

The role of selenium on autophagy

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Article Review

ABSTRACT

ARTICLE INFO

Keywords:

Selenium,
Autophagy,
ROS,
Gpx,
Trx

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DOI: 10.20885/JKKI.Vol13.Iss3.art10

History:

Received: March 15, 2021

Accepted: September 8, 2022

Online: December 5, 2022

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Selenium (Se) deficiency is associated with certain abnormalities, such as Keshan disease, cancer, cardiovascular disease (CVD), viral infections, infertility, immune system abnormalities, metabolic diseases, neurological disorders, and growth retardation. Its antioxidant properties are integrated into various selenoenzymes, mainly glutathione peroxidase (GPx) and thioredoxin reductase (Trx). These selenoenzymes act as a protective mechanism to prevent oxidative stress-induced cellular injury, regulate DNA transcription, and cell proliferation. Decreased levels of antioxidants induce reactive oxygen species (ROS) accumulation resulting in loss of mitochondrial structure and function. The antioxidant properties of selenium could depress ROS and modulates autophagy by interfering initiation of autophagy and phagophore formation. Inhibition at the initiation stage not only involves mTOR and AMPK, an autophagy-related regulators, but also autophagy markers, including Beclin 1, Atg5, LC3, and p62; thus, phagophore and autophagosome are not formed. This review will discuss the role of selenium in modulating autophagy in various organs.

Defisiensi selenium (Se) berhubungan dengan beberapa abnormalitas, seperti penyakit Keshan, kanker, penyakit jantung, infeksi virus, infertilitas, abnormalitas sistem imun, penyakit metabolik, kelainan neurologis, dan keterlambatan pertumbuhan. Sifat antioksidannya berintegrasi ke dalam beberapa selenoenzim terutama glutathione peroksidase (Gpx) dan tioredoksin reduktase (Trx). Selenoenzim tersebut berperan sebagai mekanisme proteksi untuk mencegah cedera seluler yang diinduksi oleh stres oksidatif, meregulasi transkripsi DNA, dan proliferasi sel. Penurunan level antioksidan menginduksi akumulasi ROS sehingga berefek pada kehilangan struktur dan fungsi mitokondria. Sifat antioksidan yang terkandung pada selenium dapat menurunkan ROS dan memodulasi autofagi dengan mengganggu inisiasi autofagi dan pembentukan fagofor. Inhibisi pada tahap inisiasi tidak hanya melibatkan mTOR dan AMPK, sebagai regulator terkait autofagi, tetapi juga marker-marker autofagi, seperti Beclin 1, atg5, LC3, dan p62 sehingga fagofor dan autofagosom tidak terbentuk. Ulasan ini akan membahas peran selenium dalam memodulasi autofagi dan efeknya pada berbagai organ.

INTRODUCTION

Selenium (Se) is a trace mineral in the soil that has an important role in health.

These minerals are a promising alternative treatment as an antioxidant to regulate the human body's autophagy process and ROS

level. A selenium deficiency is associated with certain abnormalities, such as Keshan disease, cardiovascular disease (CVD), viral infections, infertility, immune system abnormalities, metabolic diseases, neurological disorders, and growth retardation.¹ Naturally, selenium can be obtained from plant food, meat, and seafood sources. Selenium contained in food is mainly in the form of selenomethionine (Se-Met) and selenocysteine (Sec), but it varies geographically depending on water and soil content. The estimated values for selenium intake are 70 µg/day for men and 60 µg/day for women. This dose is according to the optimization of glutathione activity in plasma.² Selenium has antioxidant activities and is bonded within the amino acid selenocysteine (Sec). Selenium must be integrated into various selenoenzymes to fulfill its biological function. The most common selenoenzymes are glutathione peroxidase (GPx) and thioredoxin reductase (Trx). These selenoenzymes regulate DNA transcription, cell proliferation, and then, most importantly, as a protective mechanism to prevent cellular injury induced by oxidative stress. Decreased levels of antioxidants induce the accumulation of reactive oxygen species (ROS), affecting the loss of mitochondrial structure and function.³ In physiological conditions, ROS are produced as normal cell metabolism and acts as a signaling molecule in autophagy.⁴ It is important process with complex and intersecting protein networks along with apoptosis. Autophagy removes non-functioning organelles, thereby increasing cell survival.⁵

