WHAT CAN GENETICS, BIOCHEMISTRY AND PHYSIOLOGY TELL US ABOUT POTENTIALLY BENEFICIAL LIFESTYLE INTERVENTIONS IN AMYOTROPHIC LATERAL SCLEROSIS?

A theoretical research project

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1. **Introduction and Research Questions**

“Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’ disease, is a very serious and lethal condition of the central and peripheral nervous system. It has been known for over 100 years and occurs worldwide. Its cause, except for rare hereditary forms, remains unknown.” [1]

Approximately 100,000 people are diagnosed with ALS each year, and the condition is most common in men aged 50 to 70. Men are 1.6 times more likely to develop ALS than women. The incidence of ALS appears to be increasing worldwide, although younger individuals are less commonly affected, and the course of the disease varies among patients.

ALS is a progressive disease characterized by muscle twitching, fasciculations, and weakness due to loss of muscle tissue. Muscle atrophy progresses relentlessly, and patients typically die within a few years due to respiratory muscle failure. The course varies, and patients may die 8 months to 4 years after onset of the disease, although there are exceptions such as the prolonged course experienced by the famous physicist Stephen Hawking. The etiology and genetic basis of ALS are largely unknown. [2]

ALS is hereditary in 10-15% of cases and is inherited in an autosomal dominant manner. In the remaining cases, known as "sporadic cases," genetics also play a role, although only a few genetic changes associated with an increased risk of ALS have been described so far.

"The only substance with marginal therapeutic potential is the glutamate antagonist Riluzole, which leads to an average extension of life by 3 to 4 months. Therefore, symptomatic therapy is of high importance. Numerous animal experimental and clinical studies are investigating potentially neuroprotective agents for causal treatment." [2]

As there is still no cure for ALS, this research project aims to derive at potentially beneficial nutritional and lifestyle interventions that can mitigate ALS or even cause remission.

[1] https://www.dgm.org/muskelerkrankungen/amyotrophe-lateralsklerose-als#:~:text=Die%20Amyotrophe%20Lateralsklerose%20ist%20eine,f%C3%BCr%20Amyotrophe%20Lateralsklerose %20ist%20ALS.

[2] Schweikert K. Amyotrophe Lateralsklerose – nach wie vor eine Herausforderung. Schweiterisches Medizin-Forum. 2015;15(46):1068–1073

Research questions

1. What are the biochemical and physiological causes of ALS?
2. Which nutritional and lifestyle factors could potentially be useful to combat the biochemical and physiological changes that contribute to the development of ALS on theoretical grounds?
3. Is there evidence in scientific literature that theoretically beneficial nutritional and lifestyle factors can influence the course of ALS?

To answer the research questions, I will research the biochemical and physiological underpinnings of ALS and subsequently derive at a conclusion which lifestyle factors could theoretically influence these changes in a beneficial way.

A selection of the potentially beneficial factors identified, will be evaluated in a selective literary review to assess if there is scientific evidence of a clinically significant association of these factors with beneficial effects on patients with ALS.

2. Genetics

2.1 Mutations

A mutation is a change in the DNA sequence of an organism that occurs at the genetic level. DNA is the molecular carrier of an organism's genetic information and contains the genome. It consists of four nucleotides representing the letters of the genetic code: adenine (A), cytosine (C), guanine (G), and thymine (T).[3]

Mutations can arise in various ways, such as through radiation, chemicals, or errors during DNA replication. Mutations can also occur spontaneously, for example, through the random alteration of a base sequence in the DNA.

Mutations can be benign or have negative effects on the organism, depending on where they occur and how they affect the function of the affected gene. Some mutations can cause diseases, while others may confer advantages to the organism and thus be part of evolution.

However, it is important to note that not every mutation automatically leads to a change in phenotype expression. In many cases, the mutation has no effect on the function of the gene. Other mutations may lead to a change in the regulation of gene expression without affecting the function of the gene itself.[4]

In medical research, mutations play an important role in the study of diseases. By identifying mutations in specific genes, it is possible to understand the cause of a disease and develop better treatment options.

The three main types of mutations are genome mutations, chromosome mutations, and gene mutations. Genome mutations refer to changes in the entire genomic material of an organism, including DNA and RNA. Genome mutation can result in the alteration of the entire genome of a cell or organism, leading to altered function or development.

Chromosome mutations are changes in the chromosome set of an organism, including loss, gain, or rearrangement of chromosomes. This can lead to a change in the number of chromosomes and thus a change in the genetic information of a cell or organism.

[3] https://studyflix.de/biologie/mutation-2582
[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4563715/

2.1.1 Mutations in ALS

Regarding inheritance, there are two main forms of ALS: familial and sporadic ALS. Familial ALS typically occurs due to a genetic mutation that is passed down to offspring, while sporadic ALS has no known genetic cause.[5]

In familial cases of ALS, the disease is caused by mutations in specific genes that play a crucial role in the function of motor neurons. For example, a mutation in the SOD1 gene, which produces an antioxidant enzyme that neutralizes free radicals in cells, is associated with up to 20% of familial ALS cases.[6]

The way the genetic mutation is inherited depends on the specific type of mutation. Some ALS gene mutations are dominant, meaning only one parent needs to pass down the affected gene to offspring to increase the risk of the disease occurring. Other ALS gene mutations are recessive, meaning both parents must have the affected gene to increase the risk of the disease occurring in offspring.[7]

In most cases of sporadic ALS, the disease occurs without a known genetic cause. However, it is believed that both genetic and environmental factors may play a role in the onset of the disease.[7]

In summary, the inheritance of ALS depends on the specific type of genetic changes and the mode of inheritance. Familial cases of ALS increase the risk of developing the disease, but it is not guaranteed that a person with a genetic predisposition will actually develop ALS.

