Neuro-Cell Molecular Research

Research Article

Neuro-Cell Mol Res 2024;1(2):40-46

TRPM2 channel contribution to $CdCI_2$-related neurotoxicity in SH-SY5Y cells: Protective role of selenium

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Received: 31 July 2024; **Accepted:** 24 August 2024; **Published**: 31 August 2024

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DOI: 10.5281/zenodo.13623107

Abstract

Humans are most exposed to the heavy metal cadmium (Cd), known as neurotoxic. However, it is unclear how selenium (Se) protects neurons from damage caused by increased Cd-induced neurotoxicity in SH-SY5Y cells and how the TRPM2 channel functions in this process. In this study, we examined the impact of Se on $CdCI_2$-induced oxidative neurotoxicity and cell death in SH-SY5Y cells by modifying the TRPM2 channel. The Se and TRPM2 channel antagonist 2-APB was added to prevent $CdCI_2$-induced neurotoxicity in SH-SY5Y cells. Cell viability rate was determined between groups by CCK-8 assay. GSH, MDA, and ROS levels were determined in the cells with ELISA kits. Our results showed that the TRPM2 channel plays a vital role in forming $CdCI_2$-induced damage to cells by using the TRPM2 antagonist in the study. We also observed that Se reduced $CdCI_2$-induced neurotoxicity by reducing TRPM2 channel activation by suppressing oxidative stress of cells. We conclude that Se therapy and TRPM2 channel blocking can reduce $CdCI_2$-induced neurotoxicity based on our investigation, which examined the protective impact of Se and the involvement of the TRPM2 channel in $CdCI_2$-induced SH-SY5Y cells for the first time.

Keywords: Cadmium, Selenium, SH-SY5Y cells, TRPM2 channel

Introduction

Cadmium (Cd), a heavy metal element, is found in many industrial products and contaminated foods, especially cigarette smoke [1]. There have been reports that cadmium exposure, which primarily occurs by ingestion or inhalation, may have detrimental effects on several organs [2]. Furthermore, it has been highlighted that Cd is among the most neurotoxic heavy metals, causing neurotoxicity and cognitive impairments. It may also be a significant risk factor for the onset of Parkinson's and Alzheimer's diseases. It has been shown that lowering endogenous antioxidant content, producing reactive oxygen species (ROS), oxidative stress (OS), and inducing apoptosis are all linked to the neurotoxicity of Cd, which is mediated by its capacity to pass the blood-brain barrier [3-5]. In their study on Cd-induced neurotoxicity in rats, Olayan et al. showed that $CdCl_2$ causes OS, neuroinflammation, and apoptosis in the cortical tissue of rats [6]. Ren et al. used cultured neurons and microglia to investigate the toxicity of Cd in vitro. They discovered that Cd was extremely harmful to both cells and animals, causing oxidation and inflammation and severely interfering with Notch/HES-1 and BDNF-TrkB/Akt signalling [7]. In another study, in Cd-induced neurotoxicity in PC12 Cells, they found that Cd exposure reduced cell viability and increased the production of ROS [5]. Yıldız et al. found that Cd triggered neurotoxicity in rat brains by causing OS, apoptosis, and neuroinflammation [8].

Transient receptor potential (TRP) melastatin-2 (TRPM2) belongs to the TRP channel superfamily and forms a non-selective Ca^{2+} permeable cation channel gated by intracellular ADP-ribose (ADPR). In addition to being known for its intense expression in neuronal cells, the TRPM2 channel is found in many different cells in the body, and many studies have shown that this channel is sensitive to activation by OS-inducing stimuli [9-11]. There is growing evidence that TRPM2-mediated cell death is a crucial biological mechanism that connects diseased states with OS caused by different pathogenic causes. Significant advancements have been made in understanding the processes by which OS-induced TRPM2 channel activation causes neuronal cell death via necrosis, autophagy, or apoptosis. However, this area's research is still ongoing [9, 12]. Research has demonstrated that upon exposure to elevated ROS levels and other pathogenic stressors or substances known to trigger OS production, the TRPM2 channel mediates cell death [13].

