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Protective Effect of Selenium Supplementation on Cerebral Ischemia-Reperfusion Injury after Ischemic Stroke

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Abstract

With the wide application of thrombolytic drugs and the advancement of endovascular therapeutic techniques, the recanalization treatment of acute artery occlusion in ischemic stroke (IS) has made a leap forward, but ischemic brain tissues still face ischemia-reperfusion injury after recanalization. Nowadays, effective neurological protective agents still cannot completely resist the multiple damages of ischemia-reperfusion injury. As an iron-dependent mode of programmed cell death, ferroptosis occupies an important position in ischemia-reperfusion injury. Selenium plays a unique protective role in ischemia-reperfusion injury as an active site element in the center of glutathione peroxidase. Therefore, the study mainly aims to review the protective role of selenium in IS and the related mechanisms, as well as the effect of selenium on the risk factors of IS.

Keywords

Selenium, Ischemic Stroke, Cerebral Ischemia-Reperfusion Injury, GPx4

1. Background

Stroke is currently the second most common cause of death and the third leading cause of disability globally, after cardiovascular disease [1], imposing a heavy burden on society and families, with the global stroke disability-adjusted life year (DALY) increasing by 32.0% from 1990 to 2019 [1]. In China, stroke is one of the leading causes of years of life lost (YLL) [2], with the characterization of high disability and mortality rates. Therefore, how to effectively promote neurological

recovery and reduce mortality in stroke patients is the focus of stroke treatment. Most strokes are ischemic strokes caused by decreased blood flow, which accounts for approximately 71% of all types of strokes globally [3]. Ischemic stroke is usually caused by acute occlusion of the arteries supplying blood to the brain [4]. Currently, intravenous thrombolysis and endovascular thrombolysis are the most effective methods for saving cerebral ischemic tissue after stroke [3]. Cerebral ischemic tissue is functionally divided into core infarcted tissue with irreversible damage and surrounding ischemic penumbra tissue, with the core infarcted tissue consisting of dying cells located in the central region of the ischemic tissue and the surrounding ischemic penumbra tissue as an area of reduced blood flow that can be treated with early reperfusion to reverse neuronal damage [5]. However, the ischemic penumbra tissue that is successfully reperfused faces a new problem, namely ischemia/reperfusion (I/R) injury, which is an important cause of poor prognosis in stroke patients involving a range of pathophysiological mechanisms of injury, including cellular excitotoxicity, oxidative stress, inflammatory storm, apoptosis, autophagy, pyroptosis, and ferroptosis [5] [6]. Currently, there are few clinically available drugs for treating cerebral I/R injury. Therefore, the development of a new drug against ischemic stroke injury has great clinical promise.

Selenium (Se) is an essential trace mineral nutrient that is mainly consumed through the diet, with the recommended daily intake of 60 - 400 ug/d for Chinese people set by the Chinese Nutrition Society in 2011 [7]. Plants absorb selenium from the soil, which enters the food chain through plants or plant-animals, with the selenium content of plants being highly dependent on the selenium content of soil and the ability of plants to absorb and accumulate selenium [8]. China is a severely selenium-deficient country, with about 500 - 600 million people with inadequate selenium intake [7]. The main sources of selenium for human intake are selenomethionine (SeMet) and selenocysteine (Sec), with SeMet mainly coming from plants and Sec from animal products [9]. Inadequate intake of selenium can lead to Creutzfeldt-Jakob disease and arthropathy [10]. Selenium that enters the human body is widely involved in the functioning of various systems in the body mainly in the form of selenoproteins. For example, the central nervous system is highly dependent on adequate intake of selenium [10]. Many neurodegenerative disorders like Alzheimer's disease (AD) [11], Parkinson's disease (PD) [12], Huntington's disease (HD) [13], stroke and seizures are associated with selenium deficiency. Ulrich Schweizer *et al.* found that inactivation of the *Selenop* gene in mice significantly reduced selenium levels and selenoprotein activity in the brain. The selenop-deficient mice fed with recommended Se chow developed neurological symptoms including muscle dystonic gait, tremor, hyperexcitability, and seizures at weeks 4 - 5 [14]. β-amyloid (Aβ) deposition is a key factor in the development and progression of AD, with selenoprotein K levels in the brains of AD patients significantly decreased. However, selenium supplementation can increase selenoprotein K levels in patients, increase CD36 palmitoylation levels and enhance Aβ phagocytosis by microglia to slow down AD progression [15].