2.2 Environmental factors

It is known that various environmental influences are associated with the onset of amyotrophic lateral sclerosis (ALS). However, there is currently no clear explanation for the mechanisms by which certain environmental factors trigger or exacerbate the onset of the disease.

[5] https://link.springer.com/article/10.1186/1750-1172-4-3
[6]https://www.ninds.nih.gov/health-information/disorders/amyotrophic-lateral-sclerosis-als?search-term=Disorders%20All%20Disorders%20Amyotrophic%20Lateral%20Sclerosis%20Information%20Page#toc-who-is-more-likely-to-get-amyotrophic-lateral-sclerosis-als-

Some studies have shown that individuals working in certain occupations where they are exposed to toxic substances have a higher risk of developing ALS. This may indicate a potential effect of environmental toxins on motor neurons. Other studies have demonstrated a correlation between ALS and military deployments, where soldiers were exposed to toxic chemicals. However, there are also studies that have not found a link between ALS and environmental influences. Therefore, the role of environmental factors in the onset of ALS remains unclear.[7]

Most cases of ALS are idiopathic, meaning there is no known cause. It is likely that a combination of genetic factors and environmental influences play a role in the onset of the disease.[8]

Further research should be conducted to learn more about the effects of environmental influences on the onset of ALS and to develop potential prevention measures.

[7] Brown, R. H., & Al-Chalabi, A. (2017). Amyotrophic Lateral Sclerosis. New England Journal of Medicine, 377(2), 162-172. https://doi.org/10.1056/NEJMra1603471

3. Symptoms

The nerve cells in the brain and spinal cord control the movements of voluntary muscles, such as chewing, walking, or speaking. As the motor neurons degenerate and die, they stop sending information to the muscles, leading to muscle weakness, fasciculations, and atrophy. Eventually, the brain loses the ability to initiate and control voluntary movements.[8]

Early symptoms may include muscle twitching, cramps, stiff and rigid muscles (spasticity), muscle weakness, nasal-sounding speech, and difficulty chewing or swallowing. Over time, the symptoms spread to other parts of the body, causing problems such as difficulty standing or walking, getting up or going to bed, speaking, or swallowing food. Eventually, individuals become dependent on a ventilator and may die from respiratory failure, which typically occurs within 3-5 years of the onset of symptoms. However, there are also cases where people with ALS survive for a decade or longer.[9] ALS does not impair sensory perception such as taste, touch, smell, or hearing, but it can lead to anxiety and depression, dysarthria, dysphagia, dyspnea, weight loss, malnutrition, muscle cramps, neuropathy, and in rare cases, problems with speech or decision-making, or the development of dementia.[9]

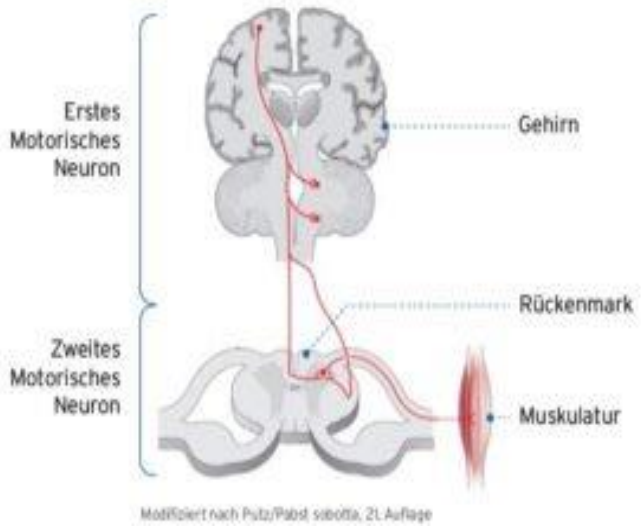

Figure 1 Anatomy of the nervous system Source: https://als-charite.de/uber-als/#als-sec-title-7

The motor neurons affected by Amyotrophic Lateral Sclerosis (ALS) are located in the brain and spinal cord. These are the nerve cells that control voluntary muscle movements. The first motor neurons originate in the brain, and their axons extend into the spinal cord. There, they make contact with the second motor neurons, which are connected to the muscles through long axons. (**figure 1**) [10]

[8] https://www.ninds.nih.gov/health-information/disorders/amyotrophic-lateral-sclerosis-als?search-term=Disorders%20All%20Disorders%20Amyotrophic%20Lateral%20Sclerosis%20Information%20Page#toc-who-is-more-likely-to-get-amyotrophic-lateral-sclerosis-als-

[9] Brown, R. H., & Al-Chalabi, A. (2017). Amyotrophic Lateral Sclerosis. New England Journal of Medicine, 377(2), 162-172. https://doi.org/10.1056/NEJMra1603471

[10] https://als-charite.de/uber-als/#als-sec-title-7

4. Disease und biological underpinnings

4.1 Disease

Muscle weakness in ALS is caused by the degeneration of the nerve cells responsible for controlling the muscles. This results in improper transmission of signals from the central nervous system, leading to muscle weakness and eventual disappearance. Both types of motor neurons, the upper motor neurons in the brain and the lower motor neurons in the spinal cord, are affected by this degeneration.[11]

There are two main forms of ALS, distinguished by the affected muscle areas. The bulbar form primarily affects the muscles in the head and neck area, causing patients to have difficulty swallowing and speaking. Conversely, Primary Lateral Sclerosis mainly affects the muscles of the limbs, making walking increasingly difficult for patients and necessitating the use of a wheelchair.[12]

