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Propofol's Neuroprotective Effect Against Cisplatin-Induced Oxidative Neurotoxicity Via Suppression of the TRPM2 Cation Channel

Propofol'ün, TRPM2 Katyon Kanalını Bastırarak Sisplatin Kaynaklı Oksidatif Nörotoksisiteye Karşı Nöroprotektif Etkisi

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ABSTRACT

Objective: Cisplatin (CSP) exhibits strong oxidant and apoptotic effects in tumors, but it also causes adverse neurodegenerative effects by stimulating the TRPM2 cation channel. By regulating mitochondrial reactive free oxygen species (ROS) and excessive Ca^{2+} entry-mediated apoptosis, propofol (PRPF) exhibits antioxidant and neuroprotective properties. However, the action of the TRPM2 in these productions in human SH-SY5Y neuronal cells has not yet been determined. In SH-SY5Y, I investigated the protective effects of PRPF by modifying TRPM2, which affects CSP-induced neuronal mitochondrial function and death.

Materials and Methods: I generated five main groups in the SH-SY5Y as control, PRPF (200 μM for 24h), CSP (25 μM for 24h), CSP + PRPF, and CSP + TRPM2 channel antagonists (25 μM ACA and 100 μM 2APB).

Results: Through TRPM2 stimulation, the incubation with CSP increased the amounts of apoptosis, caspase -3, caspase -9, cell death percentage, ROS, mitochondrial hyperpolarization, TRPM2 current densities, and intracellular free Ca^{2+}. However, the incubation of PRPF through the inhibition of TRPM2 decreased the amounts of these processes.

Conclusions: PRPF treatment via TRPM2 suppression decreased the levels of mitochondrial oxidative stress and neuronal death caused by CSP. One effective therapy option for CSP-induced mitochondrial oxidative neuronal damage is the PRPF.

Keywords: Cisplatin, neuronal injury, oxidative stress, propofol, TRPM2 channel

ÖZ

Amaç: Sisplatin (CPS), TRPM2 kanalını aktive ederek tümör hücrelerinde oksidan ve apoptotik etki meydana getirmesine rağmen bu etkilerin sinir hücrelerindeki yan etkilerinden dolayı CSP kullanımını sınırlandırmaktadır. Propofol (PRPF) mitokondriyal reaktif oksijen türleri (ROS) ve aşırı Ca^{+2} girişine bağlı apoptozisi düzenleyerek antioksidan ve nöroprotektif etki göstermektedir. Bununla birlikte, PRPF'un TRPM2 kanalını düzenleyerek antioksidan ve anti-apoptotik etki meydana getirebileceği insan SH-SY5Y sinir hücrelerinde henüz araştırılmamıştır. Bu çalışmanın amacı PRPF tedavisinin TRPM2 kanalını düzenleyerek sinir hücre ölüm ve mitokondriyal ROS üretimi üzerindeki etkilerinin SH-SY5Y hücrelerinde araştırılmasıdır.

Materyal ve Metot: SH-SY5Y hücrelerinde 5 ana grup oluşturulmuştur. Bu gruplar: Kontrol, PRPF (200 μM ve 24 saat), CSP (25 μM ve 24 saat), CSP + PRPF ve CSP + TRPM2 kanal blokörleri (25 μM ACA ve 100 μM 2APB).

Bulgular: CSP inkübasyonu, TRPM2 kanalını uyararak apoptosis, kaspaz -3, kaspaz -9, hücre ölümü yüzdesi, ROS, mitokondriyal hiperpolarizasyon, TRPM2 akım yoğunlukları ve hücre içi Ca^{+2} miktarı artırdı fakat hücre canlılığını azalttı. Bununla birlikte, PRPF, ACA ve 2APB tedavileri sonraları bu değerler normal değerlerine döndüler.

Sonuç: PRPF tedavisi TRPM2 kanalı inhibe ederek CSP neden olduğu mitokondriyal oksidan ve apoptotik etkileri azalttı. PRPF tedavisi, CSP neden olduğu mitokondriyal oksidatif stres ve sinir hücre harabiyetini önlemede potansiyel kaynak olarak gözükmektedir.

