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The Effect of Sinapic Acid on Oxidative Stress and Apoptosis in 4-Aminopyridine-Induced Neuronal Damage

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ABSTRACT

Neuronal damage, which is responsible for the development and progression of many neurological disorders, is closely linked to cellular-level mechanisms, primarily oxidative stress and apoptosis. Oxidative stress, particularly that resulting from the overproduction of reactive oxygen species (ROS), induces biochemical alterations such as lipid peroxidation, protein oxidation and DNA damage. These biochemical changes disrupt neuronal cell integrity and alter cellular functions. This process leads to the activation of intrinsic apoptotic pathways, mitochondrial dysfunction, and programmed cell death.

4-aminopyridine (4-AP) is a potassium channel blocker widely used to induce oxidative damage resulting from excessive neuronal stimulation and is commonly used in experimental neurotoxicity models.

The aim of this study is to investigate the effect of sinapic acid (SPA), a naturally occurring phenolic compound with strong antioxidant properties, on 4-AP-induced neuronal damage in human neuroblastoma cells (SH-SY5Y). In the experimental design, cells were divided into four categories: control, SPA, 4-AP, and SPA + 4-AP. In addition to total antioxidant status (TAS), total oxidant status (TOS), and malondialdehyde (MDA) levels, caspase-3 activity—a hallmark marker of apoptosis, was evaluated. According to our findings, 4-AP application led to a significant decrease in TAS levels but increased TOS, MDA, and caspase-3 levels. This suggests that 4-AP application increases oxidative stress and apoptosis in SH-SY5Y cells. In contrast, SPA pre-treatment significantly increased TAS levels and decreased TOS, MDA, and caspase-3 levels compared to the 4-AP group.

In conclusion, SPA was shown to significantly modulate oxidative stress and apoptotic processes, thereby mitigating 4-AP-induced neuronal damage. These findings have strengthened the potential of SPA as a neuroprotective agent in oxidative stress-induced neuronal damage.

Keywords: SH-SY5Y cells, 4-aminopyridine, Sinapic acid, Oxidative stress, Apoptosis

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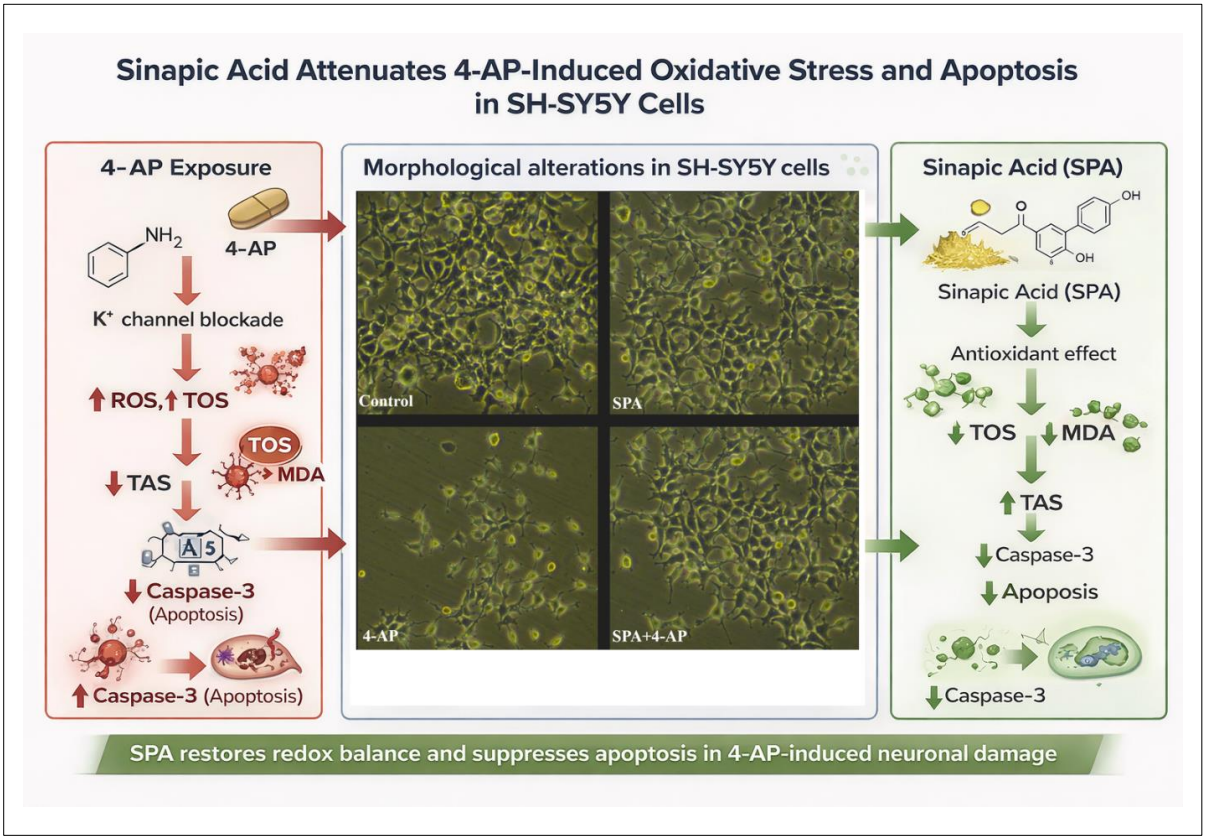