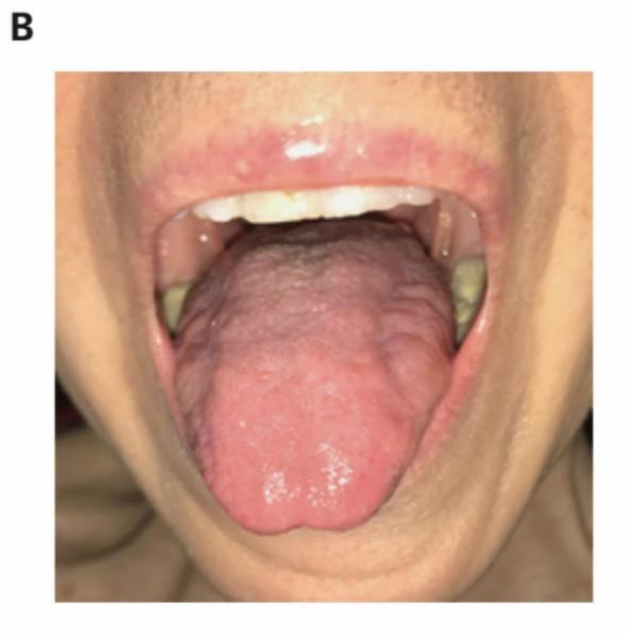

Figure 3 lateral weakness and atrophy of the tongue https://kclpure.kcl.ac.uk/portal/files/74204468/Amyotrophic_Lateral_Sclerosis_BROWN_Published13July2017_GREEN_VoR.pdf

[11] Brown, R. H., & Al-Chalabi, A. (2017). Amyotrophic Lateral Sclerosis. New England Journal of Medicine, 377(2), 162-172. https://doi.org/10.1056/NEJMra1603471

Figure B shows the lateral weakness and furrow on the tongue of a patient with ALS, attributed to the degeneration of motor neurons in the laryngeal region (bulbar form).[13]

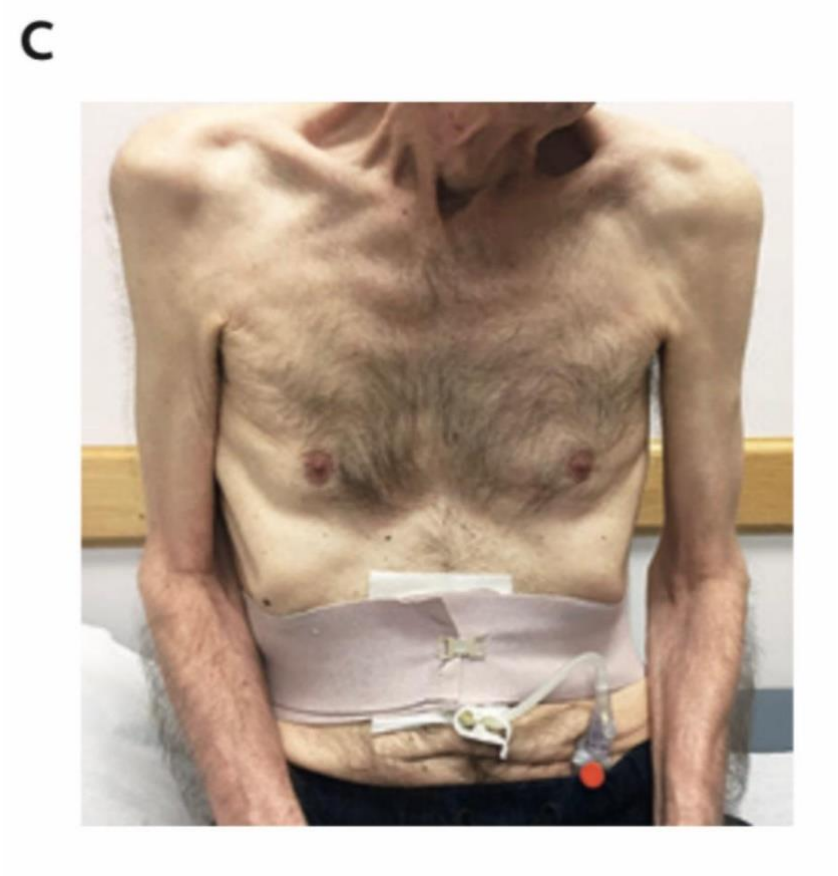

Figure 4: Flail arm syndrome
https://kclpure.kcl.ac.uk/portal/files/74204468/Amyotrophic_Lateral_Sclerosis_BROWN_Published13July2017_GREEN_VoR.pdf

Figure C depicts the slender arms and shoulders, characteristic of the flail arm syndrome, which occurs in patients with ALS and is associated with extended survival time (Primary Lateral Sclerosis).[12]

[12] Brown, R. H., & Al-Chalabi, A. (2017). Amyotrophic Lateral Sclerosis. New England Journal of Medicine, 377(2),
162-172. https://doi.org/10.1056/NEJMra1603471

4.2 Biologische Hintergründe

There are approximately 30 genes associated with the occurrence of Amyotrophic Lateral Sclerosis (ALS). Some of the most commonly affected genes include[13]:

- C9ORF72: This gene is responsible for about 40% of cases of hereditary ALS.
- SOD1: This gene plays a crucial role in oxygen processing and is associated with about 20% of cases of hereditary ALS.
- TDP-43: This protein is important for cell function and is linked to approximately 10% of ALS cases.
- FUS: This protein is crucial for cell function and is associated with about 5% of cases of hereditary ALS.[14]

