasmic proteins aggregation. All the mentioned leads to conclusion that at the clinical stage of ALS there simply cannot be one drug, on the contrary, the treatment must be complex. That is, the treatment must consist of a group of drugs and substances that altogether could affect the maximum number of mechanisms and pathways involved in the ALS pathological process.

Of all the above-mentioned compounds, the author singles out ribavirin as a particularly interesting and potentially effective drug worthy of conducting clinical trials in sALS, due to its potential effect on one of the key and early elements in pathogenesis - enteroviruses. In case of its effectiveness, in particular, at the preclinical stages of sALS, probably, given the specificity of the disease, the conduction of clinical trials of complex sALS therapy, consisting of theoretically and practically founded combination of antioxidants, antiretroviral and anti-enteroviral therapy based on ribavirin should be considered.

In addition, once again, given the specificity of the disease, as well as the known relative safety of antioxidant drugs, there possibly is a basis for the experimental prescription in clinical practice, especially in patients with a rapid rate of sALS progression, of a combination of antioxidant drugs, selected in such a way that impact on as many OS processes as possible.

Declarations

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Authors' contributions

Doroshenko O.A. conducted all of the studies, prepared figures, drafted and revised the manuscript.

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Figures

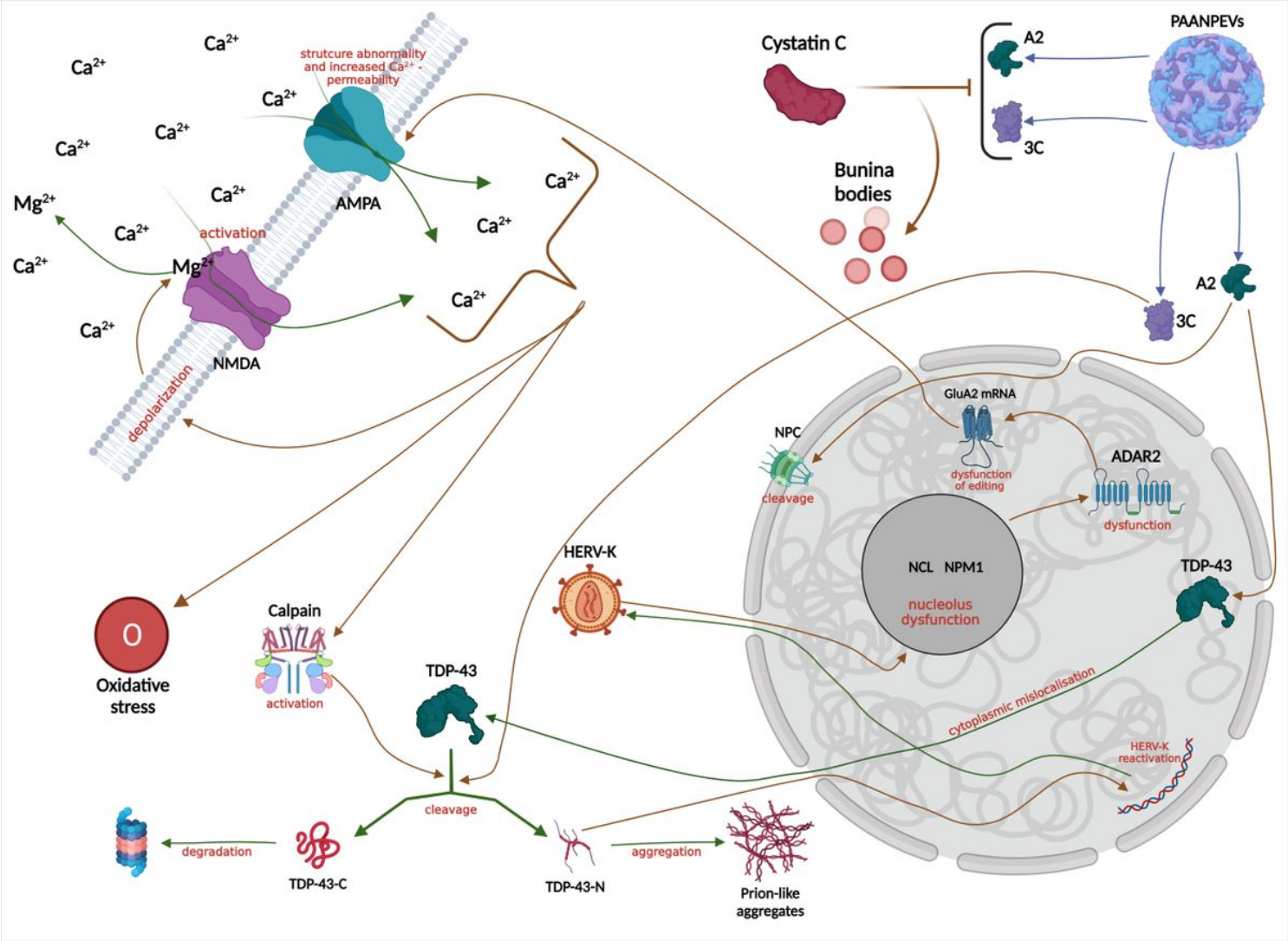

Figure 1

The link between the mechanisms of pathological process progression in sALS

PAANPEVs (possible sALS-associated non-polio enteroviruses) encodes cysteineproteases 3C and A2, which are expressed in the cell under favorable conditions. Protease A2 causes cytoplasmic mislocalization of TAR DNA binding protein 43 (TDP-43) and damage to nucleoporins, which are components of nuclear-pore complexes (NPCs). Protease 3C cleaves TDP-43, translocated into the cytoplasm into soluble TDP-43-C, which undergoes further proteasome degradation, and insoluble prion-like TDP-43-N, which is capable of both forming aggregates that cannot be proteolyzed, and, when translocated into the nucleus, bind to the human endogenous retrovirus-K (HERV-K) long terminal repeats (LTR) DNA regions, leading to HERV-K reactivation and transcription. The accumulation of HERV-K

transcripts causes nucleolar dysfunction. The nucleolar dysfunction leads to the RNA-specific editase 1 (ADAR2) dysfunction, which results in GluA2 mRNA editing impairment, and, as a result, pathological permeability of AMPA receptors to Ca^{2+}. The massive influx of Ca^{2+} into the cytoplasm leads to calpain activation mediated increase in TDP-43 cleavage, oxidative stress triggering and, due to depolarization, NMDA receptors activation. In addition, the impact of PAANPEVs proteases is a likely cause of the formation of Bunina bodies – specific for sporadic amyotrophic lateral sclerosis (sALS) inclusion bodies, that contain cysteine protease inhibitor cystatin C.