Selenium (Se) is a trace element that plays an important role in various physiological processes, including development and influencing immune responses. Additionally, it has been emphasized that Se has an antioxidant role in living things at appropriate doses [14, 15]. Based on their requirements for brain functions, Branca et al. investigated whether the elements zinc (Zn) and Se could protect neuron cells from Cd-induced excitotoxicity. Their studies showed that Zn and Se could inhibit the intracellular signalling pathway that causes Cd-induced OS and neuronal dysfunction [16]. In a different study, it was shown that Se and nanoSe particles could counteract the harmful effects of Cd on the antitivent system and may also mitigate the neurotransmitter alterations brought on by Cd intoxication [17]. When studies examining the effect of Se on TRPM2 channel activation in neurodegeneration and neurotoxicity studies were examined, it was noted that Se could modulate TRPM2 channel activation [18, 19].

After conducting a thorough literature analysis, we could not locate any papers on the function of the TRPM2 channel or the protective impact of Se in $CdCI_2$-induced SH-SY5Y cells for this investigation. Thus, our goal was to determine if Se can prevent Cd-induced neurotoxicity and what part the TRPM2 channel plays in this process.

Materials and Methods

Chemicals and reagents

Sigma-Aldrich Co. (St Louis, USA) purchased $CdCI_2$ (Cat no_655198) and 2-APB (Cat no_D9754). The supplier of Se (Cat no_214485) was Sigma-Aldrich (Sigma Aldrich, USA).

Cell culture

The supplier of the SH-SY5Y cells was Ankara Şap Institute, located in Ankara, Turkey. The culture media used to grow SH-SY5Y cells is outlined below. L-glutamine (1g/l), FBS (10%), DMEM (50%), Ham's F12 (50%), and penicillin/streptomycin (1%), in comparable amounts, made up the growth media. At 37 °C, neuronal cells were cultivated in 5% CO_2. Fresh preparations of $CdCI_2$, 2-APB, and Se were made during the experimental days. The experimental groups were subjected to the subsequent incubation protocol. Following incubation, the cells were separated from the flask floor using 0.25% Trypsin-EDTA (Sigma-Aldrich) and rinsed with new 1xPhosphate Buffered Saline (Biochrom/Germany). After completing the experimental procedures, analyses were carried out for every group.

Groups and treatments

The cells were separated into the following seven groups:

Control group: The cells were kept in a culture medium for 24 hours without treatment.

Se group: The cells were incubated with Se (1µM for 2 h) [18].

2-APB group: The cells were incubated with 2-APB (100 µM for the last 30 min) [18].

$CdCl_2$ group: The cells were incubated with $CdCl_2$ (10 µM for 24 h) [16].

$CdCl_2$+Se group: Cells were incubated with $CdCl_2$ (10 µM for 24 h) and then incubated with Se (1µM) for the last 2 h. of the 24 h of the study.

$CdCl_2$+2-APB group: Cells were incubated with $CdCl_2$ (10 µM for 24 h) and 2-APB (100 µM for the last 30 min).

$CdCl_2$+Se+2-APB group: Cells were incubated with $CdCl_2$ (10 µM for 24 h) and then incubated with Se (1µM) for the last 2 h. of the 24 h of the study, and 2-APB (100 µM for last 30 min)

Cell viability assays

According to the experimental group, $CdCl_2$, Se, and 2-APB were added to well-grown SH-SY5Y cells planted on 96-well plates at a density of 1×10^4 cells per well. Cell viability was assessed between the groups using the Cell Counting Kit-8 (CCK-8) assay. Using commercial kits and according to the kit protocol instructions, the cell viability was evaluated on the BioTek ELx808TM equipment at OD450 nm. The cell viability rate in each group was ascertained by repeating the experiment three times; the results were expressed as a percentage (%) of control compared to each group.