For a detailed overview of known genetic mutations associated with the occurrence of ALS, please refer to the individual sources. These mutations are not only present in the motor neurons but throughout the body. However, the question arises as to why there are only problems in muscle control and no difference in other cells compared to people without a predisposition to ALS. The answer is likely simple:

a The motor neurons responsible for controlling muscles have long projections (axons) of up to 1.5 meters, making them the longest cells in the body. This length requires elaborate transport pathways to supply the cell with all necessary components. However, minor deviations in cell metabolism, which do not lead to major problems in other cells, can cause difficulties in motor neurons, such as transportation or disposal of waste products. Another challenge for motor neurons is that they are only supplied with energy from outside at certain nodes, called the Ranvier nodes.[14] It is suspected that the axons are supplied with energy in the form of lactate by surrounding myelin cells, and this dysfunction of these cells contributes to the development of ALS.[15]

[13] Mejzini R, Flynn LL, Pitout IL, Fletcher S, Wiltin SD, Akkari PA. ALS Genetics, Mechanisms, and Therapeutics: Where Are We Now? Front. Neurosci. 2019 https://doi.org/10.3389/fnins.2019.01310
[14] Lee Y, Morrison BM, Li Y, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature. 2012;487(7408):443-448. doi:10.1038/nature11314
[15] Lee Y, Morrison BM, Li Y, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature. 2012;487(7408):443-448. doi:10.1038/nature11314

b The motor neurons are large and complex cells that regularly need to perform at high levels. These cells must be intensely stressed at irregular intervals, such as during muscle training, interval training, or marathon running.[16]

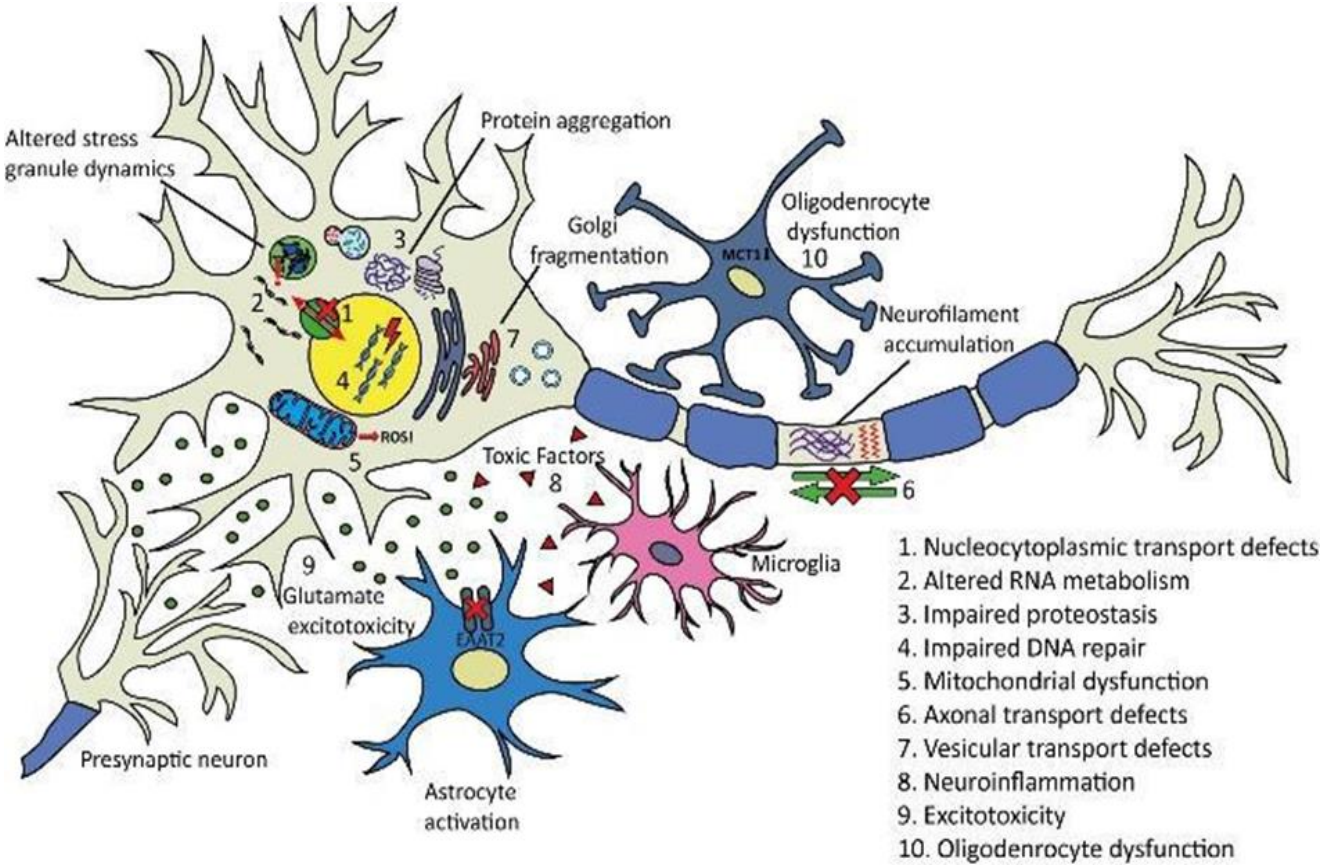

Figure 5 Cellular disease mechanisms (Mejzini et al. 2019)

In the following sections, I will discuss the genetic changes associated with ALS and how they contribute to the onset of the disease. I will also explain what conclusions we can draw from this to prevent ALS.