2. *In Vivo* Processes of Selenium

25 known selenoproteins in the human body contain Sec residues in their active sites [16]. Plants absorb inorganic selenium from the soil to convert to organic selenium, which is ingested and absorbed by the human body mainly in the form of Sec and SeMet [17]. A small amount of selenium is absorbed in the form of inorganic ions, such as selenite and selenonate. The human body absorbs organic selenium from the intestinal tract to provide it to the liver for the synthesis of selenoprotein P (SELENOP) [18]. Selenium intake is strongly correlated with SELENOP concentration [18]. The human $tRNA^{[Ser]Sec}$ gene, known as Trsp, is localized on chromosome 19q13.2 ± 13.3 and is a key molecule and a central component in the biosynthesis of selenoproteins, which contains 2 isoforms containing mcm^5U or mcm^5Um at position 34, both of which are affected by changes in selenium levels *in vivo* and regulate the synthesis of selenoproteins *in vivo*, including SELENOP and Glutathione Peroxidase 4 (GPx4) [19]. The liver transmits selenium outward to the liver through SELENOP, which transports it to the endocrine glands and important tissues like brain [18].

2.1. GPx4

Selenoproteins of the Glutathione peroxidase (GPx) family are widespread in life and are the only enzymes capable of reducing lipid hydroperoxides within biological membranes [20]. There are eight GPx analogs only in mammals, five of which (GPx1, GPx2, GPx3, GPx4, GPx6) contain Sec residues in their active site, and the Sec residues in the active site of the remaining three (GPx5, GPx7, GPx8) are replaced by Cys [19]. The biosynthesis of Sec is mediated by its own tRNA and relies on multiple enzymatic steps [21]. The synthesis of selenoproteins by Sce requires specific cis-acting progenitors in the mRNA of selenoproteins element, also known as sele-nocysteine insertion sequence (SECIS) [22] which recognizes the terminator codon UGA in organisms [21]. In eukaryotes, the SECIS element binds to the trans-acting protein factor $Sec\text{-}tRNA^{(Ser)Sec}$, which is regulated by SECIS-binding protein 2 (SBP2) and Sec-specific translation elongation factor (eEFSec) to synthesize selenoproteins through a series of complex processes of selenium-phosphate synthesizing enzyme SEPHS2, 1-seryl-tRNA (Sec) kinase PSTK, and Sec synthase SEP-SECS [19] [23]. Mammalian GPx1 was the first identified selenoprotein and the most abundant selenoprotein in mammals [19]. GPx1 is an important cellular antioxidant enzyme found in the cytoplasm and mitochondria of mammals [24] that can reduce intracellular oxidative damage by reducing hydrogen peroxide to water through the depletion of glutathione (GSH) [19]. GPx1 and GPx4 can exert brain protection and scavenge reactive oxygen species (ROS) by inhibiting the phosphorylation cascade after preventing the inactivation of phosphatases by hydrogen peroxide [25].

Gene inactivation studies of GPx4 in mice have shown that GPx4 is an essential selenoprotein for several types of neuronal cells, with embryos with inactivation of the GPx4 gene being lethal around day [26] Similarly, deletion of the *Trsp* gene

can also lead to embryonic death [10]. GPx4 plays an essential role in mammalian cells, with three different isoforms of mitochondrial (MGPX4), cytoplasmic (CGPX4), and spermatid nuclear (SNGPX4) having been found in GPx4 [27]. The human GPX4 gene consists of seven exons and six introns [27] localized on chromosome 19, band 19q13.3, including 197 residues, with a molecular mass of 22 kDa and the typical thioredoxin motifs [28]. Mutations in any one of the residues on GPx4 can decrease the GPx4 activity, where mutation of Sec to cysteine reduces GPx4 activity by 90% [28], suggesting that the role of GPx4 in exerting cerebral protective effect is highly dependent on the presence of Se.

GPx4 differs from GPx1 in the role that GPx4 was found to play a key inhibitory role in cellular ferroptosis by Xuejun Jiang *et al.* [29] In the cytoplasm, cells reverse the exchange of glutamate with cysteine through the Xc^- system and synthesize GSH in the cytoplasm as a GPx4 substrate via the Xc^--GSH-GPx4 pathway, which reduces phospholipid hydroperoxides (PLOOHs) to their corresponding alcohols (PLOHs), reducing the ferroptosis process triggered by PLOOHs [29]. If GPx4 is inactivated, the PLOOHs will react with phospholipids containing chains of polyunsaturated fatty acids (PUFA-PLs), which ultimately results in the formation of myriad subclasses of products, the disruption of cell membrane integrity, and organelle rupture [29]. Although recent studies have shown that 2 other pathways are thought to initiate ferroptosis in addition to the Xc^--GSH-GPx4 pathway, namely the NAD(P)H/FSP1/CoQ10 and the GCH1/BH4/DHFR systems [28] [30]. In fact, the Xc^-/GSH/GPX4 axis system is still referred to as the core pathway [31], with its upstream nuclear transcription factor E2-related factor 2 (Nrf2) also involved in the regulation of this axis, and an active Nrf2 directly or indirectly upregulated the expression of GPx4 to protect the cells against ferroptosis [31].