Biochemical parameter measurement in SH-SY5Y cells using ELISA kits

Each group's cells were put in a different sterile tube. The tubes were centrifuged according to the kit's instructions for 20 minutes at 1000 rpm. The cell pellets were suspended in PBS (pH 7.4) to create a cell solution at a concentration of around 1 x 10^6/ml after the supernatants were removed. Repeated rounds of freezing and thawing were used to lyse cells and release their internal components. It was centrifuged at 4000 rpm for 10 minutes at 4°C. Supernatants were gathered in order to perform a biochemical study. The total protein levels in the samples were ascertained using the Bradford protein assay kit (Merck Millipore, Darmstadt, Germany). Using commercial ELISA kits and according to the kit method, the levels of GSH (Cat_KTE62857), MDA (Cat_KTE61683), and ROS (Cat_E3524Hu) were measured at OD450 nm using the BioTek ELx808TM equipment. The results were expressed as a percentage (%) of the control group.

Statistical Analysis

The data analysis in this study was done using SPSS and one-way ANOVA, with all data reported as mean ± standard deviation. The post-hoc Tukey test was used to measure any data that showed a statistically significant difference. Every single data point represents a minimum of three separate, triplicate tests. A p-value of less than 0.05 was deemed statistically significant.

Results

Effect of Se and TRPM2 channel antagonists on SH-SY5Y cells viability exposed to $CdCl_2$

The viability of the cells was found to be considerably lower in the $CdCl_2$-treated SH-SY5Y group after 24 hours of incubation ($p < 0.05$) compared to the control and Se groups. The $CdCl_2$+Se group's cell viability rate was observed to be greater than that of the $CdCl_2$ group (Figure 1).

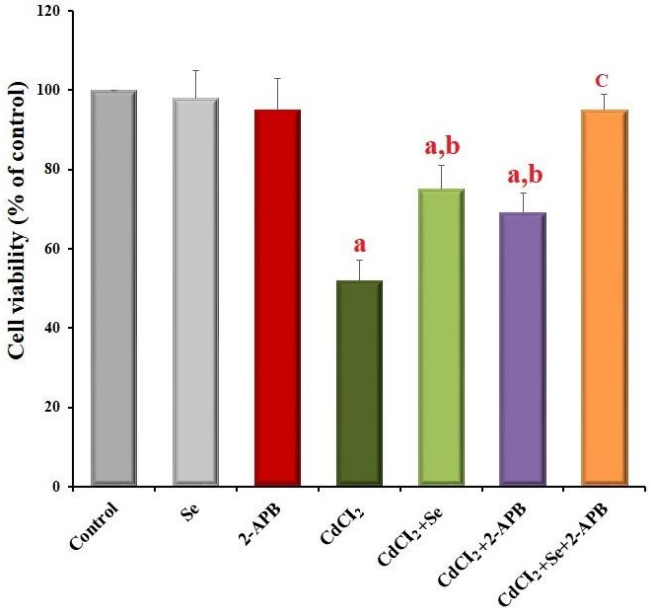

Figure 1. *Cell viability assay (CCK-8) in SH-SY5Y cells after incubations. (Data are expressed as mean ± SD of three experiments). ([a]p<0.05 considers significant as compared with control, Se, and 2-APB groups. [b]p<0.05 considers significant as compared with the $CdCl_2$ group. [c]p<0.05 considers significant as compared with the other $CdCl_2$ groups.*

Compared to the $CdCl_2$ group, the cell viability rate of the $CdCl_2$+Se group rose considerably ($p < 0.05$). Moreover, the $CdCl_2$+Se group's cell viability rate rose with 2-APB incubation. There was no significant difference ($p > 0.05$) between the cell viability rate and that of the control and Se

groups, which were found to be similar. According to our findings, Se therapy and TRPM2 channel inactivation are essential for shielding SH-SY5Y cells from the $CdCI_2$-induced decline in cell viability.