4.2.1 Superoxide Dismutase

The function of Superoxide Dismutase (SOD) is crucial for cellular metabolism. This larger molecule is responsible for scavenging free oxygen radicals that arise during cellular energy metabolism. In this way, it prevents these radicals from damaging important molecules such as DNA within the cell. There are several subforms of SOD: SOD1 is the most common form.[16] Two forms of ALS - familial and sporadic - can be caused by genetic changes in the SOD1 gene. It is estimated that 15-30% of familial ALS cases and 2% of sporadic cases are attributed to a mutation in the SOD1 gene.[17] Insufficient SOD1 or the absence of SOD1 does not lead to ALS in various disease models. Therefore, it is not a loss of function of the gene. Several mechanisms are described through which changes in the molecule, function, or metabolism can lead to problems in cellular metabolism:[18]

- SOD1 with an incorrect spatial structure, meaning they are “misfolded”.

  These cannot be well metabolized by the cell and may accumulate within the cell as aggregates of many SOD1 molecules, impairing cell function. This form of SOD1 molecules can, similar to prions, "infect" other cells, causing the proteins in these cells to also misfold.[17]

- Copper deficiency of the SOD molecule.

  SOD1 is also known as Cu/Zn-SOD1. It contains copper and zinc molecules that appear to be important for its function and is also crucial for copper metabolism in the cell. Studies have already shown that copper deficiency in SOD1 could be detected in patients with early-stage ALS.[19]

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[16] Mejzini R, Flynn LL, Pitout IL, Fletcher S, Wiltin SD, Akkari PA. ALS Genetics, Mechanisms, and Therapeutics: Where Are We Now? Front. Neurosci. 2019 https://doi.org/10.3389/fnins.2019.01310

[17] Zou, Z.-Y., Zhou, Z.-R., Che, C.-H., Liu, C.-Y., He, R.-L., and Huang, H.-P. (2017). Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatr. 88, 540–549

[18] Mejzini R, Flynn LL, Pitout IL, Fletcher S, Wiltin SD, Akkari PA. ALS Genetics, Mechanisms, and Therapeutics: Where Are We Now? Front. Neurosci. 2019 https://doi.org/10.3389/fnins.2019.01310

[19] Tokuda E, Nomura T, Ohara S, Watanabe S, Yamanaka K, Morisaki Y, Misawa H, Furukawa Y. A copper-deficient form of mutant Cu/Zn-superoxide dismutase as an early pathological species in amyotrophic lateral sclerosis. Biochim Biophys Acta Mol Basis Dis. 2018;1864(6 Pt A):2119-2130. doi: 10.1016/j.bbadis.2018.03.015

- In later stages of ALS, SOD1 relocates to the cell nucleus and likely has a partially protective function here.[20]
- Even normal SOD1 molecules that have reacted too strongly with oxygen radicals can be toxic to the cell.[21]