2.2. Ferroptosis

The term "ferroptosis" was formalized in 2012, which is a unique cell death pathway mediated by iron-dependent phospholipid peroxidation, with many organ injuries and degenerative changes mediated by ferroptosis [29]. Lipoxygenases (LOXs) play a pro-inflammatory role in the body [32]. In ferroptosis, elemental oxygen is added to the polyunsaturated tails of cell membrane phospholipids to produce lipid hydroperoxides, a process mediated by LOXs, long-chain acyl-coenzyme A (CoA) synthase 4 (ACSL4) and other enzymes [29] [33] [34]. Cells inhibiting GPx4 with RSL3 or depleting GSH with erastin exhibited elevated sensitivity to ferroptosis, with cells treated by ferrostatin-1 and liproxstatin-1 enhancing resistance to ferroptosis [35]. Cui Y *et al.* found that down-regulation of ACSL4 exhibited cerebral protective effects in mouse cerebral ischemia and inhibited the expression of inflammatory factors in microglia [36]. Ferroptosis occupies an important part of cell death in human organs and is the main mechanism of cell death associated with ischemic organ injury, including ischemic heart disease, brain injury, and renal failure [37]. Inhibition of the ferroptosis process through multiple pathways can effectively improve the prognosis of many diseases,

especially organ I/R injury.

There is an inseparable relationship between GPx4 and ferroptosis, with selenium utilization by GPx4 necessary to prevent the induction of ferroptosis [38]. For now, selenium supplementation to combat ferroptosis is a very promising therapeutic approach.

3. Selenium and Ischemic Stroke

IS presents a rather paradoxical I/R injury in reperfusion of acutely occluded vessels. I/R injury involves a variety of pathological processes, including cellular injury (apoptosis, necrosis, and ferroptosis), oxidative stress, inflammatory response, blood-brain barrier disruption, extracellular matrix remodeling, and angiogenesis [39], determining that I/R injury is difficult to intervene effectively. Edaravone is a commonly used post-stroke antioxidant in clinical practice that can improve the clinical prognosis of IS by quenching hydroxyl radicals and inhibiting the peroxidative system [40]. However, there are still fewer drugs available to resist I/R injury in IS, which still fail to cover the various stages of I/R injury. Therefore, the development of a new drug for the amelioration of I/R injury would be of great practical significance.

It was found in a case-control study that the risk of IS associated with selenium quartiles shows a downward trend, with lower plasma selenium concentrations increasing the probability of IS [41]. In the Chinese region, plasma selenium levels are significantly negatively correlated with the risk of first IS, with the risk of developing a first ischemic stroke significantly lower in participants with plasma selenium levels ranging from 65.8 to 77.8 μg/L [42]. Furthermore, Zhao K *et al.* also found a linear relationship between serum selenium levels and IS [43]. It was noted in a study encompassing the Chinese National Health and Nutritional Intake Survey from 2003 to 2018 that there was a negative correlation between dietary selenium and the risk of stroke in adults and that a daily intake of approximately 105 μg of selenium was effective in the prevention of IS [44]. Selenium in the human body seems to be inseparably linked to stroke, with HEK293 cells selectively upregulating selenoproteins (GPx1, GPx4, TR1, SeIS, SeIK, and Sps2) to protect against oxidative damage in response to oxidative stress in vitro cultured cells [45]. The only other selenoprotein that has been shown to play an important role in the brain is selenoprotein T, whose exact mechanism of action remains unclear [26]. Selenium influences the human body to develop IS and I/R injury through various pathways in the form of selenoproteins. Therefore, selenium supplementation acting as a means of resisting brain I/R injury and reducing the probability of IS occurrence would be practical and have unique advantages in reducing cellular ferroptosis.

In IS, the ischemic penumbra is a key area for treatment and also for I/R injury. Selenium compounds not only inhibit ROS generation during I/R and hypoxia but also activate the physiological function of mitochondria, and increase the intracellular levels of ATP and Ca^{2+} to promote cell survival in the ischemic