Autophagy is a catabolic process in which the degradation of cytoplasmic contents occurs, such as proteins and cellular organelles. This process is induced by stress stimuli, such as starvation, hypoxia, oxidative stress, and other harmful stress stimuli, by eliminating and recycling damaged organelles. Autophagy is initiated by Beclin-1, microtubule-associated proteins 1A/1B light chain 3B (LC3-I and LC3-II), and autophagy-related (Atg5, Atg7, and Atg12) proteins. Organelles will be degraded by lysosomes, and then autophagosomes

regulated by Atg proteins are formed.⁶ Autophagy is the key of cellular homeostasis, but not all autophagic processes have beneficial effects. In certain circumstances, autophagy is inhibited to maintain cellular homeostasis. Selenium can activate and/or inhibit the autophagic process from maintaining cellular function. The activation and inhibition mechanism are associated with certain diseases' origin and therapeutic targets.⁷ Studies on selenium as an antioxidant is well known. Nevertheless, the role of selenium on autophagy in certain pathological conditions is still unclear. Therefore, further studies are required to investigate the beneficial effects of selenium in autophagy to repair these pathological conditions and its effects as a preventive agent.

This review aims to determine the alteration of autophagy in several pathological conditions and how selenium is present to repair those changes by activating or inhibiting autophagy molecularly. Table 1 shows the effects of selenium on autophagy in various organs, both in vivo and in vitro studies.

Selenium (Se)

Selenium is a trace mineral bonded within the amino acid selenocysteine (Sec). Proteins that have Sec in their polypeptide chains are called selenoprotein.⁷ It carries out biological purposes such as antioxidant defence, redox signaling, metabolism, and others. Therefore, selenoprotein is closely related to selenium status.⁸ Selenium is absorbed from the soil by plants in the form of selenate or selenite, and selenomethionine (Se-Met) is synthesized. Se-Met is the most common form contained in daily food. Selenoproteins that have been identified include glutathione peroxidase (Gpx1-Gpx4 and Gpx6), thioredoxin reductase (Trx), iodothyronine deiodinases (DIO1-3), selenoprotein P (SelP), selenoprotein W (SelW), selenoprotein H (SelH), selenoprotein R/selenoprotein X (SelR/SelX), selenoprotein N (SelN), selenoprotein K (SelK), selenoprotein M (SelM), selenoprotein S (SelS), selenoprotein T (SelT), selenoprotein O (SelO), and selenoprotein V (SelV).⁷ These selenoproteins play several

major physiological roles including cancer prevention or development, male fertility, thyroid metabolism, immune functions, central nervous system functions, muscle functions, and others. It has been suggested to have a preventive and therapeutic role in certain diseases through

selenoprotein function. It works primarily as an antioxidant by reduction of hydrogen peroxide (H_2O_2) and various peroxides, reducing phospholipid and cholesterol hydroperoxides, and is involved in various redox systems.⁹

Table 1. In vivo and in vitro studies to examine the effects of selenium on autophagy

| Model & specificity | Treatment | Results | Reference |
|---|--|---|-----------|
| Hippocampal neuronal HT22 cell | Sodium selenite and glutamate exposure | Selenium prevents glutamate-induced cell death. Selenium decreases levels of glutamate and hypoxia-induced ROS. Selenium decreases damage caused by ischemia and prevents autophagy activation (normalized ischemic-induced autophagy). | 1 |
| Hippocampal neuronal HT22 cell | Sodium selenite and glutamate exposure | Selenium prevents glutamate-induced cell death. Selenium increases antioxidant levels and decreases ROS levels. It decreases glutamate-induced autophagy marked by decreased LC3-II protein. | 10 |
| Hippocampal neuronal HT22 cell | Selenium H and glutamate exposure | Overexpression of selenium H decreases glutamate-induced ROS levels and protects cells against cell death. It also decreases the transformation of LC3-I to LC3-II as marker of autophagy. Thus, glutamate-induced autophagy can be inhibited. | 11 |
| Hippocampus and cerebral cortex of mice | Se-yeast | Se-yeast increases mTOR activation (autophagy inhibitor); simultaneously, activation of AMPK (autophagy initiation) is also inhibited. | 12 |
| Brain of mice | SeMet | Se-Met decreases mTOR levels and increases AMPK in both hippocampus and cerebral cortex. It also increases LC3-II protein and decrease p62 protein. Thereby, Se-Met regulates the autophagy mediated by the AMPK-mTOR pathway. | 13 |
| Anterior pituitary of mice | Sodium biselenite | Selenium significantly increases the activity of catalase and glutathione. Selenium inhibits mercury-induced intoxication by inhibiting apoptosis (Bax, Bcl2, and caspase) and increasing autophagy (Beclin1, LC3-II). | 14 |
| Cardiomyocytes of chicken | Sodium selenite | Selenium deficiency significantly decreases autophagy-related proteins, including Beclin1, Atg5, LC3-I and dynein. Conversely, apoptosis-associated proteins are increased, including caspase-3, caspase-8, caspase-9, and Bax. | 15 |
| Myocardium of mice | Sodium selenate | Selenate improves cardiac remodelling by regulating the Akt signaling pathway parallel with p62 flux and autophagy degradation. | 16 |
| Human endomyocardial left ventricular | Selenium | Selenium deficiency in cardiac muscle is related to decreased Gpx activity. LC3-II accumulation occurs in cardiomyopathy patients due to selenium malabsorption. | 17 |
| Spleen of chicken | Selenium | Selenium inhibits metal-induced intoxication by reducing oxidative stress and preventing excessive activation of autophagy. | 18 |
| Lymphoid tissue of chicken | Selenium | Selenium deficiency increases LC3-II, Beclin 1, and dynein protein in the spleen and decreases LC3-II protein in the bursa of Fabricius. Selenium deficiency also increases Beclin 1 protein and decreases LC3-II and dynein protein in the thymus. | 19 |