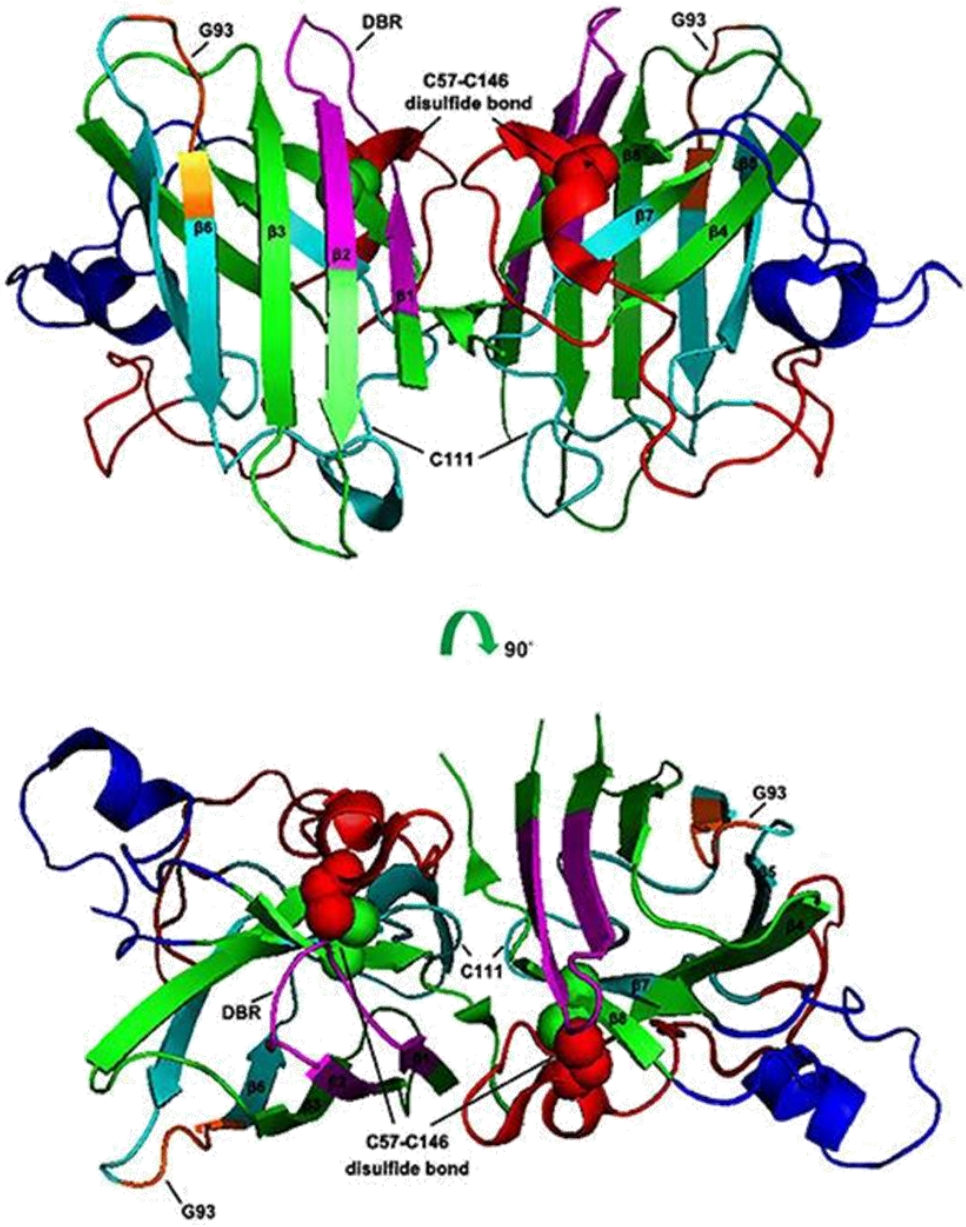


Figure 6 Human Superoxide Dismutase 1 with its spacial (tertiären) structure (Source: Huai J, Zhang Z. Structural Properties and Interaction Partners of Familial ALS-Associated SOD1 Mutants. Front. Neurol. 2019 https://doi.org/10.3389/fneur.2019.00527)

[20] Wang J, Swanson RA. Superoxide and Non-ionotropic Signaling in Neuronal Excitotoxicity. Front Neurosci. 2020 Sep 3;4:861. doi: 10.3389/fnins.2020.00861

It seems that dysfunction of SOD1 can, over decades, lead to ALS.[21],[22] The logical consequence is: if malfunction of SOD1 is harmful to the motor neurons, leading to the fatal disease ALS, and low levels of SOD1 do not lead to major problems, then it may be beneficial to restrict the production of SOD1 as much as possible to delay the disease by several decades, or until the person dies from another cause.

This raises the question: what situations prompt the cell to produce SOD?

SOD1 is an antioxidant specifically designed to neutralize oxygen radicals. SOD1 is primarily present in the cytosol and the mitochondrial intermembrane space (IMS).[23] Cells are designed to maintain a stable state. Therefore, it stands to reason that increased cellular energy production, which generates many oxygen radicals in the mitochondria, will lead the cell to produce more SOD1 to capture these oxygen radicals. This is especially true if this increased production of oxygen radicals occurs more frequently.[22,24]

When does such an increased production of oxygen radicals occur? It occurs, for example, when the cell is heavily stressed by intense exercise and needs to transmit many signals to the muscles.[22,24,24] When does such an increased production of oxygen radicals occur? It occurs, for example, when the cell is heavily stressed by intense exercise and needs to transmit many signals to the muscles.[25]

[21] Mejzini R, Flynn LL, Pitout IL, Fletcher S, Wiltin SD, Akkari PA. ALS Genetics, Mechanisms, and Therapeutics: Where Are We Now? Front. Neurosci. 2019 https://doi.org/10.3389/fnins.2019.01310

[22] Tokuda E, Nomura T, Ohara S, Watanabe S, Yamanaka K, Morisaki Y, Misawa H, Furukawa Y. A copper-deficient form of mutant Cu/Zn-superoxide dismutase as an early pathological species in amyotrophic lateral sclerosis. Biochim Biophys Acta Mol Basis Dis. 2018;1864(6 Pt A):2119-2130. doi: 10.1016/j.bbadis.2018.03.015

[23] Powers SK, Jackson MJ. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. Physiol Rev. 2008;88:1243-1276. doi:10.1152/physrev.00031.2007

[24] Lee Y, Morrison BM, Li Y, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature. 2012;487(7408):443-448. doi:10.1038/nature11314

[25] Tokuda E, Nomura T, Ohara S, Watanabe S, Yamanaka K, Morisaki Y, Misawa H, Furukawa Y. A copper-deficient form of mutant Cu/Zn-superoxide dismutase as an early pathological species in amyotrophic lateral sclerosis. Biochim Biophys Acta Mol Basis Dis. 2018;1864(6 Pt A):2119-2130. doi: 10.1016/j.bbadis.2018.03.015

What measures could theoretically be taken to reduce the production of SOD and thereby decrease the damage to the motor neurons?

1. Avoiding intense exercise to limit the amount of oxygen radicals produced in the mitochondria.

2. Taking enough copper to prevent copper deficiency in the SOD molecule.

3. Taking antioxidants to intercept oxygen radicals in an alternative way, so that the production of SOD is not stimulated.