Effect of Se and TRPM2 channel antagonists on GSH and MDA levels in SH-SY5Y cells exposed to $CdCI_2$

After cell viability rates were determined between the groups, changes in GSH and MDA levels were determined using commercial ELISA kits (Figure 2, 3). It was observed that the GSH level decreased, and the MDA level increased in SH-SY5Y cells after $CdCI_2$ exposure ($p < 0.05$) (Figure 2). It was noted that Se treatment and incubation with TRPM2 channel antagonists modulated the $CdCl_2$-induced decrease in GSH level and increase in MDA level (Figure 3).

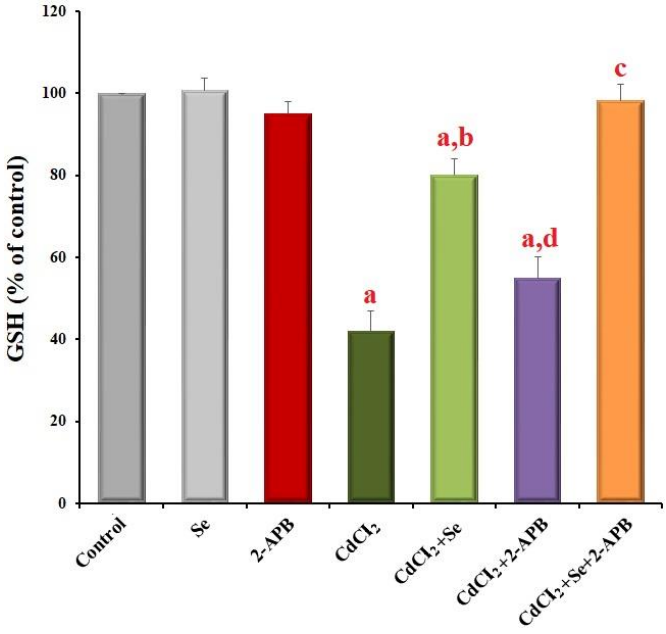

Figure 2. *The SH-SY5Y cell's GSH levels were performed by using the commercial ELISA kit. (Data are expressed as mean ± SD of three experiments). ([a]p<0.05 considers significant as compared with control, Se, and 2-APB groups. [b]p<0.05 considers significant as compared with the $CdCl_2$ group. [c]p<0.05 considers significant as compared with the other $CdCl_2$ groups. [d]p<0.05 considers significant as compared with the $CdCl_2$+Se group.*

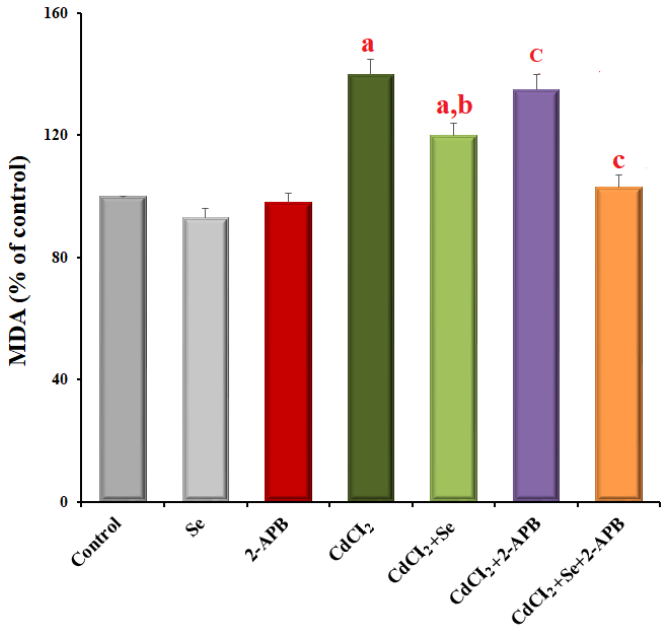

Figure 3. *The SH-SY5Y cell's MDA levels were performed by using the commercial ELISA kit. (Data are expressed as mean ± SD of three experiments). ([a]p<0.05 considers significant as compared with control, Se, and 2-APB groups. [b]p<0.05 considers significant as compared with the $CdCl_2$ group. [c]p<0.05 considers significant as compared with the other $CdCl_2$ groups.*