Effects of selenium on lymphoid organs

Recent evidence suggests that selenium plays an important role in immunity. Selenium as an immunostimulant increases T cell activation, cytotoxic tumours-mediated cytotoxic lymphocytes, and natural killer cell activation. In the human study, subjects treated with selenium yeast (400 µg per day) significantly enhanced the number of T cells by 27% compared to the placebo.²⁰

A previous study by Han et al. showed the enhancement of autophagy proteins such as Beclin 1, dynein, LC3-I, and LC3-II, as well as inhibition of the mammalian target of rapamycin (mTOR) in Pb intoxication.¹⁸ Selenium has antagonistic properties to counteract metal-induced toxicity by suppressing ROS-induced oxidative stress and preventing excessive autophagy.²¹ Other investigations by Khoso et al. suggest that selenium deficiency impacts immune organs such as the spleen, bursa of Fabricius (lymphatic organ), and thymus.¹⁹ They found that selenium deficiency affects autophagy-related proteins, including Beclin 1, LC3-II, dynein, and Atg5. It can be concluded that selenium deficiency increased the autophagic process, in which excessive increase in autophagy can cause damage to lymphoid.¹⁹

Effects of selenium on the brain

The brain is one of the susceptible organs to oxidative stress. Mitochondrial damage, excessive ROS production, excitotoxicity, and nitric oxide levels correlate with neurological disorders such as Alzheimer's, ischemic stroke, Parkinson's, and Huntington's.^{3,22}

In the last few decades, many studies on supplementation have the potential to be neuroprotective, one of which is selenium. Selenium is an important element for the brain. Therefore the amount is always maintained.²⁰ Neuroprotective effect of selenium is related to its antioxidant activity.¹¹ Decreased activities of selenoenzymes caused neuronal loss and dysfunction, resulting in irreversible brain injury and progressive degeneration of

neurons.^{1,23}

Ischemic stroke

Ischemic stroke is a neurogenerative disorder in response to hypoxia and cerebral ischemia due to excessive glutamate release and excitotoxicity.¹⁰ These conditions generate mitochondrial damage, elevate ROS production, and mitigate adenosine triphosphate (ATP) production.¹ Previous research by Mehta et al. showed that treatment with selenium prevents cell death and preserves cell survival in glutamate and hypoxia exposed in vitro models. In addition, it protects cells by decreasing ROS accumulation, maintaining the mitochondrial membrane potential, and preserving mitochondrial function through mitochondrial biogenesis.¹ The enhancement of antioxidant enzymes induced by selenium reduces the accumulation of ROS levels. In ischemic and hypoxic models, increased mitochondrial biogenesis is associated with increased nuclear respiratory factor 1 (NRF 1) and peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α).¹ These data supported by Savaskan et al. discovered that selenite prevents glutamate-induced cell death by elevating Gpx activity, inhibiting ROS production, and modulating the phosphoinositide 3-kinases/Akt (PI3K/Akt) pathway, which benefits cell metabolism and proliferation.²⁴ Similar to these findings, Wojewoda et al. proved that selenite supplementation increased NRF 1 levels.²⁵ Study by Mehta et al. demonstrated that the induction of glutamate in cerebral ischemia caused the accumulation of ROS, thereby activating autophagy.¹ This is seen from the increase in autophagy-associated protein, including Beclin 1 and LC3-II, in the ischemic model. Autophagy activation aims to recycle damaged cells and prevent cell death, however the excessive autophagy could be dangerous to cellular survival. Thus, selenium decreases Beclin protein and the breakdown of LC3-II. This finding supports the hypothesis that selenium decreases ROS production. Consequently,