penumbra [46]. Shi Y *et al.* found that selenium supplementation significantly attenuated oxidative stress and inhibited iron accumulation in the MCAO model and N2A cells in the middle cerebral artery occlusion (MCAO) model and oxygen-glucose deprivation reoxygenation (OGD/R) N2a cell model in mice, up-regulating Mfn1 expression to promote mitochondrial fusion and mitigate oxidative stress and ferroptosis [47]. Furthermore, Yang B *et al.* found that selenium also reversed PI3K/AKT/mTOR pathway-mediated cellular autophagy, attenuated blood-brain barrier damage induced by I/R injury during hyperglycemia, and increased tight junction (TJ) expression in a diabetic rat model of MCAO [48]. Selenium concentration in the region of the ischemic penumbra is also a key factor influencing the efficacy of selenium supplementation. Large amounts of selenium supplementation may even trigger selenocytotoxicity because of the narrow safe dosage range of selenium in the body [49]. However, selenium nanoparticles (SeNPs) have the advantage over traditional dietary selenium supplementation in that they are low toxicity and highly efficient [46] and can even be transported in a targeted manner to the site of oxidative stress [50] [51]. Elena G *et al.* found that a 100 nm-sized nano-selenium particles composite (Se-TAX) consisting of SeNPs and firnin can inhibit ROS production in neurons and astrocytes under OGD/R conditions, addressing the issue of potentially insufficient concentrations of selenium in conventional supplementation [52].

Selenium not only has a protective effect against IS but also has an inhibitory effect on the risk factors leading to IS. Atherosclerotic lesions in the human body involve the recruitment and transit of leukocytes by vascular endothelial cells, a process that requires the involvement of adhesion factors (e.g., VCAM-1, ICAM-1, E-selectin, etc.) and cytokines. In addition, a decrease in selenium levels in the body correlates with an increase in adhesion factors, which is a process that can exacerbate atherosclerosis and ultimately lead to cardiovascular and cerebral vascular disease [53]. However, the supplementation with SeMet can significantly reduce aortic atherosclerotic plate formation, improve vascular function, and reduce the accumulation of M1 inflammatory macrophages in mice [54]. Swart R *et al.* found that selenium had a long-term vascular protective effect in Africans with normal selenium levels [55]. At the same time, lower serum selenium levels were an independent predictor of undermined vascular endothelial function as evidenced by lower values of flow-mediated dilatation [56]. Nano-selenium has also been shown to have a significant effect on arterial atherosclerosis as well [49] [57], which can inhibit blood homocysteine-induced mitochondrial oxidation and apoptosis by increasing vascular endothelial cells GPx1 and GPx4 to effectively prevent vascular endothelial dysfunction in rats [57]. In addition, dyslipidemia is also an important risk factor for IS, and a case-control study of elderly people from a Chinese community suggests that a high level of selenium in the urine has a protective effect on dyslipidemia risk protective effect. A case-control study of Chinese community-dwelling older adults suggested that high urinary selenium levels were protective against the risk of dyslipidemia and that appropriate

selenium supplementation could reduce the incidence of dyslipidemia [58]. A meta-analysis suggested that selenium may have a role in lowering total cholesterol and very low-density lipoprotein [59]. Statins are commonly used to ameliorate dyslipidemia, with long-term use of stains (mevalonate pathway inhibitors) found to inhibit translation of selenoproteins by Friedmann Angeli JP and coworkers [60] and that increased selenoprotein activity may exert a vascular endothelial protective effect by reducing abnormal cell adhesion induced by proinflammatory cytokines and destroying cholesterol accumulating in the vascular wall [13], suggesting that appropriate selenium supplementation in dyslipidemic populations has some positive effects.

4. Conclusion

In conclusion, selenium supplementation through dietary supplementation or supplementation with selenium nanoparticles can achieve improvement of neurological function in IS patients by scavenging ROS as well as inhibiting many processes of ferroptosis in the I/R injury produced after IS, but there is still a lack of effective and safe selenium supplements for the treatment of IS in the clinic. The unique mechanism of selenoprotein GPx4 to inhibit ferroptosis makes selenium supplements have an irreplaceable role in resisting I/R injury, and the successful translation of selenium supplements from animal and cellular experiments to the clinic will be exciting. In addition, selenium also has a certain protective effect on atherosclerosis in the human body, with a broad development prospect in the secondary prevention of cardiovascular and cerebrovascular diseases.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Feigin, V.L., Stark, B.A., Johnson, C.O., Roth, G.A., Bisignano, C., Abady, G.G., *et al.* (2021) Global, Regional, and National Burden of Stroke and Its Risk Factors, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *The Lancet Neurology*, **20**, 795-820. https://doi.org/10.1016/s1474-4422(21)00252-0

[2] Zhou, M., Wang, H., Zeng, X., Yin, P., Zhu, J., Chen, W., *et al.* (2019) Mortality, Morbidity, and Risk Factors in China and Its Provinces, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *The Lancet*, **394**, 1145-1158. https://doi.org/10.1016/s0140-6736(19)30427-1

[3] Campbell, B.C.V., De Silva, D.A., Macleod, M.R., Coutts, S.B., Schwamm, L.H., Davis, S.M., *et al.* (2019) Ischaemic Stroke. *Nature Reviews Disease Primers*, **5**, Article No. 70. https://doi.org/10.1038/s41572-019-0118-8