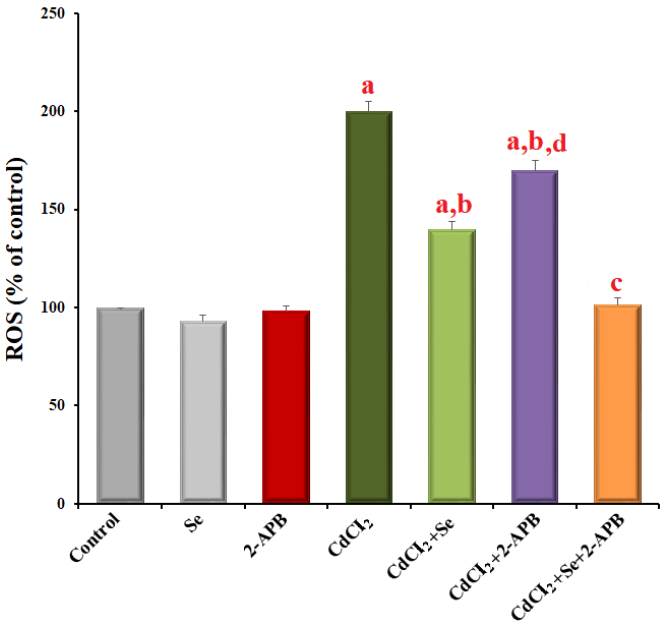

Figure 4. *The SH-SY5Y cell's ROS levels were performed by using the commercial ELISA kit. (Data are expressed as mean ± SD of three experiments). ([a]p<0.05 considers significant as compared with control, Se, and 2-APB groups. [b]p<0.05 considers significant as compared with the $CdCl_2$ group. [c]p<0.05 considers significant as compared with the other $CdCl_2$ groups. [d]p<0.05 considers significant as compared with the $CdCl_2$+Se group.*

Effect of Se and TRPM2 channel antagonists on ROS level in SH-SY5Y cells exposed to $CdCI_2$

A commercial ELISA kit examined how cell ROS levels changed due to $CdCl_2$ exposure (Figure 4). When the ROS levels of the groups were compared, it was seen that the $CdCl_2$ group had the highest ROS level ($p < 0.05$). No significant difference in ROS levels was observed between the control and Se groups ($p > 0.05$). When the $CdCl_2$+Se group was compared with the $CdCl_2$ group, it was determined that Se treatment significantly reduced the ROS level in the cells ($p < 0.05$). When the groups were incubated with TRPM2 channel antagonists, it was noted that TRPM2 channel inactivation played a role in reducing the increased amounts of ROS caused by $CdCl_2$ ($p < 0.05$).

Discussion

Cadmium (Cd) is a toxic material that damages the body's tissues and organs. It alters explicitly the blood-brain barrier permeability, which impacts the central nervous system. After Cd reaches the brain, many chemical processes result in OS. The generation of reactive oxygen species (ROS), inhibition of the electron transport chain (ETC) in the mitochondria, and glutathione (GSH) depletion are the causes of this stress. When exposed to modest doses of Cd, the body's antioxidant response may initially lessen the generation of ROS. On the other hand, oxidative damage can build up and harm cells [20, 21]. This work aimed to examine if selenium (Se) can prevent neurotoxicity caused by Cd and how the TRPM2 channel functions in this process.