selenium preserves mitochondrial function, reduces ROS, and inhibits autophagy to protect neurons from damage. This finding is supported by Ma et al., which demonstrated that selenium inhibits mitochondrial fission and suppresses autophagy by inhibiting the transformation of LC3-I to LC3-II and preventing cell death.¹⁰

Alzheimer's disease

Alzheimer's disease (AD) is an irreversible and progressive cognitive decline in the elderly due to Tau hyperphosphorylation and deposition of amyloid beta (A β) plaques. An imbalanced production and degradation of A β is the major cause of this condition. As a consequence, A β accumulates in the central nervous system. Autophagy dysfunction is directly related to AD pathogenesis. It is an important mechanism in the degradation and metabolism of A β and Tau.¹² In the early stage, autophagy is increased in AD to enhance degradation. Along with the progression of AD, pathological alteration in autophagy results in the accumulation of A β and Tau and leads to deterioration. Therefore, A β and Tau are potential targets in AD treatment. Antioxidants have been known as neuroprotective agents. Selenium is of powerful supplement with antioxidant activity.²⁶ Decreased levels of selenium are connected to an increase in AD events. Song et al. explained that Se-yeast modulates the AMPK/Akt/mTOR/p70S6K pathway to avoid autophagy initiation and restore autophagy flux, causing A β degradation, thereby, accumulation of A β can be inhibited.¹² In contrast, Zhang et al. found that treatment of se-Met for 12 weeks reduced Tau hyperphosphorylation through Akt activity and inhibited glycogen synthase kinase 3 beta (GSK3 β) as well as degradation of Tau protein through AMPK/mTOR-mediated autophagy in AD mice.¹³ Furthermore, they stated that Se-Met could lower mTOR levels in both in vitro and in vivo studies. AMP-activated protein kinase (AMPK) activation and mTOR inhibition indicate the early stage of autophagy Se-Met-induced. Se-Met prevents cognitive

decline in neurodegenerative diseases through autophagy activation in AD mice.¹³

Effects of selenium on cardiovascular

Several risk factors contribute to cardiovascular disease (CVD), including obesity, hypertension, diabetes, and other chronic diseases. The important cascade of the mechanism involves disruption of the autophagic process. Autophagy alteration is known to contribute to cellular impairment and cell death.¹⁶ A previous study suggested that cellular impairment and cell deaths due to the elevation of oxidative stress in CVD were linked to selenium deficiency.¹⁵ Selenium has antioxidant properties and is integrated into various selenoenzymes, such as GPx. Therefore, many studies have been on the effects of selenium as a prevention of cardiovascular and other chronic diseases. CVD due to selenium deficiency involves either autophagy or apoptosis, or both of them.

The interplay between apoptosis and autophagy could be parallel or opposite. According to research by Li et al., selenium deficiency significantly depressed autophagy biomarkers (Beclin 1, LC3-I, dynein, and Atg5) simultaneously apoptotic biomarkers (Caspase-3, Caspase-8, Caspase-9, and Bax) increase in chicken cardiomyocytes. This finding indicates that selenium deficiency causes mitochondrial dysfunction in cardiomyocytes, thereby inducing cell death in response to necrosis.¹⁵ This result is in line with Luo et al. that selenium deficiency may increase apoptotic markers (Bax and Caspase-3). Bcl 2-associated-X protein (Bax) inhibits autophagy through the breakdown of Beclin 1 and Atg5, indicating apoptosis suppresses autophagy.²⁷ Based on a meta-analysis study, a 24% reduction in coronary heart risk is associated with an increase of plasma selenium level by 50%.² In the study by Zhang et al., using selenate, the cardioprotective effect was linked to autophagy alteration. Selenate can improve hyperlipidemia, cardiac hypertrophy, and

fibrosis, ultimately improving cardiac function. Selenate ameliorates cardiac remodelling by regulating the Akt signaling pathway along with the fluctuations in sequestosome-1/p62 expression and autophagy degradation.¹⁶ Liu et al. demonstrated that selenium deficiency generates excessive miR-2954 expression in the myocardium leading to autophagy and apoptosis during the progression of cardiac injury through PI3K pathway regulation.²³