Anahtar Kelimeler: Oksidatif stres, propofol, sinir hasarı, sisplatin, TRPM2 kanalı

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INTRODUCTION

Numerous physiological and pathological circumstances can produce excessive reactive free oxygen species (ROS).[1,2] Some Ca^{2+} permeable cation channels were stimulated by the ROS, resulting in neuron injury. TRP melastatin 2 (TRPM2) is a member of the transient receptor potential (TRP) class.[3,4] While non-specific antagonists such 2-aminoethoxydiphenyl borate (2APB) and N-(p-amylcinnamoyl) anthranilic acid (ACA) decrease TRPM2 activation, oxidants (such as H_2O_2) and ADP-ribose (ADPR) enhance it.[2,5] Recently, it was shown that ACA and 2APB modulate apoptosis and ROS in neuronal cells, including SH-SY5Y cells, by inhibiting TRPM2.[6,7] Through the simulation of caspase -3 and -9, TRPM2 stimulation causes mitochondrial oxidative neurotoxicity and apoptosis, although antioxidant therapy that inhibited it reduced the oxidative and apoptotic activities via the inhibition of TRPM2 in human SH-SY5Y neuronal cells and mouse dorsal root ganglion (DRG).[6,7]

Cisplatin (CSP) is used to treat solid tumors and malignancies. However, significant side effects of CSP, namely oxidative neurotoxicity and apoptosis, restrict its chemotherapeutic potential and cause a decline in the use of CSP.[8,9] Moreover, anticancer medications cause the generation of ROS, which reduce the antioxidant activity of CSP without TRPM2 activation,[10] but glioblastoma tumor cells are killed by CSP-mediated TRPM2 stimulation and ROS.[11] According to recent studies, TRPM2-channel stimulation-induced apoptosis and ROS are highly correlated with increases in CSP-induced nephrotoxicity and optic nerve damage.[12-14]

Propofol (PRPF) is a commonly utilized intravenous sedative-hypnotic drug that is used for anesthesia and sedation.[15] The antioxidant structure of PRPF exhibits similarities to the structure of vitamin E due to the presence of a phenolic hydroxyl group.[8,15] Studies on mouse hippocampus neurons and SH-SY5Y cell lines have shown that PRPF has anti-apoptotic and antioxidant properties.[8,15] By inhibiting the receptor (N-methyl-D-aspartic acid, NMDA) stimulation-caused Ca^{2+} influx in rodent brain, PRPF also reduced oxidative stress.[16-18] According to findings, PRPF inhibited TRP ankyrin 1 (TRPA1) and TRP vanilloid 1 (TRPV1)-mediated in rats to promote cardioprotection.[20,21] In contrast to previous results, PRPF enhanced pain sensitivity by activating the TRPV1 channel in the mouse and human DRGs.[21,22]

To my knowledge, no research has been done on how CSP stimulates TRPM2 in SH-SY5Y neuronal cells to cause oxidative neurotoxicity and apoptosis. Therefore, the purpose of the current investigation was to assess the impact of PRPF on CSP-induced mitochondrial oxidative damage and apoptosis using SH-SY5Y.

MATERIALS AND METHODS

Ethics Committee Approval: The study was approved by the ethics committee and used cells that were grown using commercially available cell culture. This study doesn't need to have ethics committee approval.

Cells: For CSP and PRPF studies, a significant number of SH-SY5Y cells was used.[14,16] According to the results of a recent study,[4] SH-SY5Y cells naturally expressed TRPM2. Two reasons led to the use of SH-SY5Y (ATCC, VA, USA) in the current investigation. The SH-SY5Y was grown in a cell culture environment, as described in previous studies.[4,14] Ten percent fetal bovine serum, 1% antibiotic mixture, and 90% DMEM/Ham's F12 equal mixture made up the medium combination.[4,27]

Experimental Groups: Five 25 cm^2 sterile flasks containing $1x10^6$ SH-SY5Y cells were utilized for the five groups: control (CNT), PRPF, CSP, CSP + PRPF, and CSP + ACA or CSP + 2APB. For twenty -four hours, the SH-SY5Ys of the CNT were kept in the incubator. The cells in the PRPF and CSP + PRPF groups were treated with 200 uM of PRPF, and they were then incubated for a full day.[23] For a whole day, the cells of the CSP received CSP (25 μM).[11,14] The cells of CSP + ACA and CSP + 2APB groups were one hour incubated with 25 μM ACA and 100 μM 2APB after the 25 μM CSP (24h) incubation.[4]

The SH-SY5Y were cultured in Mattek Corporation bottom-glass plates (Ashland, MA, USA) in order to conduct research using an Axio Observer for laser confocal microscopy (LSM-800). Plan-Apochromat 40x1.3 oil objective with Z1/7 microscope (Zeiss, Oberkochen, Germany). In order to prepare for the plate reader and electrophysiology investigations, the cells were grown in sterile flasks.