INTRODUCTION

Neuronal damage is a fundamental pathophysiological component underlying many neurological disorders, particularly epilepsy and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Neuronal damage is particularly associated with oxidative stress and apoptosis mechanisms [1]. Excessive production of reactive oxygen species (ROS) disrupts cellular redox homeostasis, triggering lipid peroxidation and halting mitochondrial function. As a result, apoptotic pathways are triggered. A review of the literature reveals that oxidative stress-induced neuronal damage also enhances excitotoxic signalling, thereby accelerating disease progression [2–4]. 4-AP, widely used in experimental neurotoxicity models, delays repolarisation of the action potential by inhibiting voltage-gated K^+ channels, prolonging the action potential and, consequently, increasing neurotransmitter release from synaptic terminals. This situation disrupts intracellular ion homeostasis, particularly Ca^{2+} accumulation, leading to weakened mitochondrial function and a significant increase in ROS production. Increased ROS levels deepen oxidative damage in lipids, proteins, and nucleic acids, initiating pathogenic processes at the cellular level. Consequently, this molecular chain of events contributes to the development of oxidative stress-mediated neuronal damage [5–7].

However, while current studies have elucidated some aspects of this process, the detailed molecular mechanisms underlying 4-aminopyridine (4-AP)-induced oxidative and apoptotic damage remain incompletely understood. Furthermore, targeted therapeutic approaches that can effectively limit or prevent this damage process are not yet sufficiently developed.

In recent years, interest in natural phenolic compounds has been increasing due to their strong antioxidant and neuroprotective properties. Sinapic acid (SPA), a naturally occurring derivative of hydroxycinnamic acid found in various plants, is one of the most notable of these compounds due to its significant free radical scavenging capacity and anti-inflammatory effects. Current studies report that SPA protects mitochondrial integrity by reducing ROS production and has protective effects on neuronal cells by modulating apoptotic signaling pathways [8–10]. However, data on the effects of SPA on oxidative stress and apoptosis, particularly in the context of 4-AP-induced neuronal damage, are still quite limited.

A literature search revealed no studies evaluating the protective effect of SPA as a pre-treatment against 4-AP-induced neuronal damage in SH-SY5Y cells. In this context, the present study investigated the potential neuroprotective effects of SPA administered prior to 4-AP exposure in the human neuroblastoma cell line SH-SY5Y. The study analysed total antioxidant capacity (TAS), total oxidant status (TOS),

and malondialdehyde (MDA) levels to assess oxidative stress, and also examined caspase-3 levels as an indicator of apoptotic activity.