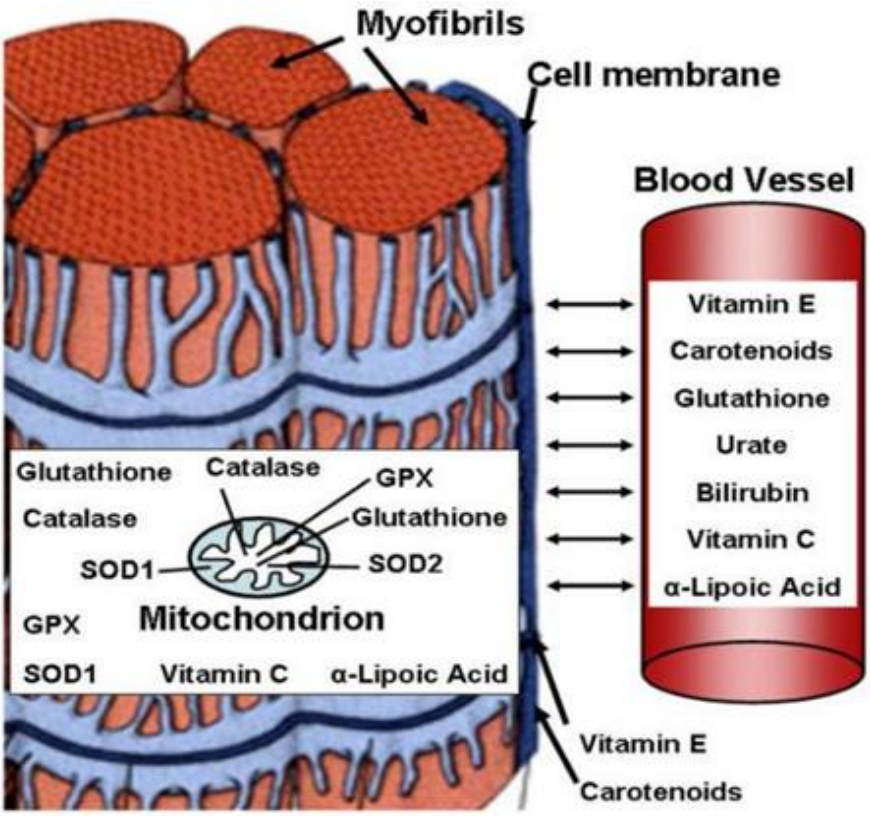
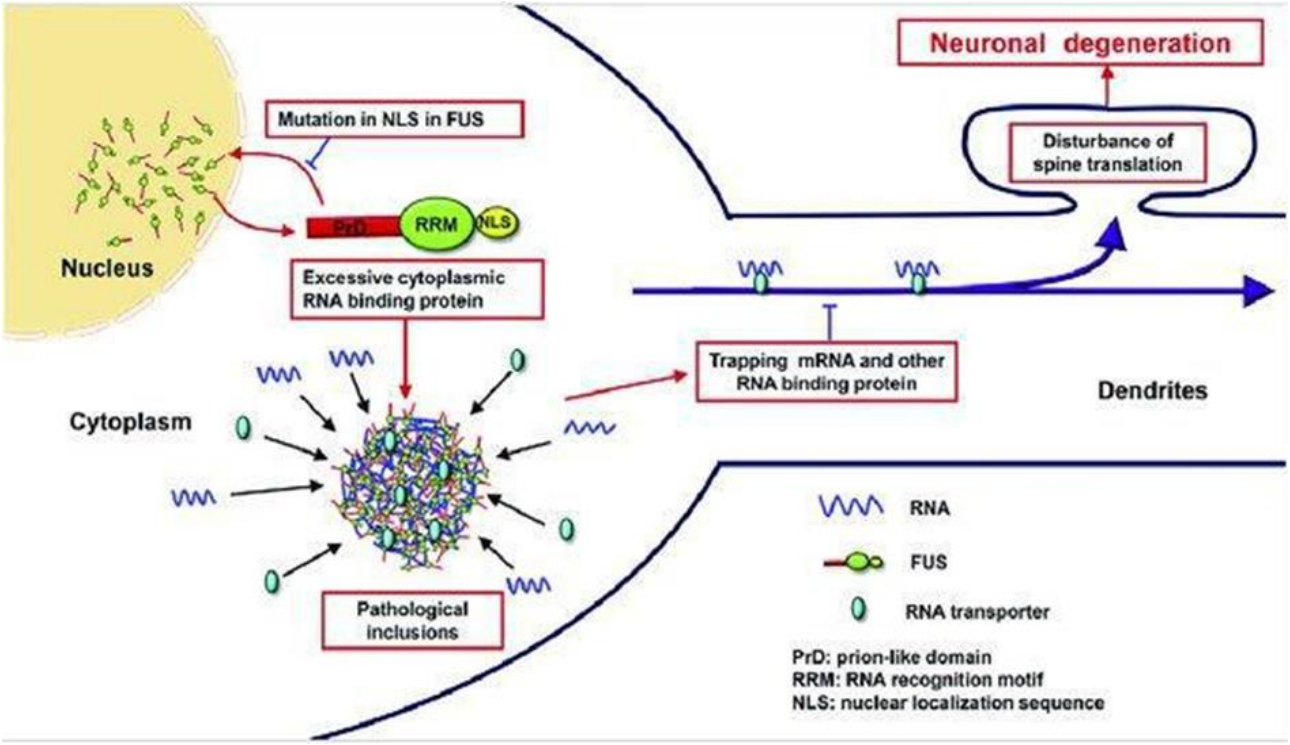


Figure 7 Production und removal von free radicals in the cell (Powers, 2008)

4.2.2 Fused-in-Sarcoma Protein

The Fused-in-Sarcoma protein is a molecule in the cell that plays a role in the cell's energy metabolism and binds to RNA. It is associated with the occurrence of ALS and also with a form of dementia called "frontotemporal dementia".26,27 In changes associated with these diseases, aggregates of FUS are observed in the cell, while there is much less FUS present in the cell nucleus than normal.28 It's not yet clear whether the loss of FUS in the cell



nucleus, or the increased presence of FUS in the cytoplasm, where it undergoes more frequent reactions with glucose than normal, or even a combination of both, causes the demise of the nerve cells underlying ALS.28 It is believed that both the altered distribution and an increased susceptibility to cell death are caused by the changes.28.29 ALS-causing FUS mutations have also been found to hinder the processes that consume the most energy in cell metabolism: the neuronal signaling and the axonal transport of the components carried along the nerve fibers.[29]

Figure 8 postulated disease mechanism of the Fused-in-Sarcoma (FUS) protein (Shihashi, 2017)