Effects of selenium on liver

The liver is an affected organ when selenium deficiency occurs.²⁸ Selenium prevents apoptosis, necrosis, and other damage as a result of oxidative stress. It suppresses the upregulation of metal-induced autophagy. Excessive autophagy may induce cell death in prolonged oxidative stress. Zhang et al., demonstrated that selenium depresses excessive regulation of cadmium-induced autophagy in the liver. This protective effect involves the Nrf2 signaling pathway. Nrf2 is the main regulator of oxidative stress responses in cellular defence mechanisms to comply with its role as a transcription factor.²⁹ Wenzhong et al. determined that selenium deficiency leads to enhancement of H₂S level in the liver. This event increases autophagy markers such as Beclin-1, LC3-II and Atg5 aim to protective mechanism

against cell damage.²⁸ Similar evidence was proven by Liu et al. that decreased mTOR levels followed by increased autophagy markers (Beclin-1, LC3-I, LC3-II, and Atg5) are present in the selenium deficiency group. This result shows that autophagy is a key to direct damage induced by selenium deficiency.³⁰

CONCLUSIONS

Selenium has antioxidant properties and is integrated into various selenoenzymes. These antioxidant activities directly protect cells from oxidative stress by lowering ROS production, thus, preventing cell damage. Selenium preserves a proper regulation of autophagy. Under normal conditions, autophagy eliminates and recycles damaged organelles to maintain cellular homeostasis. However, the upregulation of autophagy may induce cell death. This adverse effect is blocked by selenium through its ability to interfere initiation of autophagy and phagophore formation. Autophagy inhibition at the initiation stage not only involves mTOR and AMPK an autophagy regulators, but also autophagy markers, including Beclin 1, Atg5, LC3, and p62; thus, phagophore and autophagosome are not formed. The mechanism of autophagy inhibited by selenium can be clearly explained in Figure 1.

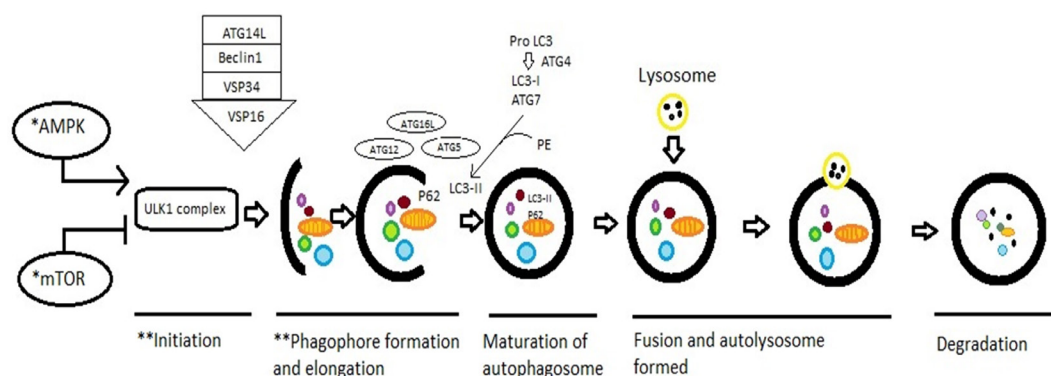


Figure 1. Schematic representation of autophagic stages, which are inhibited by selenium. *Selenium affects AMPK and mTOR activation. **Selenium not only increase autophagy but also inhibit autophagy mainly via Beclin1, Atg5, LC3-II and P62. Therefore, initiation and phagophore formation does not occur.^{31,22}

CONFLICT OF INTEREST

The author declares no conflicts of interest in this work.

ACKNOWLEDGEMENT

I would like to thank my supervisors for their guidance and contribution to designing the manuscript. This article was supported by Internal Research Grand Unpad RKDU No: 3855/UN6.C/LT/2019 and Internal Research Grand Unpad 1427/UN6.3.1/LT/2020 to HG.

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