Long-term exposure to a polluted environment may cause Cd to accumulate in the human body, leading to dementia and other disorders, according to Chen et al. They found that PC12 and SH-SY5Y neuronal cells exhibited Cd-induced apoptosis after exposing them to Cd to investigate the mechanism of Cd-induced neurodegeneration [22]. In a study in which they modeled the in vitro toxicity caused by Cd, mercury and lead on SH-SY5Y neuroblastoma cells, Mallamaci et al. reported that Cd increased cytotoxicity in a time- and concentration-dependent manner after incubation at different doses and times [23]. In a study investigating whether Zn and Se could protect against Cd-induced excitotoxicity, they determined that Cd inhibited neurite growth, induced OS, and led neurons to apoptosis. They observed that Zn and Se may significantly protect Cd-induced excitotoxicity [16]. Wang et al. emphasized that Cd may cause ROS-dependent cell death in their investigation into whether the protective effect of Se against Cd-induced cytotoxicity is connected to the selenoprotein thioredoxin reductase-1 in nerve cells. After the investigation, they discovered that the content of sodium selenite strongly correlated with the number of SH-SY5Y cells. Furthermore, the MTT experiment observed that a considerable rise in selenite concentration was associated with improved cell viability and proliferation [24]. In our study, we observed that cell viability was significantly reduced compared to the control and Se groups after incubating SH-SY5Y cells with the selected $CdCl_2$ concentration (10 µM for 24 hours). We noted that Se treatment increased cell viability, which decreased $CdCl_2$-induced, and this was in line with studies in the literature showing that Se reduced $CdCl_2$-induced damage. It was noted that the TRPM2 channel antagonists, which we tried for the first time in our study, increased the $CdCl_2$-induced decreased cell viability with 2-APB incubations (Figure 1). These results showed that $CdCl_2$-induced cell damage can also be ameliorated by Se and that the TRPM2 channel plays a crucial role in this damage mechanism.

In an experimental study conducted on mice, Chen et al. reported that Cd decreased Cu/Zn-SOD, catalase, and GSHP-x activities, and glutathione levels in the brain and caused brain damage or neuronal cell death due to ROS induction [25]. Our previous study reported that glutamate cytotoxicity decreased cell viability and increased caspase 3 MDA levels in C6 cells [26]. A study was conducted to investigate whether $CdCl_2$ has an apoptotic effect on the hippocampus of rats and whether resveratrol provides neuroprotection against it. The results showed that resveratrol enhances the synthesis of GSH, inhibits the production of ROS, and upregulates the inhibition of Bcl-2 induced by GAAD 153 through the activation of SIRT1-induced AMKP and Akt. In addition, resveratrol was also reported to inhibit $CdCl_2$-induced endoplasmic reticulum stress in hippocampal cells due to its antioxidant potential [27]. Our study found that exposure to $CdCl_2$ caused a decrease in GSH levels and increased MDA levels in SH-SY5Y cells, which is consistent with previous research (Figure 2, 3). However, treatment with Se and incubation with TRPM2 channel antagonists helped to alleviate these effects. In addition, the group exposed to $CdCl_2$ had the highest ROS levels, but Se treatment significantly reduced ROS levels in the cells. Furthermore, the inactivation of TRPM2 channels played a role in reducing the increased amounts of ROS caused by $CdCl_2$ (Figure 4).

Conclusion

In this study, we determined that cell viability rate and antioxidant level decreased and OS increased in $CdCl_2$-induced SH-SY5Y cells. We also observed that TRPM2 channel activation plays a vital role in this damage mechanism in $CdCl_2$-induced SH-SY5Y cells. On the other hand, neurotoxicity levels and $CdCl_2$-induced oxidative damage were mitigated by Se treatment and decreased TRPM2 channel activity. According to these findings, $CdCl_2$-induced neurotoxicity might be inhibited by Se therapy and TRPM2 channel inactivation.

Conflicts of interest

The authors have no conflicts of interest associated with the publication of this article.

Data availability

Data will be made available on request.

Ethics committee approval

The study is not subject to ethics committee approval.

Funding

The authors have no funding to disclose.

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