The Determination of Free Intracellular Ca^{2+} ($[Ca^{2+}]_i$) Amount: To find out how CSP and PRPF affected the $Ca^{2+}]_i$ amount in the cells, I stained the SH-SY5Y by using a fluorescent dye (Fluo 3⁄AM, Cat # F1242, Invitrogen, Istanbul, Türkiye), and they were analyzed in the LSM-800 confocal microscope.[4,6] The TRPM2 channel was blocked by 100 μM 2APB, whereas H_2O_2 (1 mM) activated it. The fluorescence intensity variability was expressed in arbitrary units (a.u.).

Electrophysiology: Using a HEKA EPC-10 double amplifier (Lamprecht, Germany) and a room-temperature patch clamp, conventional electrophysiological measurements (whole-cell) were performed.[3] The components of the intracellular (patch pipette) and extracellular (patch chamber) solutions

were identified by earlier studies.[3,4,5] To produce the Na^+-free extracellular solution, 150 mM Ca^{2+} chelator (N-methyl-D-glucamine, $NMDG^+$) was added. The voltage of cells was adjusted to -60 mV. To lower the intracellular (1 mM ADPR)-generated TRPM2 currents in cells, the study used an extracellular (25 μM ACA) TRPM2 antagonist. As pA/pF, the TRPM2 current findings were shown.

Assays for Caspase-3, -9, Apoptosis, and Cell Viability: Using an automated Infinite PRO 200 microplate reader of Tecan GmbH (Groedig, Austria), the changes in cell viability (MTT) absorbance were evaluated at 490 and 650 nm. An APOPercentage commercial kit (Biocolor Ltd., Co Antrim, UK) was used to assess SH-SY5Y apoptosis. Changes in apoptosis in absorbance at 550 nm were detected using the plate reader (Infinite PRO200). Apoptosis occurs when Ac-DEVD-AMC, a protease substrate of caspase-3, is activated. Moreover, Ac-LEHD-AMC is a fluorogenic substrate of caspase-9. The substrate cleavages at 380–460 were assessed using the Infinite PRO 200 plate reader following obtaining the two substrates from Bachem AG (Bubendorf, Switzerland).

Analysis of Cell Death: In the cell culture conditions, Hoechst 33342 (9 μM) and PI (2 μM) were incubated in the incubator. The LSM-800 was equipped with an inverted microscope (Axio Observer.Z1/7, Zeiss) and an objective (Plan-Apochromat 40x/1.3 Oil DIC-UV) in order to take images of red PI-positive (death) SH-SY5Y and blue live Hoechst 33342. Black and white bright field (BF) pictures of the cells were taken by the Axiocam 702 camera.[4]

Assays for the Production of ROS: For measuring the quantity of ROS in the LSM-800, the ROS probe (DCFH-DA) (Cat # D399, Thermo Fisher Sci.) was used.[24] The ROS studies used the 504 nm excitation and 525 nm emission wavelengths, whereas the green DCFH-DA records kept the argon laser stimulation wavelength at 488 nm.[4]

The Assessment of the Hyperpolarization of the Mitochondrial Membrane (mHP): A cationic carbocyanine dye called JC-1 accumulates in mitochondria. When membrane potentials are hyperpolarized in living cells, the JC-1 probe manifests as an orange -fluorescent J-aggregate and appears as a green-fluorescent monomer, as described by the manufacturer (Thermo Fischer Scientific).[14] The JC-1 fluorescence was also measured with the LSM-800. The laser stimulation wavelengths (488 nm) of LSM-800 were used in the orange JC-1 records, whereas the 593 nm excitation and 595 emission wavelengths were used for recording the images.

Statistical Assays: I presented the results using the mean and standard deviation (SD). The statistical significance was assessed using variance, also known as ANOVA, using the SPSS software (25.0). To determine the statistical significance, a p-value of less than $p < 0.05$ was used.