[4] Campbell, B.C.V. and Khatri, P. (2020) Stroke. *The Lancet*, **396**, 129-142. https://doi.org/10.1016/s0140-6736(20)31179-x

[5] Tuo, Q., Zhang, S. and Lei, P. (2021) Mechanisms of Neuronal Cell Death in Ischemic Stroke and Their Therapeutic Implications. *Medicinal Research Reviews*, **42**, 259-305. https://doi.org/10.1002/med.21817

[6] Xu, D., Kong, T., Shao, Z., Liu, M., Zhang, R., Zhang, S., *et al.* (2021) Orexin—A Alleviates Astrocytic Apoptosis and Inflammation via Inhibiting OX1R-Mediated NF-κB and MAPK Signaling Pathways in Cerebral Ischemia/Reperfusion Injury. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1867**, Article ID: 166230. https://doi.org/10.1016/j.bbadis.2021.166230

[7] Zhang, L., Song, H., Guo, Y., Fan, B., Huang, Y., Mao, X., *et al.* (2020) Benefit-Risk Assessment of Dietary Selenium and Its Associated Metals Intake in China (2017-2019): Is Current Selenium-Rich Agro-Food Safe Enough? *Journal of Hazardous Materials*, **398**, Article ID: 123224. https://doi.org/10.1016/j.jhazmat.2020.123224

[8] Zhao, B., Zhou, S., Wu, X., Xing, K., Zhu, Y., Hu, L., *et al.* (2018) Distribution and Accumulation of Selenium in Plants and Health Risk Assessment from a Selenium-Rich Area in China. *Polish Journal of Environmental Studies*, **27**, 2873-2882. https://doi.org/10.15244/pjoes/80693

[9] Huang, X., Dong, Y., Li, T., Xiong, W., Zhang, X., Wang, P., *et al.* (2021) Dietary Selenium Regulates microRNAs in Metabolic Disease: Recent Progress. *Nutrients*, **13**, Article 1527. https://doi.org/10.3390/nu13051527

[10] Avery, J. and Hoffmann, P. (2018) Selenium, Selenoproteins, and Immunity. *Nutrients*, **10**, Article 1203. https://doi.org/10.3390/nu10091203

[11] Solovyev, N., Drobyshev, E., Bjørklund, G., Dubrovskii, Y., Lysiuk, R. and Rayman, M.P. (2018) Selenium, Selenoprotein P, and Alzheimer's Disease: Is There a Link? *Free Radical Biology and Medicine*, **127**, 124-133. https://doi.org/10.1016/j.freeradbiomed.2018.02.030

[12] Pyka, P., Garbo, S., Fioravanti, R., Jacob, C., Hittinger, M., Handzlik, J., *et al.* (2024) Selenium-Containing Compounds: A New Hope for Innovative Treatments in Alzheimer's Disease and Parkinson's Disease. *Drug Discovery Today*, **29**, Article ID: 104062. https://doi.org/10.1016/j.drudis.2024.104062

[13] Ye, R., Huang, J., Wang, Z., Chen, Y. and Dong, Y. (2022) The Role and Mechanism of Essential Selenoproteins for Homeostasis. *Antioxidants*, **11**, Article 973. https://doi.org/10.3390/antiox11050973

[14] Schweizer, U., Wirth, E.K., Klopstock, T., Hölter, S.M., Becker, L., Moskovitz, J., *et al.* (2022) Seizures, Ataxia and Parvalbumin-Expressing Interneurons Respond to Selenium Supply in Selenop-Deficient Mice. *Redox Biology*, **57**, Article ID: 102490. https://doi.org/10.1016/j.redox.2022.102490

[15] Ouyang, P., Cai, Z., Peng, J., Lin, S., Chen, X., Chen, C., *et al.* (2024) Selenok-Dependent CD36 Palmitoylation Regulates Microglial Functions and Aβ Phagocytosis. *Redox Biology*, **70**, Article ID: 103064. https://doi.org/10.1016/j.redox.2024.103064

[16] Weekley, C.M. and Harris, H.H. (2013) Which Form Is That? The Importance of Selenium Speciation and Metabolism in the Prevention and Treatment of Disease. *Chemical Society Reviews*, **42**, 8870-8894. https://doi.org/10.1039/c3cs60272a

[17] Hossain, A., Skalicky, M., Brestic, M., Maitra, S., Sarkar, S., Ahmad, Z., *et al.* (2021)

Selenium Biofortification: Roles, Mechanisms, Responses and Prospects. *Molecules*, **26**, Article 881. https://doi.org/10.3390/molecules26040881

