Trifluoperazine an Antipsychotic Drug and Inhibitor of Mitochondrial Permeability Transition Protects Cytarabine and Ifosfamide-Induced Neurotoxicity

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ABSTRACT

The link between Ca^{2+} dysregulation, mitochondria damages, oxidative stress and cellular derangement is particularly evident in neurotoxicity induced by chemotherapeutic agents. In the current study, we investigated effects of trifluoperazine (TFP) as an inhibitor of calmodulin against the cytotoxicity induced by cytarabine (Ara-C) and Ifosfamide (IFOS) on isolated rat neurons and also the mechanisms involved in this toxicity. Isolated rat neurons were pretreated with TFP (100 µM) for 5 min at 37 °C, then Ara-C (226 µM) and IFOS (290 µM) were added in separate experiments. After 3 h, the cytotoxicity, reactive oxygen species (ROS), lysosomal membrane destabilization, mitochondrial membrane potential (MMP), lipid peroxidation (LP), glutathione (GSH) and glutathione disulfide (GSSG) levels were measured. Ara-C and IFOS treatments caused a significant decrease in cellular viability, which was accompanied by ROS generation, GSSG/GSH ratio, lipid peroxidation and lysosomal and mitochondrial damages. On the other hand, TFP (100 µM) pre-treatment attenuated Ara-C and IFOS -induced decrease in cell viability. In addition, TFP (100 µM) pre-treatment significantly protected against Ara-C and IFOS -induced increase in ROS generation, lysosomal and mitochondrial damages, lipid peroxidation levels and decrease in GSH/GSSG ratio. Our data provided insights into the mechanism of protection by TFP against Ara-C and IFOS neurotoxicity, which is related, to neuronal ROS formation and mitochondrial damages.

Introduction

Chemotherapy induced neurotoxicity is the main limitations in cancer patients [1]. Around 30–40 % of patients undergoing chemotherapy experience neurotoxicity, sensory disturbances and symptoms of pain [2]. The most frequent agents causing neurotoxicity are chemotherapy agents [2]. A common mechanism underlying the neurotoxicity is physical damage to the neurons by chemotherapeutic agent [3]. The physical damage induced by anticancer drugs leads to mitochondrial damages, oxidative stress, inflammation, apoptosis, electrophysiological disturbances functional and impairment in neurons [3]. Chemotherapeutic agents produce ROS and induce apoptosis in cancer cells [4]. However, ROS produced during cancer therapy may intervene with the normal tissues and cells and may lead to the various toxic events like neurotoxicity, ne-

phrotoxicity cardio toxicity and other toxicities. Mammalian nerves are well-known to be more sensitive to oxidative stress due to their mitochondria rich axoplasm weak cellular antioxidant defenses and high content of phospholipids [5]. It has been reported that functional and structural deteriorations caused by chemotherapeutic agents enhance mitochondrial free radical production [6]. Oxidative stress caused by mitochondria pathway lead to bioenergetic failure, depletion of antioxidant defenses, mitochondrial dysfunction, bio molecular damage, microtubular disruption, neuroinflammation, mitophagy impairment, ion channel activation, demyelination, and finally neuronal death through apoptosis [7]. Accumulation of dysfunctional mitochondria due to chemotherapeutic agents increase the vicious cycle of oxidative damage to the mitochondria and bio molecules that leads a feed-forward mechanism and more accumulation of ROS and reactive nitrogen species (RNS) in the neurons [8]. In this study, we focused on two main chemotherapeutic drugs, cytarabine and ifosfamid with neurotoxicity potential.