RESULTS

While Figure 1A shows the green pictures of the fluorescent dye in four groups (CNT, PRPF, CSP, and CSP + PRPF), Figures 1B and 1C show the mean fluorescence intensities as a result of H_2O_2 stimulation and 2APB inhibition, respectively. Compared to the CNT and PRPF, the CSP had greater ($p < 0.05$) variations in Fluo 3/AM intensity (Figure 1B). However, the changes were less noticeable in the CSP + PRPF compared to the CSP alone ($p < 0.05$). As a result, I observed that by activating TRPM2, applying PRPF to SH-SY5Y decreased the CSP-mediated rise of $[Ca^{2+}]_i$ amount.

When SH-SY5Y was not stimulated by ADPR (Figure 2A), the TRPM2 current of cells did not alter. On the other hand, TRPM2 was activated by ADPR (1 mM) stimulation [Figs. 2B and 2B (I-V)]. The pA/pF values of TRPM2 in the cells were greater in the CNT plus ADPR compared to the CNT (Figure 2F) ($p < 0.05$). The pA/pF values of TRPM2 in the cells were further ($p < 0.05$) increased in the CSP plus ADPR by stimulating ADPR [Figures 2C and 2C (I-V)]. In comparison to CSP plus ADPR and CNT plus ADPR, the pA/pF value of TRPM2 in the cells was considerably ($p < 0.05$) lower in the CSP plus ADPR plus ACA and CNT plus ADPR plus ACA (Figure 2F). TRPM2 currents did not increase after ADPR stimulation by treatment PRPF (Figure 2D) or CSP plus PRPF (Figure 2E). The pA/pF values of TRPM2 currents in the cells were considerably ($p < 0.05$) lower in the PRPF and CSP plus PRPF groups than in the CSP plus ADPR group.

Cell viability (Figure 3A) decreased ($p < 0.05$) in the CSP compared to the CNT and PRPF but increased ($p < 0.05$) in the CSP plus PRPF and CSP plus ACA. Apoptosis (Figure 3B), caspase -3 (Figure 3C), and caspase -9 (Figure 3D) activity were also elevated in the CSP, although they were decreased in the CSP plus PRPF and CSP plus ACA groups by the treatment of PRPF and ACA ($p < 0.05$).

BF, PI (red), Hoechst 33342 (blue), and their overlay and 2.5D merge images were indicated in the Figure 4A. The PI positive SH-SY5Y percentage in the CSP was greater ($p < 0.05$) in the PI/Hoechst pictures than in the CNT and PRPF; however, the percentages in the CSP plus PRPF and CSP plus ACA groups were lower ($p < 0.05$) than in the CSP group alone (Figure 4B).