METHODS

Chemicals and Reagents

SPA and 4-AP were obtained from Sigma-Aldrich (St. Louis, MO, USA). Dulbecco's Modified Eagle Medium (DMEM), fetal bovine serum (FBS) and antibiotics used for cell culture were also supplied by the same company. SPA was dissolved in dimethyl sulfoxide (DMSO), and the final DMSO concentration was adjusted to no more than 0.1% in all experimental groups.

Cell Line and Culture Conditions

This study utilised the SH-SY5Y cell line, derived from human neuroblastoma, which is widely used to investigate neuronal damage and neuroprotective mechanisms. Cells were obtained from the American Type Culture Collection (ATCC, USA). Cells were cultured in DMEM containing 10% FBS, 1% penicillin-streptomyciand 1% L-glutamine. Cells were maintained in a humidified incubator at 37 °C with 5% CO_2. Cells were passaged when they reached 80% density, and experiments were performed between passages 10 and 12. This study used a commercially available cell line; therefore, ethical committee approval was not required.

Experimental Design

The incubation time and SPA dose (400 µM) were selected based on a previous study by Tungalag et al. [11]. The duration and dose for 4-AP (6 mM) were determined according to the study by Taşkıran et al. [12].

To ensure methodological consistency and eliminate potential time-dependent variability, the total incubation time was standardised across all treatment groups. Accordingly, the exposure time in each experimental group was adjusted to maintain equal total incubation times.

Experiments were performed by dividing cells into four groups:

Control group: No treatment was applied; cells were kept under the same incubation conditions for the same total time.

SPA group: Cells were treated with 400 µM SPA for 1 hour, then incubated under standard conditions to match the total incubation time.

4-AP group: Cells were treated with 6 mM 4-AP for 3 hours.

SPA + 4-AP group: Cells were pretreated with 400 µM SPA for 1 hour, then incubated with 6 mM 4-AP for 3 hours.

Preparation of Cell Lysates

Following drug administration, cells were trypsinised and centrifuged. Cell pellets were washed with phosphate-buffered saline (PBS, pH 7.4). Three freeze-thaw cycles were performed to lyse the cells. Following commercially available kit procedures, samples were centrifuged at 10,000 rpm for 15–20 minutes at 4 °C to obtain supernatants, which were then used in biochemical analyses.

Measurement of TAS, TOS, MDA and Caspase-3 Levels

TAS and TOS levels were measured using commercial colourimetric kits (Rel Assay Diagnostics, Turkey) according to manufacturer instructions. TAS results were expressed as µmol Trolox equivalent/mg protein, and TOS results were expressed as µmol H_2O_2 equivalent/mg protein. MDA levels, an indicator of lipid peroxidation, were determined using commercial kits based on the thiobarbituric acid reactive substances method. Caspase-3 levels, an indicator of apoptosis, were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits. Absorbance values were determined using a microplate reader at a wavelength of 450 nm. Total protein content in cell lysates was determined using the Bradford method and used to normalise biochemical parameters.

Statistical Analysis

Data are expressed as mean ± standard deviation (Mean ± SD). Statistical analyses were performed using SPSS software. Intergroup comparisons were made using one-way analysis of variance (ANOVA), and the Tukey post hoc test was used to determine significant differences. A $p < 0.05$ value was considered statistically significant.

RESULTS

The Effect of SPA on TAS Levels in 4-AP-Induced Neuronal Damage

As shown in **Figure 1**, 4-AP administration significantly reduced TAS levels compared to the control and SPA groups ($p < 0.05$), indicating a marked impairment in cellular antioxidant capacity. Pre-treatment with SPA significantly increased TAS levels compared to the 4-AP group ($p < 0.05$), demonstrating a partial restoration of antioxidant defense. No statistically significant difference was observed between the control and SPA groups ($p > 0.05$), suggesting that SPA alone does not alter basal antioxidant status.