Ara-C, as first line chemotherapy is used in treatment of hematological cancers especially in acute myeloid leukemia [9]. A recent study showed that cytarabine inhibits DNA polymerase γ and leads to reduction in mitochondrial DNA (mtDNA) content, ROS generation and oxidative damage in neurons. This study suggests that cytarabine neurotoxicity in neurons originates in mitochondria and continuous with oxidative stress [10]. Also, IFOS, a structural analog of cyclophosphamide, is an alkylating chemotherapy agent used for a wide range of solid and hematologic malignancies [10]. IFOS has been reported to have adverse neurological effects [11]. Limited works were done to address mechanisms underlying neurotoxicity of IFOS. It has been suggested that chloroethylamine as an IFOS metabolite induce the formation of thialysine ketamine which inhibits electron-binding flavoproteins in the mitochondrial respiratory chain that probably leads to mitochondrial damages and oxidative stress [12]. Oxidative stress and mitochondrial damages have been reported of cyclophosphamide as a structural analog IFOS [13].

TFP, a long-established high potency typical antipsychotic drug used in the treatment of schizophrenia-like and schizophrenia illnesses. Also, TFP as an inhibitor of calmodulin, can reduce the cellular and mitochondrial Ca^{2+} overload [14, 15]. It has been reported that TFP can interact with the inner membrane of mitochondria, acquired antioxidant activity toward processes with potential toxicity in cell death, such as ROS formation, lipid peroxidation of the membrane and MMP collapse and release of cytochrome c [16]. Several studies have also been reported that TFP, significantly protected mitochondria against the deleterious effects of Ca^{2+} and hydrogen peroxide [17, 18]. The aim of our study was therefore to explore the effects of Ara-C and IFOS on isolated rat neurons as well as assessing the protective effects of TFP against Ara-C and IFOS -induced oxidative stress and mitochondrial damage.

Materials and Methods

Animals

Clean grade wistar rats weighting 150 – 200 g were purchased from the Pasteur Institute of Iran (Tehran, Iran). This study was approved by the Research Ethics Committee at the Shahid Beheshti University of Medical Sciences, and performed strictly in accordance with institutional and international guide for animal care.

Chemicals

Fetal Bovine Serum (FBS), B-27TM supplement (50X), Neurobasal TM medium, serum free medium, Dulbecco's Modified Eagle Medium (DMEM), Trypsin, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), Ethylenediaminetetraacetic Acid (EDTA), β-NGF and L-glutamine (200 mM) were purchased from GIBICO (Gaithersburg, MD, USA). Trifluoperazine (TFP), cytarabine (Ara-C) and Ifosfamide (IFOS) was purchased from Abidi Pharmaceutical Co. (Tehran, Iran). L- carnitine (LC), Sodium Pyruvate, Glutamine, Hank's Balanced Salt Solution (HBSS), trypan blue, 2′,7′-Dichlorofuorescin Diacetate (DCFH-DA), Acridine Orange (AO), N-ethylmaleimide (NEM), Rhodamine123, N-(2-hydroxyethyl) piperazine-N′-(2-ethanesulfonic acid) (HEPES), bovine serum albumin (BSA), were obtained from the Chemical Co. were purchased from Sigma (Cambridge, MA, USA).

Isolation of primary rat brain neurons

The rats were sacrificed by cervical dislocation. The brain was removed and put in HBSS buffer. The blood vessels and pia mater were removed. The brain was incubated in 0.125 % trypsin at 37 °C for 10 – 15 min, rinsed twice with HBSS, and prepared into cell suspension in DMEM containing 10 % FBS. The cell suspension was filtered through a sterile 70 µm filter, and seeded into DMEM supplemented with 10 % FBS, 1 % sodium pyruvate and 1 % glutamine. After 4 h, the medium was replaced with neurobasal medium containing 2 % B27 and 1 % glutamine [19].

Cell viability assay

The cell viability was measured by the MTT assay. Cells at 70 % confluence in 6-well plates were incubated for 3 h in normal medium or medium with different concentration of Ara-C (0–1000) and IFOS (0–1000) or IC50 3 h Ara-C/IFOS + 100 µM TFP. Cells were collected and stained using trypan blue exclusion dye under optical microscope at 10x.