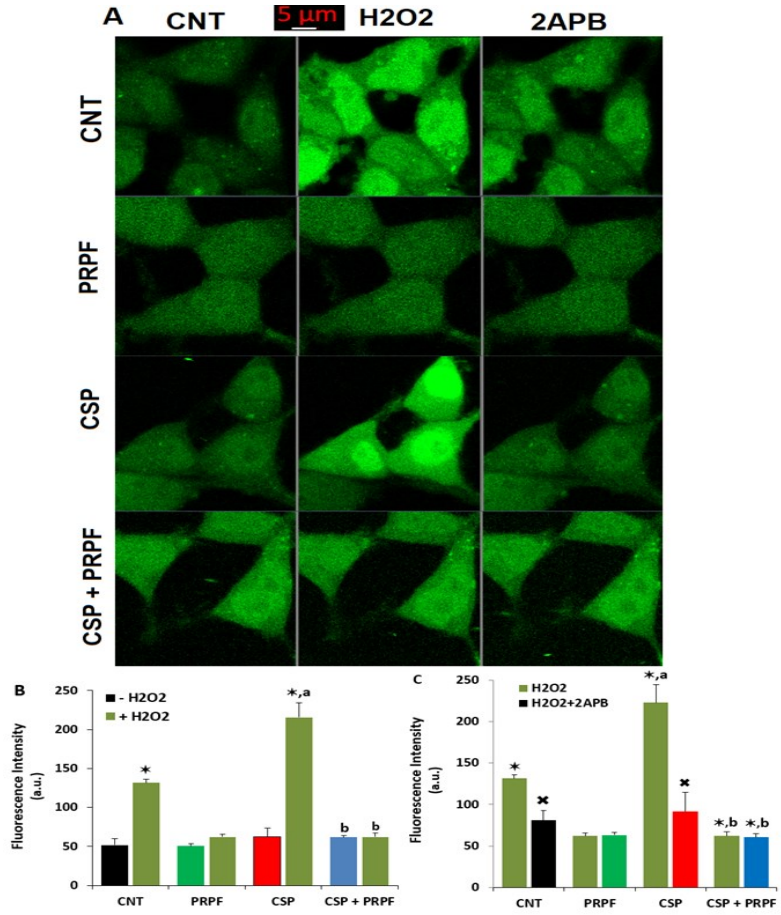

Figure 1. The incubation of propofol (200 µM) modulated cisplatin (25 mM ACA)-caused the increase of $[Ca^{2+}]_i$ in the SH-SY5Y cells. (Mean ± SD); For TRPM2 stimulation, 1 mM H_2O_2 was used, although 100 uM 2APB used for the TRPM2 inhibition; **A**: The Fluo 3/AM typical images; **B:** CNT and CNT + H_2O_2 **C**. CNT + H_2O_2 and CNT + H_2O_2 +2APB; Arbitrary unit: a.u; Scale bar: 5 µm. ([a]$p < 0.05$ versus (vrs.) CNT and PRPF; [b]: $p < 0.05$ vrs. CSP; [ē]: $p < 0.05$ vrs. (- H_2O_2 group); [O]: $p < 0.05$ vrs. (+ H_2O_2 group).

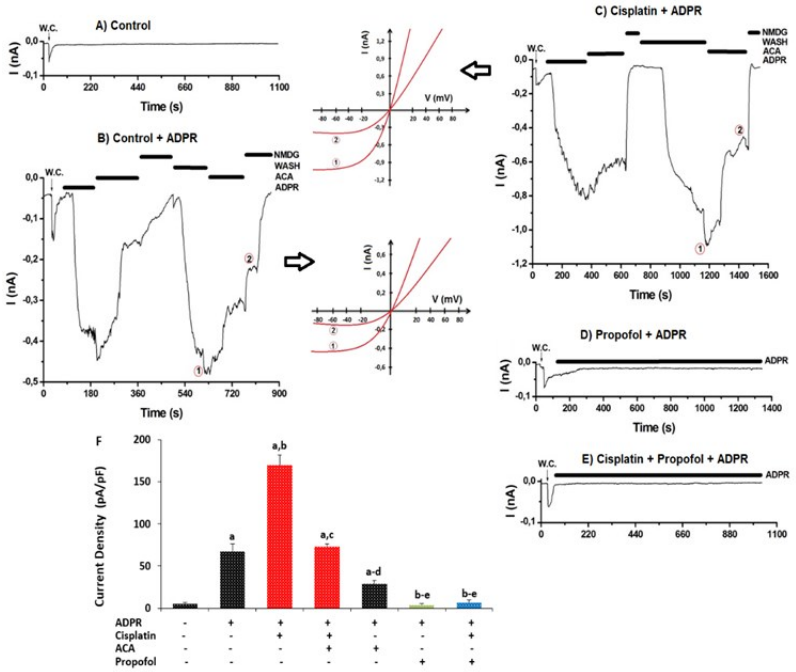

Figure 2. Treatments of propofol (200 µM for 24h) reduced the cisplatin (25 µM for 24h)-mediated TRPM2 pA/pF values. (n = 4 and mean ± SD); The pA/pF values of TRPM2 were induced when 1 mM ADPR was given intracellularly to the cells using a patch pipette; however, these currents were blocked by 25 uM ACA and $NMDG^+$; The whole cell: W.C.; A: Control; B: Control plus ADPR; C: ADPR with cisplatin; D: Propofol; E: Cisplatin plus Propofol plus ADPR; F: The average TRPM2 current densities. The voltage ramps caused by ADPR and ACA in the cells shown in Figs. 3B and 3C, respectively, were denoted by the numbers 1 and 2; The corresponding I-V relationships from Figs. 3B and 3C were displayed in Figs. 3B-I/V and 3C-I/V. ([a:] $p < 0.05$ *vrs*. Control; [b]: $p < 0.05$ *vrs.* control plus ADPR; [c]: $p < 0.05$ *vrs.* cisplatin plus ADPR; [d]: $p < 0.05$ *vrs.* cisplatin plus ADPR plus ACA; [e:] $p < 0.05$ *vrs.* Control+ADPR+ACA).