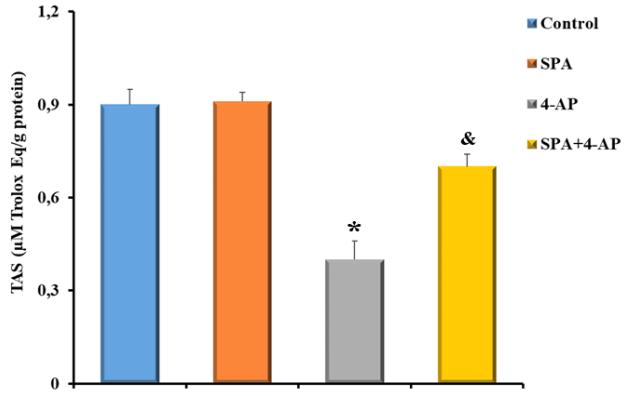

*Figure 1. Effects of SPA on TAS level in 4-AP-induced neuronal damage. 4-AP markedly suppressed TAS, whereas SPA pre-treatment significantly improved antioxidant levels. Values are mean ± SD. *p < 0.05 vs. 4-AP group; &p < 0.05 vs. SPA+4-AP group.*

Effect of SPA on TOS Levels in 4-AP-Induced Neuronal Damage

As shown in **Figure 2**, 4-AP exposure led to a significant increase in TOS levels compared with the control and SPA groups ($p < 0.05$), indicating an elevated oxidative burden. SPA pre-treatment significantly decreased TOS levels compared with the 4-AP group ($p < 0.05$), indicating attenuation of oxidative stress.

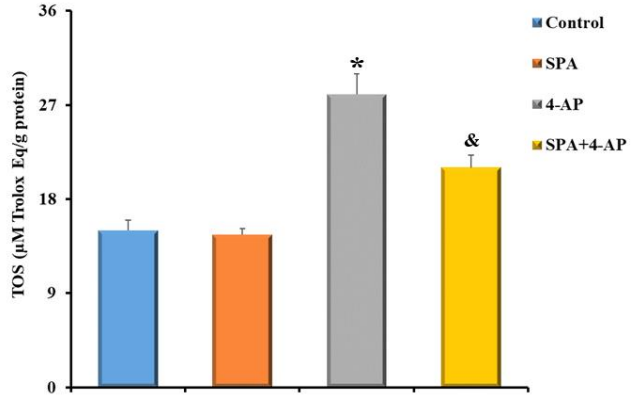

*Figure 2. Effects of SPA on TOS level in 4-AP-induced neuronal damage. 4-AP markedly increased TOS, whereas SPA pre-treatment significantly reduced oxidative levels. Values are mean ± SD. *p < 0.05 vs. 4-AP group; &p < 0.05 vs. SPA+4-AP group.*

Effect of SPA on MDA Levels in 4-AP-Induced Neuronal Damage

Figure 3 shows that MDA levels were significantly elevated in the 4-AP group compared with the control and SPA groups ($p < 0.05$), indicating increased lipid peroxidation. SPA pretreatment significantly reduced MDA levels compared with the 4-AP group ($p < 0.05$), suggesting a protective effect against membrane lipid damage. The SPA group did not differ significantly from the control group ($p > 0.05$).

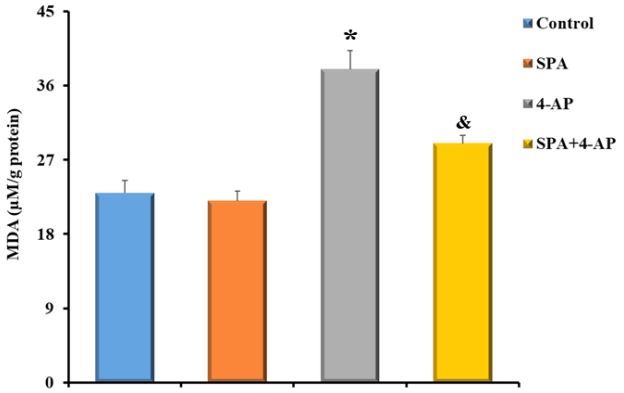

*Figure 3. Effects of SPA on MDA level in 4-AP-induced neuronal damage. 4-AP markedly increased MDA, whereas SPA pre-treatment significantly reduced lipid peroxidation. Values are mean ± SD. *p < 0.05 vs. 4-AP group; &p < 0.05 vs. SPA+4-AP group.*