[18] Schomburg, L. (2022) Selenoprotein P—Selenium Transport Protein, Enzyme and Biomarker of Selenium Status. *Free Radical Biology and Medicine*, **191**, 150-163. https://doi.org/10.1016/j.freeradbiomed.2022.08.022

[19] Labunskyy, V.M., Hatfield, D.L. and Gladyshev, V.N. (2014) Selenoproteins: Molecular Pathways and Physiological Roles. *Physiological Reviews*, **94**, 739-777. https://doi.org/10.1152/physrev.00039.2013

[20] Yang, W.S. and Stockwell, B.R. (2016) Ferroptosis: Death by Lipid Peroxidation. *Trends in Cell Biology*, **26**, 165-176. https://doi.org/10.1016/j.tcb.2015.10.014

[21] Peeler, J.C. and Weerapana, E. (2019) Chemical Biology Approaches to Interrogate the Selenoproteome. *Accounts of Chemical Research*, **52**, 2832-2840. https://doi.org/10.1021/acs.accounts.9b00379

[22] Fradejas-Villar, N. (2018) Consequences of Mutations and Inborn Errors of Selenoprotein Biosynthesis and Functions. *Free Radical Biology and Medicine*, **127**, 206-214. https://doi.org/10.1016/j.freeradbiomed.2018.04.572

[23] Santesmasses, D., Mariotti, M. and Gladyshev, V.N. (2020) Bioinformatics of Selenoproteins. *Antioxidants & Redox Signaling*, **33**, 525-536. https://doi.org/10.1089/ars.2020.8044

[24] Handy, D.E. and Loscalzo, J. (2022) The Role of Glutathione Peroxidase-1 in Health and Disease. *Free Radical Biology and Medicine*, **188**, 146-161. https://doi.org/10.1016/j.freeradbiomed.2022.06.004

[25] Brigelius-Flohé, R. and Flohé, L. (2020) Regulatory Phenomena in the Glutathione Peroxidase Superfamily. *Antioxidants & Redox Signaling*, **33**, 498-516. https://doi.org/10.1089/ars.2019.7905

[26] Schweizer, U., Bohleber, S., Zhao, W. and Fradejas-Villar, N. (2021) The Neurobiology of Selenium: Looking Back and to the Future. *Frontiers in Neuroscience*, **15**, Article 652099. https://doi.org/10.3389/fnins.2021.652099

[27] Pei, J., Pan, X., Wei, G. and Hua, Y. (2023) Research Progress of Glutathione Peroxidase Family (GPX) in Redoxidation. *Frontiers in Pharmacology*, **14**, Article 1147414. https://doi.org/10.3389/fphar.2023.1147414

[28] Weaver, K. and Skouta, R. (2022) The Selenoprotein Glutathione Peroxidase 4: From Molecular Mechanisms to Novel Therapeutic Opportunities. *Biomedicines*, **10**, Article 891. https://doi.org/10.3390/biomedicines10040891

[29] Jiang, X., Stockwell, B.R. and Conrad, M. (2021) Ferroptosis: Mechanisms, Biology and Role in Disease. *Nature Reviews Molecular Cell Biology*, **22**, 266-282. https://doi.org/10.1038/s41580-020-00324-8

[30] Conrad, M. and Proneth, B. (2020) Selenium: Tracing Another Essential Element of Ferroptotic Cell Death. *Cell Chemical Biology*, **27**, 409-419. https://doi.org/10.1016/j.chembiol.2020.03.012

[31] Liu, Y., Wan, Y., Jiang, Y., Zhang, L. and Cheng, W. (2023) GPX4: The Hub of Lipid Oxidation, Ferroptosis, Disease and Treatment. *Biochimica et Biophysica Acta* (*BBA*)—*Reviews on Cancer*, **1878**, Article ID: 188890. https://doi.org/10.1016/j.bbcan.2023.188890

[32] Horn, T., Adel, S., Schumann, R., Sur, S., Kakularam, K.R., Polamarasetty, A., *et al.* (2015) Evolutionary Aspects of Lipoxygenases and Genetic Diversity of Human Leukotriene Signaling. *Progress in Lipid Research*, **57**, 13-39. https://doi.org/10.1016/j.plipres.2014.11.001

[33] Ding, K., Liu, C., Li, L., Yang, M., Jiang, N., Luo, S., *et al.* (2023) Acyl-CoA Synthase ACSL4: An Essential Target in Ferroptosis and Fatty Acid Metabolism. *Chinese Medical Journal*, **136**, 2521-2537. https://doi.org/10.1097/cm9.0000000000002533

[34] Ye, L.F. and Stockwell, B.R. (2017) Transforming Lipoxygenases: Pe-Specific Enzymes in Disguise. *Cell*, **171**, 501-502. https://doi.org/10.1016/j.cell.2017.10.006