Measurement of ROS

The rate of ROS generation was evaluated by using the probe DCFH-DA. In the presence of ROS, DCFH is oxidized to highly fluorescent dichlorofluorescein (DCF). Cells at 70 % confluence were treated for 1, 2 and 3 h in normal medium or medium with different concentrations of Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) or IC50 3 h Ara-C/IFOS 100 µM TFP. After the incubation time, medium was replaced by 10 µM DCFH-DA containing medium, after 15 min incubation, the fluorescence intensity was measured by fluorescence spectrophotometer (Shimadzu RF5000U) at the excitation wavelength of 495 nm and the emission wavelength of 530 nm [20].

Measurement of MMP collapse

The change in the MMP in the isolated neurons were measured by using the cationic fluorescent dyerhodamine-123. Cells at 70 % confluence were treated for 1, 2 and 3 h in normal medium or medium

with different concentrations of Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) or IC50 3 h Ara-C/IFOS + 100 µM TFP. After the incubation time, medium was replaced by 1 µM rhodamine-123 containing medium, after 15 min incubation, the medium was removed, and the fluorescence intensity was measured by fluorescence spectrophotometer (Shimadzu RF5000U) at the excitation wavelength of 470 nm and the emission wavelength of 540 nm [21].

Measurement of lysosomal membrane destabilization

The isolated neurons lysosomal membrane integrity was assessed from the redistribution of the lipophilic dye acridine orange. Cells at 70 % confluence were treated for 1, 2 and 3 h in normal medium or medium with different concentrations of Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) or IC50 3 h Ara-C/IFOS + 100 µM TFP. After the incubation time, medium was replaced by 5 µM acridine orange containing medium. After 10 min incubation, the fluorescence intensity was measured by fluorescence spectrophotometer (Shimadzu RF5000U) at the excitation wavelength of 470 nm and the emission wavelength of 540 nm [22].

Measurement of lipid peroxidation

Lipid peroxidation was measured by using the thiobarbituric acid assay and malondialdehyde (MDA) formation. The cells were exposed for 1, 2 and 3 h with different concentrations of Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) or IC50 3 h Ara-C/IFOS + 100 µM TFP. After the incubation, cells were washed with PBS, and then lysed with PBS contain 2 % triton. 100 µl of cell lysate was mixed with 200 µl of thiobarbituric acid (TBA) reagent (containing 3.75 % TCA and 0.0925 % TBA) and the mixture was incubated at 90 °C for 60 min. After cooling, the mixture was centrifuged at 1000 × g for 10 min. Calorimetric absorption was measured at 530 nm [23].

Measurement of GSH and GSSG

GSH and GSSG levels in Ara-C/IFOS-treated isolated neurons were measured by Hissin and Hilf method [24]. After treatment of isolated neurons with different concentrations of Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) or IC50 3 h Ara-C/IFOS + 100 µM TFP, the cells were lysed with 0.5 ml of trichloroacetic acid (TCA) 10 % and centrifuged at 11 000 × g for 2 min. For assessment of GSH, supernatant was diluted with phosphate-EDTA buffer and incubated with 100 µl of the o-phthalaldehyde (OPT) solution for 15 min at room temperature. For determination of GSSG, cells supernatant was diluted with NaOH 0.1N solution and before incubation with OPT, 200 µl of N-ethylmaleimide (NEM) solution was incubated with supernatant for 30 min. The fluorescence intensity was measured by fluorescence spectrophotometer (Shimadzu RF5000U) at the excitation wavelength of 350 nm and the emission wavelength of 420 nm.

Statistical analysis

All data are presented as the Mean ± Standard Deviation (SD) with three separate experiments. Data were analyzed by GraphPad Prism 5 (GraphPad Software, La Jolla, CA) using one and two-way analysis of variance followed by post hoc Tukey and Bonferroni test. P value of less than 0.05 was considered as statistically significant.

Results

Cell Viability

Cytotoxic effects of Ara-C (0–1000 µM) or IFOS (0–1000 µM) on isolated neurons showed in the ▶ **Fig. 1 a-b**. Ara-C and IFOS caused dose dependent cytotoxicity on the cells and significantly ($P < 0.05$) reduced cell viability in all used concentrations. The presented data at ▶ **Fig. 1 c-d** demonstrated that TFP (100 µM), as a mitoprotective agents prevent of cytotoxicity induced by Ara-C and IFOS.