Effect of SPA on Caspase-3 Levels in 4-AP-Induced Neuronal Damage

As illustrated in **Figure 4**, caspase-3 levels were significantly increased in the 4-AP group compared to the control and SPA groups ($p < 0.05$), indicating activation of apoptotic pathways. SPA pretreatment significantly reduced caspase-3 levels compared with the 4-AP group ($p < 0.05$), demonstrating an anti-apoptotic effect. No significant difference was observed between the control and SPA groups ($p > 0.05$)

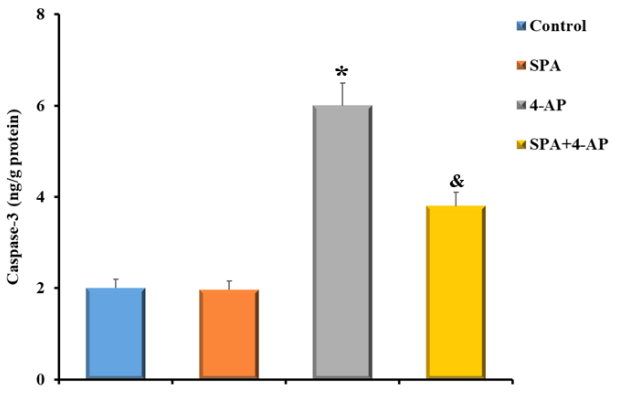

*Figure 4. Effects of SPA on caspase-3 level in 4-AP-induced neuronal damage. 4-AP markedly increased caspase-3 activity, whereas SPA pretreatment significantly reduced apoptosis. Values are mean ± SD. *p < 0.05 vs. 4-AP group; &p < 0.05 vs. SPA+4-AP group.*

DISCUSSION

The data obtained from this study have clarified the possible critical roles of oxidative stress and apoptosis mechanisms in neuronal damage caused by 4-AP and have also revealed that SPA has a significant protective effect against these processes. The decrease in TAS levels after 4-AP administration, while TOS, MDA and caspase-3 levels increased, indicates a disruption of cellular redox balance, which is closely related to apoptotic processes.

Our findings are consistent with some studies in the current literature, which report that the mechanism of neuronal damage caused by 4-AP is mediated by oxidative stress [13,14]. In addition, the current literature emphasizes that oxidative stress is not only a consequence but also an active factor that accelerates neurodegenerative processes [15,16]. A mechanism has been proposed: 4-AP increases neuronal excitability by blocking voltage-dependent K^+ channels, leading to Ca^{2+} overload and mitochondrial dysfunction, thereby increasing ROS production [5–7]. This process leads to increased oxidative stress and deepening of cellular damage. Similarly, some studies have shown a strong correlation between increased ROS production and neuronal death in experimental epilepsy and neurodegeneration models [17]. The increase in TOS and decrease in TAS observed in our study strongly suggest that 4-AP shifts cellular redox homeostasis towards the pro-oxidant direction.

SPA, which has strong antioxidant properties thanks to its phenolic structure, stands out especially for its free radical scavenging activity [10]. The fact that SPA pre-treatment decreased TOS levels while increasing TAS levels in our study suggests that this compound supports cellular antioxidant defense systems. Our findings appear consistent with previous studies reporting that SPA reduces ROS production and protects mitochondrial function [11,18,19].