[35] Shah, R., Shchepinov, M.S. and Pratt, D.A. (2018) Resolving the Role of Lipoxygenases in the Initiation and Execution of Ferroptosis. *ACS Central Science*, **4**, 387-396. https://doi.org/10.1021/acscentsci.7b00589

[36] Cui, Y., Zhang, Y., Zhao, X., Shao, L., Liu, G., Sun, C., *et al.* (2021) ACSL4 Exacerbates Ischemic Stroke by Promoting Ferroptosis-Induced Brain Injury and Neuroinflammation. *Brain, Behavior, and Immunity*, **93**, 312-321. https://doi.org/10.1016/j.bbi.2021.01.003

[37] Gao, M., Yi, J., Zhu, J., Minikes, A.M., Monian, P., Thompson, C.B., *et al.* (2019) Role of Mitochondria in Ferroptosis. *Molecular Cell*, **73**, 354-363.e3. https://doi.org/10.1016/j.molcel.2018.10.042

[38] Ingold, I., Berndt, C., Schmitt, S., Doll, S., Poschmann, G., Buday, K., *et al.* (2018) Selenium Utilization by GPX4 Is Required to Prevent Hydroperoxide-Induced Ferroptosis. *Cell*, **172**, 409-422.e21. https://doi.org/10.1016/j.cell.2017.11.048

[39] Zhang, M., Liu, Q., Meng, H., Duan, H., Liu, X., Wu, J., *et al.* (2024) Ischemia-Reperfusion Injury: Molecular Mechanisms and Therapeutic Targets. *Signal Transduction and Targeted Therapy*, **9**, Article No. 12. https://doi.org/10.1038/s41392-023-01688-x

[40] Feng, S., Yang, Q., Liu, M., Li, W., Yuan, W., Zhang, S., *et al.* (2011) Edaravone for Acute Ischaemic Stroke. *Cochrane Database of Systematic Reviews*, No. 12, CD007230. https://doi.org/10.1002/14651858.cd007230.pub2

[41] Wen, Y., Huang, S., Zhang, Y., Zhang, H., Zhou, L., Li, D., *et al.* (2019) Associations of Multiple Plasma Metals with the Risk of Ischemic Stroke: A Case-Control Study. *Environment International*, **125**, 125-134. https://doi.org/10.1016/j.envint.2018.12.037

[42] Wang, Z., Hu, S., Song, Y., Liu, L., Huang, Z., Zhou, Z., *et al.* (2022) Association between Plasma Selenium and Risk of Ischemic Stroke: A Community-Based, Nested, and Case-Control Study. *Frontiers in Nutrition*, **9**, Article 1001922. https://doi.org/10.3389/fnut.2022.1001922

[43] Zhao, K., Zhang, Y. and Sui, W. (2023) Association between Blood Selenium Levels and Stroke: A Study Based on the NHANES (2011-2018). *Biological Trace Element Research*, **202**, 25-33. https://doi.org/10.1007/s12011-023-03649-5

[44] Shi, W., Su, L., Wang, J., Wang, F., Liu, X. and Dou, J. (2022) Correlation between Dietary Selenium Intake and Stroke in the National Health and Nutrition Examination Survey 2003-2018. *Annals of Medicine*, **54**, 1395-1402. https://doi.org/10.1080/07853890.2022.2058079

[45] Zahia, T., Yona, L., Anne-Laure, B. and Laurent, C. (2014) Selective Up-Regulation of Human Selenoproteins in Response to Oxidative Stress. *Free Radical Biology and Medicine*, **75**, S25. https://doi.org/10.1016/j.freeradbiomed.2014.10.745

[46] Varlamova, E.G., Turovsky, E.A. and Blinova, E.V. (2021) Therapeutic Potential and Main Methods of Obtaining Selenium Nanoparticles. *International Journal of Molecular Sciences*, **22**, Article 10808. https://doi.org/10.3390/ijms221910808

[47] Shi, Y., Han, L., Zhang, X., Xie, L., Pan, P. and Chen, F. (2022) Selenium Alleviates Cerebral Ischemia/Reperfusion Injury by Regulating Oxidative Stress, Mitochondrial

Fusion and Ferroptosis. *Neurochemical Research*, **47**, 2992-3002. https://doi.org/10.1007/s11064-022-03643-8

[48] Yang, B., Li, Y., Ma, Y., Zhang, X., Yang, L., Shen, X., *et al.* (2021) Selenium Attenuates Ischemia/Reperfusion Injury-Induced Damage to the Blood-brain Barrier in Hyperglycemia through PI3K/AKT/mTOR Pathway-Mediated Autophagy Inhibition. *International Journal of Molecular Medicine*, **48**, Article No. 178. https://doi.org/10.3892/ijmm.2021.5011