ROS production

The effects of Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) on the generation of ROS in isolated neurons are shown in ▶ **Fig. 2 a-b**. Ara-C/IFOS has induced dose and time dependent ROS generation in isolated neurons. When the isolated neurons were simultaneously treated with Ara-C/IFOS + TFP (100 µM), the mean fluorescence intensities were significantly decreased compared to treated groups with Ara-C/IFOS (▶ **Fig. 2 a-b**).

MMP collapse

The effects of Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) on the MMP of isolated rat neurons were presented in the ▶ **Fig. 3 a-b**. Ara-C/IFOS induced statistically ($P < 0.05$) MMP collapse in dose and time dependent manner. As shown in the ▶ **Fig. 3 a-b**, collapse of mitochondrial membrane potential was inhibited after treatment of neurons with Ara-C/IFOS by TFP (100 µM) at toxic doses.

Lysosomal membrane destabilization

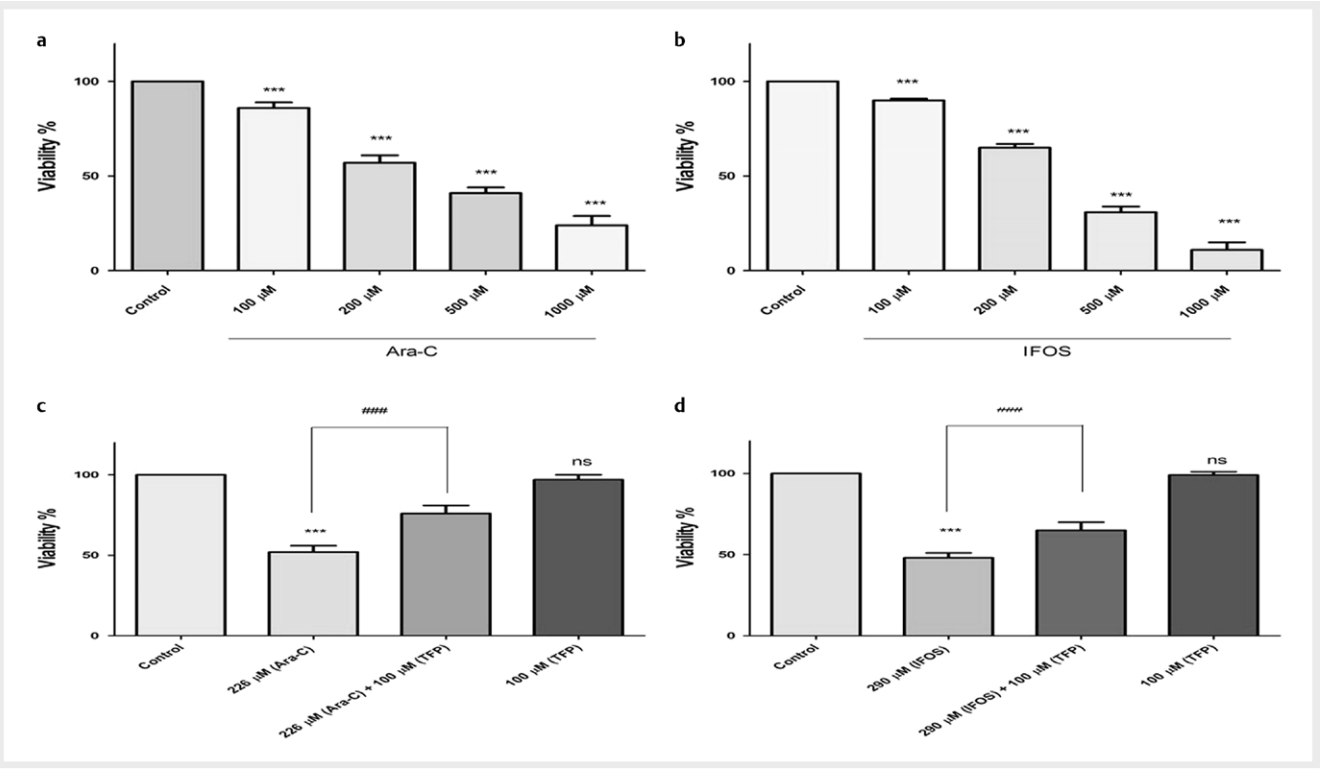
The effect of Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) showed in ▶ **Fig. 4a-b**. Ara-C/IFOS induced statistically lysosomal damages in dose and time dependent manner. Lysosomal membrane destabilization was inhibited after treatment of isolated neurons with Ara-C/IFOS by TFP (100 µM) at toxic doses (▶ **Fig. 4 a-b**).