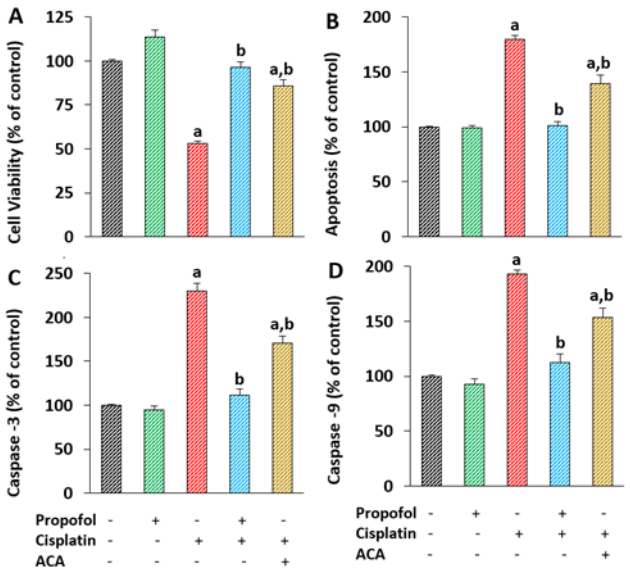

Figure 3. Cisplatin incubation-induced increases in apoptosis and caspases were diminished by the incubations with propofol and ACA (25 µM). (n = 3 and mean ± SD); **A**: Cell Viability; **B**: Apoptosis; C: Caspase-3; **D:** Caspase-9; ([a]p <0.05 *vrs*. CNT. [b]p <0.05 *vrs.* cisplatin).

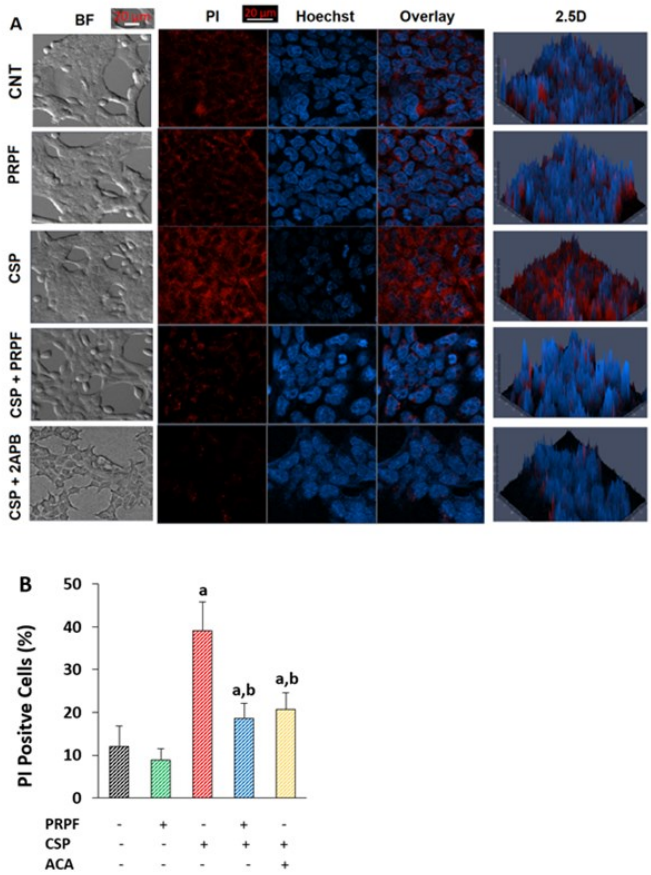

Figure 4. The percentage of PI-positive SH-SY5Y cells was increased by CSP, however this effect was mitigated by the incubation of PRPF. (Mean ± SD); **A**: BF: Bright field, red (PI), blue (Hoechst), overlay, and 2.5D images; **B**: The average percentage changes of PI-positive cells. ([a]: p <0.05 *vrs.* CNT and PRPF; [b]: p <0.05 *vrs*. CSP).

The orange (JC-1), green (DCFH-DA), overlay, and 2.5D (Figure 5A) pictures were saved in the LSM-800 microscope. The mean values of JC-1 (Figure 5B) and DCFH-DA (Figure 5C) were upregulated after CSP incubation ($p < 0.05$). However, the impact of CSP was reduced ($p < 0.05$) by PRPF and 2APB by preventing the production of ROS and mHP in the SH-SY5Y.