[49] Zhu, M., Wang, G., Wang, H., Guo, Y., Song, P., Xu, J., *et al.* (2019) Amorphous Nano-Selenium Quantum Dots Improve Endothelial Dysfunction in Rats and Prevent Atherosclerosis in Mice through Na^+/H^+ Exchanger 1 Inhibition. *Vascular Pharmacology*, **115**, 26-32. https://doi.org/10.1016/j.vph.2019.01.005

[50] Umar, M., Rehman, Y., Ambreen, S., Mumtaz, S.M., Shaququzzaman, M., Alam, M.M., *et al.* (2024) Innovative Approaches to Alzheimer's Therapy: Harnessing the Power of Heterocycles, Oxidative Stress Management, and Nanomaterial Drug Delivery System. *Ageing Research Reviews*, **97**, Article ID: 102298. https://doi.org/10.1016/j.arr.2024.102298

[51] Amani, H., Habibey, R., Shokri, F., Hajmiresmail, S.J., Akhavan, O., Mashaghi, A., *et al.* (2019) Selenium Nanoparticles for Targeted Stroke Therapy through Modulation of Inflammatory and Metabolic Signaling. *Scientific Reports*, **9**, Article No. 6044. https://doi.org/10.1038/s41598-019-42633-9

[52] Varlamova, E.G., Khabatova, V.V., Gudkov, S.V., Plotnikov, E.Y. and Turovsky, E.A. (2022) Cytoprotective Properties of a New Nanocomplex of Selenium with Taxifolin in the Cells of the Cerebral Cortex Exposed to Ischemia/Reoxygenation. *Pharmaceutics*, **14**, Article 2477. https://doi.org/10.3390/pharmaceutics14112477

[53] Lopes Junior, E., Leite, H.P. and Konstantyner, T. (2019) Selenium and Selenoproteins: From Endothelial Cytoprotection to Clinical Outcomes. *Translational Research*, **208**, 85-104. https://doi.org/10.1016/j.trsl.2019.01.004

[54] Zhang, Y., Cartland, S.P., Henriquez, R., Patel, S., Gammelgaard, B., Flouda, K., *et al.* (2020) Selenomethionine Supplementation Reduces Lesion Burden, Improves Vessel Function and Modulates the Inflammatory Response within the Setting of Atherosclerosis. *Redox Biology*, **29**, Article ID: 101409. https://doi.org/10.1016/j.redox.2019.101409

[55] Swart, R., Schutte, A.E., van Rooyen, J.M. and Mels, C.M.C. (2018) Selenium and Large Artery Structure and Function: A 10-Year Prospective Study. *European Journal of Nutrition*, **58**, 3313-3323. https://doi.org/10.1007/s00394-018-1875-y

[56] Gać, P., Urbanik, D., Pawlas, N., Poręba, M., Martynowicz, H., Prokopowicz, A., *et al.* (2020) Total Antioxidant Status Reduction Conditioned by a Serum Selenium Concentration Decrease as a Mechanism of the Ultrasonographically Measured Brachial Artery Dilatation Impairment in Patients with Arterial Hypertension. *Environmental Toxicology and Pharmacology*, **75**, Article ID: 103332. https://doi.org/10.1016/j.etap.2020.103332

[57] Zheng, Z., Liu, L., Zhou, K., Ding, L., Zeng, J. and Zhang, W. (2020) Anti-Oxidant and Anti-Endothelial Dysfunctional Properties of Nano-Selenium *in Vitro* and *in Vivo* of Hyperhomocysteinemic Rats. *International Journal of Nanomedicine*, **15**, 4501-4521. https://doi.org/10.2147/ijn.s255392

[58] Zhang, Z., Wang, R., He, P., Dai, Y., Duan, S., Li, M., *et al.* (2023) Study on the Correlation and Interaction between Metals and Dyslipidemia: A Case-Control Study in Chinese Community-Dwelling Elderly. *Environmental Science and Pollution Research*, **30**, 105756-105769. https://doi.org/10.1007/s11356-023-29695-z

[59] Kelishadi, M.R., Ashtary-Larky, D., Davoodi, S.H., Clark, C.C.T. and Asbaghi, O. (2022) The Effects of Selenium Supplementation on Blood Lipids and Blood Pressure in Adults: A Systematic Review and Dose-Response Meta-Analysis of Randomized Control Trials. *Journal of Trace Elements in Medicine and Biology*, **74**, Article ID: 127046. https://doi.org/10.1016/j.jtemb.2022.127046

[60] Friedmann Angeli, J.P. and Conrad, M. (2018) Selenium and GPX4, a Vital Symbiosis. *Free Radical Biology and Medicine*, **127**, 153-159. https://doi.org/10.1016/j.freeradbiomed.2018.03.001