Lipid peroxidation

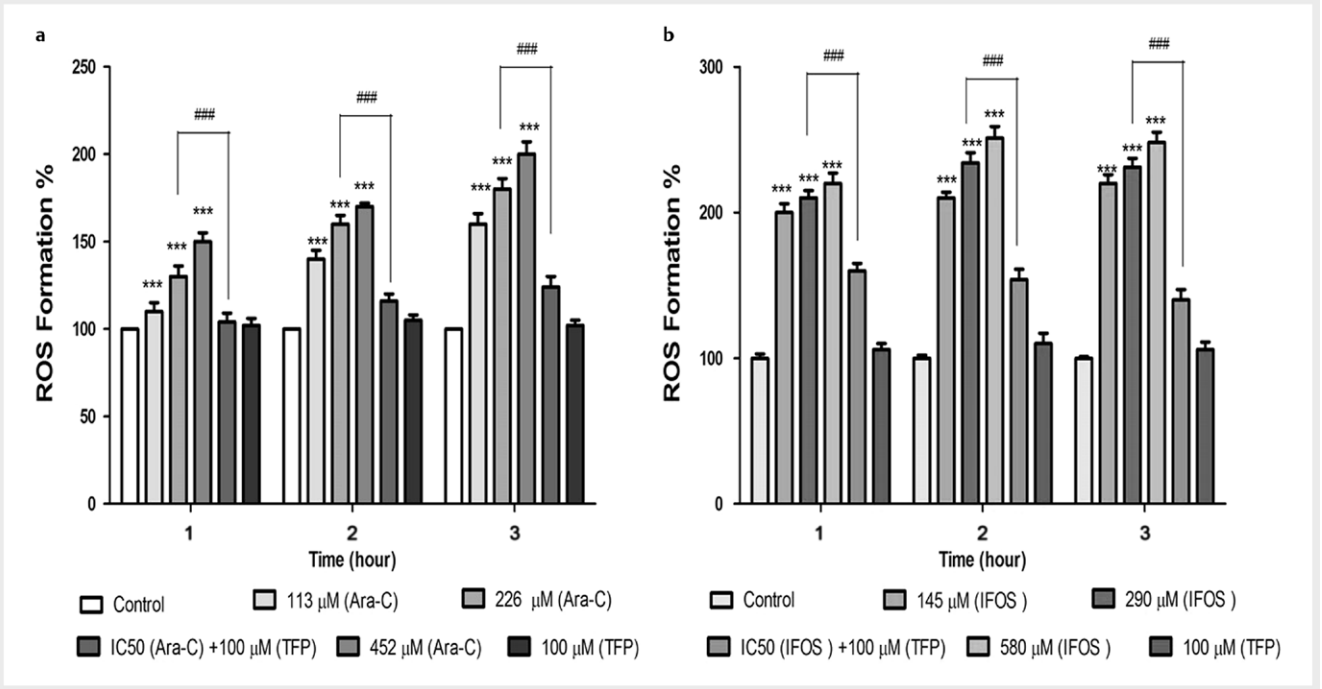
Lipid peroxidation as an indicator of oxidative damage to the lipids was measured in isolated neurons using MDA assay as a byproduct of lipid peroxidation. We showed that the amount of MDA as the result of lipid peroxidation significantly ($P < 0.05$) increased when cells incubated Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) at toxic dose during 1 – 3 h (▶ **Fig. 5 a-b**). Pretreatment of isolated neurons with by TFP (100 µM) at toxic doses significantly ($P < 0.05$) decreased the MDA level after 3 h. incubation time (▶ **Fig. 5 a-b**).