In addition, recent studies have reported that phenolic compounds regulate cellular redox balance by activating antioxidant defense pathways such as Nrf2/HO-1 [20]. This suggests that SPA is not only limited to having a chemical antioxidant effect, but is also a biological agent that modulates cellular defense mechanisms. Lipid peroxidation, a significant consequence of oxidative stress, was assessed in our study using MDA levels [21, 22, 23]. The increase in MDA levels after 4-AP application suggests that oxidative damage occurs in the cell membranes. Lipid peroxidation, which disrupts membrane integrity and increases ion permeability, also leads to loss of cellular function [12,24]. The significant decrease in MDA levels observed following SPA pretreatment demonstrates that this compound protects membrane lipids from oxidative damage. These results are similar to studies reporting that phenolic compounds protect cellular structure by inhibiting lipid peroxidation [25–27]. Some recent studies have shown that lipid peroxidation plays an important role in neurodegenerative diseases and that antioxidant compounds have a neuroprotective effect in these disease processes [15]. From an apoptotic mechanism perspective, the increase in caspase-3 levels in the 4-AP group reveals that oxidative stress activates intrinsic apoptotic pathways. Increased ROS, impaired mitochondrial membrane permeability, cytochrome c release, and caspase activation are considered the fundamental mechanisms of apoptosis in neuronal cells [24]. Our finding of a decrease in caspase-3 levels observed after SPA pre-treatment is consistent with previous studies reporting that SPA reduces apoptotic markers and supports cellular survival [11,28]. Current studies report that antioxidant compounds can prevent cell death by regulating the interaction between oxidative stress and apoptosis [20]. In addition, it is known that neuronal damage induced by 4-AP is not limited to oxidative stress but also indirectly affects Ca^{2+} dependent signaling pathways. This mechanism is explained by the fact that increased Ca^{2+} levels deepen cellular damage by strengthening apoptotic signaling along with oxidative stress. This suggests that the antioxidant effect of SPA may also indirectly suppress Ca^{2+} dependent damage mechanisms. Studies in the literature show that antioxidant compounds exhibit neuroprotective effects by targeting multiple pathophysiological processes [29–32]. The findings obtained from our study, showing that SPA simultaneously improves all parameters, also support this multifaceted mechanism of action.

A significant strength of this study is the simultaneous evaluation of biochemical markers reflecting distinct stages of oxidative stress and apoptosis. TAS and TOS are parameters indicating the general redox status, MDA lipid peroxidation, and caspase-3 apoptotic activity. The observation of consistent changes in all these parameters strengthens the biological significance and mechanistic integrity of the findings. However, the study also has some limitations. Firstly, this study is based on an in vitro cell model, and the findings must be validated in in vivo systems. Furthermore, a more detailed investigation of SPA's molecular mechanism of action (e.g., ROS measurements, mitochondrial membrane potential, Bax/Bcl-2 ratio, Nrf2 pathways) provides an important roadmap for future studies. In conclusion, this study demonstrates that SPA has a strong protective effect against 4-AP-induced neuronal damage. This protective effect is explained by the suppression of oxidative stress, the reduction

of lipid peroxidation, and the inhibition of apoptotic processes.

Our findings support the possibility of SPA as a potential therapeutic agent in oxidative stress-based neurological diseases and provide an important scientific basis for further mechanistic studies.

CONCLUSION

4-AP induced significant neuronal damage in SH-SY5Y cells by disrupting redox balance and activating apoptotic pathways. Pre-treatment with sinapic acid effectively attenuated these effects by restoring antioxidant capacity, reducing oxidative stress and lipid peroxidation, and suppressing apoptosis. These findings demonstrate that SPA exerts a clear neuroprotective effect against 4-AP-induced neuronal injury. However, further in vivo and mechanistic studies are required to confirm its therapeutic potential.

Authors Contributions

E.C. and B.U. conceived and designed the study. E.C. and Y.E.A. performed the literature search. B.U. and E.C. conducted the statistical analysis. B.U., E.C., and Y.E.A. contributed to manuscript preparation. E.C. and B.U. drafted the manuscript. B.U. supervised the study. All authors critically reviewed, revised, and approved the final version of the manuscript.

Disclosure

The authors have reported no conflicts of interest in preparing and publishing this article.

Ethics committee approval

Ethics committee approval is not required in this study. The study was conducted following the international declaration, guidelines, etc.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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