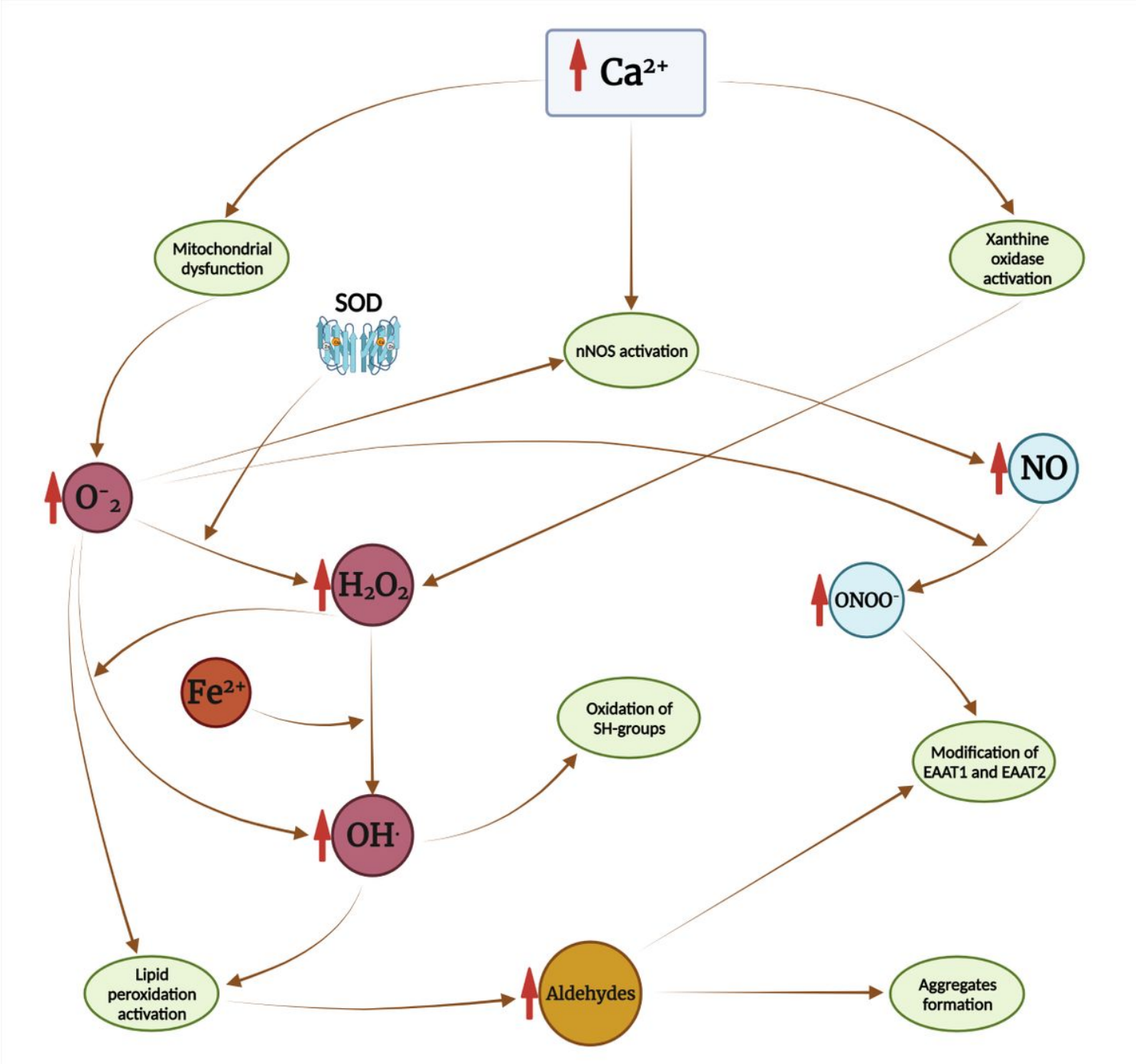

Figure 2

The major ROS and the mechanisms of their formation

The initiating mechanism that causes increased reactive oxygen species (ROS) formation in the cell is an increase in the Ca^{2+} concentration, which primarily causes mitochondrial dysfunction, in the form of oxidative phosphorylation disturbance and molecular oxygen reduction. As a result, the excessive production of superoxide radical (O_2^-) occurs. In addition, an increased concentration of Ca^{2+} activates xanthine oxidase (XO). The generated O_2^- under the influence of superoxide dismutase (SOD), dismutes into hydrogen peroxide (H_2O_2). Apart from that, the H_2O_2 is formed in consequence of reactions mediated by X O. By the means of Fenton reaction with Fe^{2+}, as well as the Haber-Weiss reaction with the superoxide radical, the H_2O_2 is utilized with the hydroxyl radical ($OH^{\cdot}$) formation. The newly formed hydroxyl radical causes lipid peroxidation (LPO), abundant aldehydes formation, and sulfhydryl (SH-) groups oxidation. In addition, Ca^{2+} and O_2^- cause nitric oxide synthase (NOS) hyperactivation, which catalyzes the formation of nitric oxide (NO). The nitric oxide, for its part, by reacting with superoxide, leads to peroxynitrite ($ONOO^-$) formation – the strongest of the ROS. Peroxynitrite and aldehydes, resulted from LPO, interact with glutamate carrier proteins (EAAT1/2), disrupt their function, and increase the ability of cytoplasmic proteins to aggregate.