[26] Mejzini R, Flynn LL, Pitout IL, Fletcher S, Wiltin SD, Akkari PA. ALS Genetics, Mechanisms, and Therapeutics: Where Are We Now? Front. Neurosci. 2019 https://doi.org/10.3389/fnins.2019.01310
[27] Scekic-Zahirovic J, Sendscheid O, El Oussini H, et al. Toxic gain of function from mutant FUS protein is crucial to trigger cell autonomous motor neuron loss. EMBO J. 2016;35:1077-1097
[28] ShiihashiG, Ito D, Arai I, et al. Dendritic Homeostasis Disruption in a Novel Frontotemporal Dementia Mouse Model Expressing Cytoplasmic Fused in Sarcoma. EBioMedicine. 2017; 24 DOI: 10.1016/j.ebiom.2017.09.005
[29] 12 Vandoorne, T., Veys, K., Guo, W. et al. Differentiation but not ALS mutations in FUS rewires motor neuron metabolism. Nat Commun. 2019; 10:, 4147 https://doi.org/10.1038/s41467-019-12099-4

From the publications, it became clear that the mechanism is not yet fully understood.[30],[31],[32],[33] Given the only partially elucidated disease mechanisms, the following possible beneficial factors can be derived:

1. No overexertion of the muscles

   Because the cell's transport capability is reduced and the cell may have problems with energy supply, it is logical that the cell will be less efficient than a normal cell. Therefore, the cell should be less strenuously taxed.

2. Glucose metabolism

   Although glucose metabolism in the cell may also play a role, it's not clear whether reduced sugar intake would help or hinder the cell. Therefore, no clear recommendation can be made regarding sugar or carbohydrate intake.

[30]Mejzini R, Flynn LL, Pitout IL, Fletcher S, Wiltin SD, Akkari PA. ALS Genetics, Mechanisms, and Therapeutics: Where Are We Now? Front. Neurosci. 2019 https://doi.org/10.3389/fnins.2019.01310

[31] Scekic-Zahirovic J, Sendscheid O, El Oussini H, et al. Toxic gain of function from mutant FUS protein is crucial to trigger cell autonomous motor neuron loss. EMBO J. 2016;35:1077-1097

[32] ShiihashiG, Ito D, Arai I, et al. Dendritic Homeostasis Disruption in a Novel Frontotemporal Dementia Mouse Model Expressing Cytoplasmic Fused in Sarcoma. EBioMedicine. 2017; 24 DOI: 10.1016/j.ebiom.2017.09.005

[33] Vandoorne, T., Veys, K., Guo, W. et al. Differentiation but not ALS mutations in FUS rewires motor neuron metabolism. Nat Commun. 2019; 10:, 4147 https://doi.org/10.1038/s41467-019-12099-4

5 Discussion and Conclusion

5.1 SOD

I have formulated the following recommendations for patients with a possible mutation in the SOD1 gene:

1. Avoid intense physical exercise to limit the production of oxygen radicals.

2. Take sufficient copper to prevent copper deficiency in the SOD molecule.

3. Take antioxidants to scavenge oxygen radicals and prevent stimulation of SOD production.

Could my recommendations prove effective in practice?

There are some scientific observations that suggest that this might be the case:

1. Avoiding intense physical exercise: potentially beneficial

   It seems that ALS is more prevalent in people with professions with a higher rate of exercise and intensive training, such as athletes, police officers and soldiers.[34] For this reason, the first recommendation may be a sensible option.

2. Copper supplements: undefined

   In a study among rare cases of ALS in which a reversal of symptoms or even remission could be observed, more patients took supplements containing copper, than patients without improvement.[35] On the other hand, some studies show higher copper levels in patients with ALS.[36] For this reason, the culprit may not be copper deficiency, but possible a change in copper metabolism. It is possible, that copper

[34] Ingre C, Roos PM, Piehl F, Kamel F, Fang F. Risk factors for amyotrophic lateral sclerosis. Clin Epidemiol. 2015;7:181-193. Published 2015 Feb 12. doi:10.2147/CLEP.S37505

[35] Harrison D, Mehta P, van Es MA, Stommel E, Drory VE, Nefussy B, van den Berg LH, Crayle J, Bedlack R, the Pooled Resource Open-Access ALS Clinical Trials Consortium. “ALS reversals”: demographics, disease characteristics, treatments, and co-morbidities, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2018;19:7-8, 495-499, DOI: 10.1080/21678421.2018.1457059

[36] Zou, Z.-Y., Zhou, Z.-R., Che, C.-H., Liu, C.-Y., He, R.-L., and Huang, H.-P. (2017). Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatr. 88, 540–549

beneficial is for a subgroup of patients, but it remains uncertain if this is true and a negative effect cannot be ruled out.

3. Antioxidants: potentially beneficial

   In several studies, supplementation with antioxidants is associated with a prolonged lifespan and with rare remissions in ALS patients.[37,37]

5.2 FUS

For patients with FUS, I derived at the recommendation, to avoid exercise with intensive muscle exertion, to avoid overexerting the less metabolically capable cell.

Some research suggests that patients who perform light exercise regularly, live longer and patients who perform intensive muscle training live significantly shorter.[38]

Conclusion: this recommendation is probably beneficial.

Conclusion

All in all, there seem to be some potentially beneficial lifestyle and nutritional factors that can be derived from theoretical reasoning according to biochemical mechanisms that are tentatively supported by evidence.

These lifestyle and nutritional factors can be influenced by patients with ALS on their own accord and seem to have a clinically significant benefit in some situations. More research is needed to confirm any such effect in a real-world setting and more research is needed to tailor any recommendations to individual patients.

[37] Tokuda E, Nomura T, Ohara S, Watanabe S, Yamanaka K, Morisaki Y, Misawa H, Furukawa Y. A copper-deficient form of mutant Cu/Zn-superoxide dismutase as an early pathological species in amyotrophic lateral sclerosis. Biochim Biophys Acta Mol Basis Dis. 2018;1864(6 Pt A):2119-2130. doi: 10.1016/j.bbadis.2018.03.015

[38] Miller R, McDade S. Exercise: Helpful or Harmful in ALS? 2015 www.alsworldwide.org