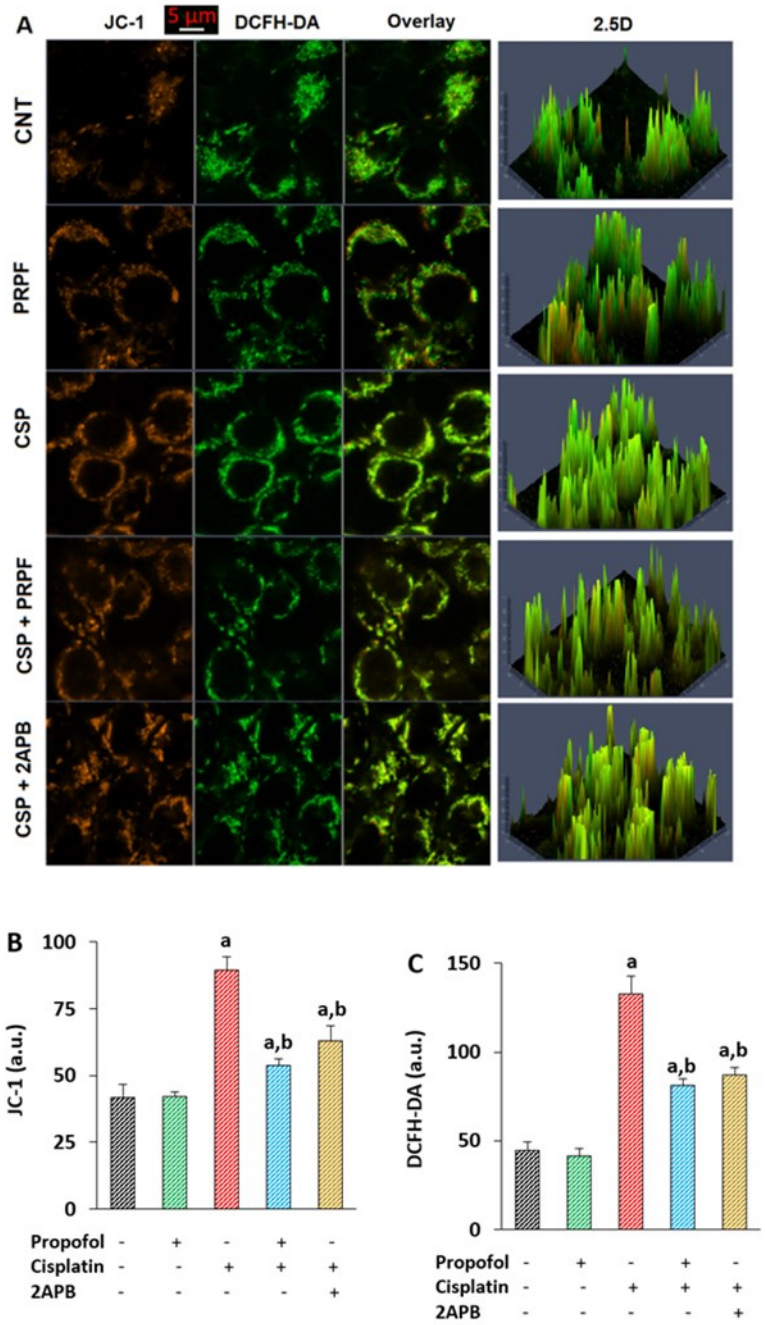

Figure 5. Propofol (200 µM) changed the effects of cisplatin (25 µM) and led to a decrease in ROS and mitochondrial membrane hyperpolarization (mHP). (Mean ± SD); (**A**). The JC-1 (**B**) and DCFH-DA (**C**) mean values are expressed as an a.u.; Scala bar = 5 µm. ([a]$p < 0.05$ *vrs.* CNT and PRPF; [b]: $p < 0.05$ *vrs.* CSP).

DISCUSSION AND CONCLUSION

In the current study. I noticed that the administration of PRPF to the neuronal cells reduced the CSP-mediated elevation of oxidative neurotoxicity and neuronal death through the suppression of TRPM2.

Vitamin E is thought to possess similar properties and could be the source of the PRPF effect.[8,11] Vitamin E and other antioxidants were utilized to inhibit the TRPM2 channel.[3,4,25] According to the current findings, the mHP and ROS of the PRPF treatment group decreased as a result of CSP. It has been demonstrated that many antioxidants offer a variety of protective advantages against harm induced by CSP.[8,10,14,26] Research on SH-SY5Y cell lines and animal hippocampal neurons has demonstrated that PRPF possesses anti-apoptotic and ROS inhibitory characteristics.[8,15]

In the current investigation, I found that PRPF inhibited TRPM2 current density in the cells, which reduced $[Ca^{2+}]_i$, ROS and apoptosis caused by CSP. With the exception of the TRPM2 channel in neural cells, the regulatory function of PRPF has been documented in NMDA receptors and TRP channels. According to the current findings, PRPF inhibited the NMDA receptor in the parenchymal arterioles and hypoglossal motoneurons of the rat brain, which also decreased oxidative stress.[16-18] It is demonstrated that PRPF inhibits the rise in $[Ca^{2+}]_i$ amount caused by NMDA receptor activation in cultivated rat hippocampal neurons.[19] The findings of a recent study showed that PRPF promoted cardioprotection in rats by inhibiting TRPV1.[20] The TRPA1-mediated nitric oxide generation was decreased in the DRG cell line by blocking TRPV1.[20] Activating the TRPV1 channel in the mouse and human DRGs, PRPF increased pain sensitivity, in contradiction to earlier findings.[21,22] As a result, multiple cell-specific mechanisms, including ROS, apoptosis, and TRPM2-stimulation, may be at work when PRPF affects cells.

When CSP is administered, an increase in mitochondrial Ca^{2+} uptake in SH-SY5Y, glioblastoma, and kidney cells causes an increase in the production of ROS and cell death indicators (PI positive cell percentage, apoptosis, caspase -3, and -9) that are caused by mHP.[11,13,14] TRPM2 stimulator effects of CSP on SH-SY5Y cells have been documented.[14] Consequently, the actions raise mHP, which in turn causes the ROS and cell death markers to be upregulated.[4] On the other hand, the suppression of TRPM2 lowers the percentage of PI positive cells, apoptosis, and ROS formation in neuronal cells, including SH-SY5Y.[4,26] Based on the available data, the elevation of mHP in SH-SY5Y was caused by CSP-induced TRPM2 activation (by excess Ca^{2+} influx). This, in turn, led to the overexpression of ROS, cell death, and apoptosis through the rise of caspase -3 and -9, but a decrease in cell viability. Treatment with PRPF and TRPM2 blockers (ACA and 2APB) modulated the alterations. The current findings show that in mouse hippocampus HT22 cells, PRPF therapy reduced cytokine-induced increases in mitochondrial dysfunction, nitric oxide, caspases, and mitochondrial Ca^{2+} buildup.[27] During oxygen glucose deprivation/reperfusion damage, PRPF improved cardiomyocyte cell survival, reduced ROS and mitochondrial dysfunction levels, and prevented apoptosis, caspase -3, and caspase -9.[28] PRPF attenuates H_2O_2-induced ROS and apoptosis (caspase -3 and caspase -9) via the stimulation of mitochondria dysfunction-mediated pathways and antioxidants such as glutathione and superoxide dismutase in neonatal rat cardiomyocytes.[29] In contrast to the results, the experimental animal studies report that administration of PRPF causes brain cell death and neurodegeneration in neonatal rats.[30]

In conclusion, due to the downregulation of TRPM2 stimulation-induced neuronal damage, SH-SY5Y cells were protected from CSP-mediated apoptosis, cell death, and oxidative mediators by incubating PRPF through the attenuation of TRPM2. CSP-induced oxidative damage may be caused by activating TRPM2-mediated excessive Ca^{2+} influx, apoptotic, and oxidant mediators, even if PRPF treatment decreases CSP-induced oxidative neurotoxicity and apoptosis. Further studies in mouse neurons are required to completely understand the molecular and cellular mechanisms behind the identified role of PRPF in TRPM2 stimulation-mediated oxidative and apoptotic neurotoxicity.

Ethics Committee Approval: There are no human and animal data available. This study doesn't need to have ethics committee approval.

Conflict of Interest: No conflict of interest was declared by the author.

Author Contributions: Concept – HÖO; Supervision – HÖO; Materials – HÖO; Data Collection and/or Processing – HÖO; Analysis and/or Interpretation – HÖO; Writing – HÖO.

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