GSH and GSSG content

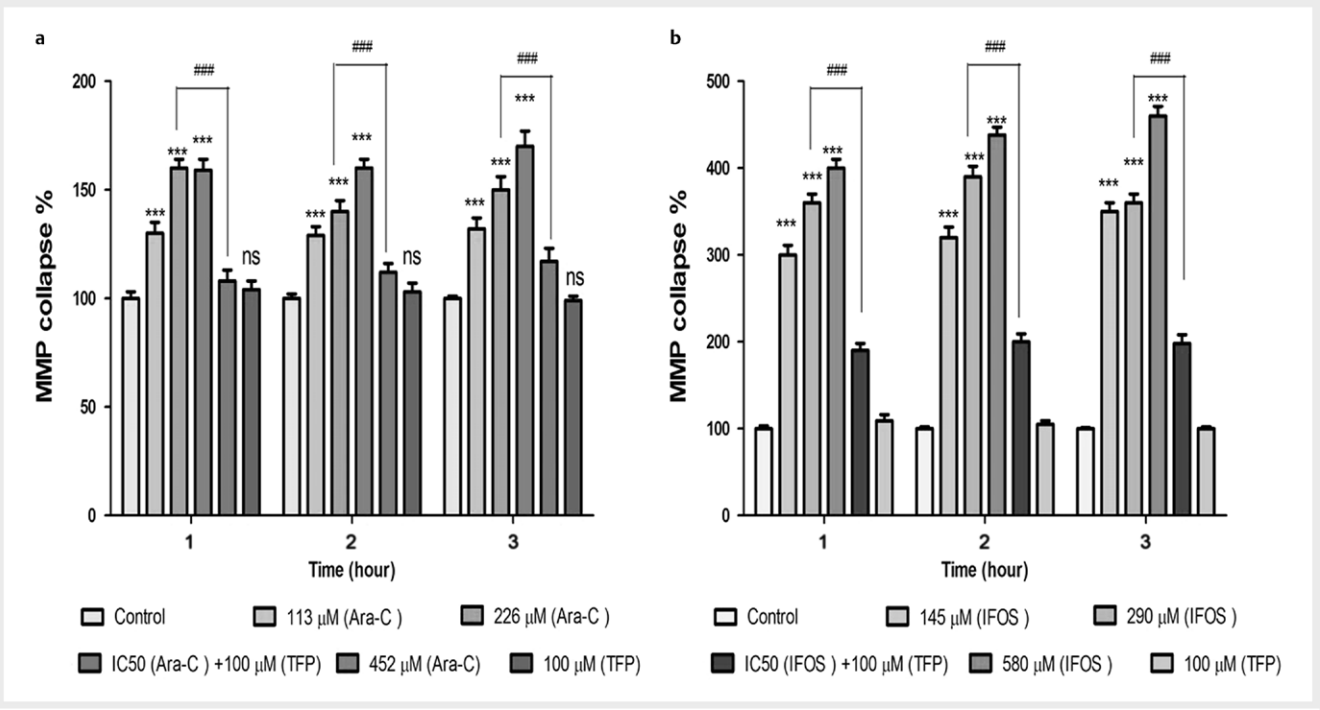
Isolated neurons were treated with Ara-C (113, 226 and 452 µM) or IFOS (145, 290 and 580 µM) and 1 h after treatment decrease in GSH/GSSG ratio were observed. The effects of Ara-C/IFOS on GSH and GSSG content are shown in ▶ **Fig. 6 a-b**. This finding indicates a significant ($P < 0.001$) changes in GSH/GSSG ratio in concentration-dependent manner. Pretreatment of isolated neurons with TFP (100 µM) inhibited decrease of GSH/GSSG ratio. GSH/GSSG



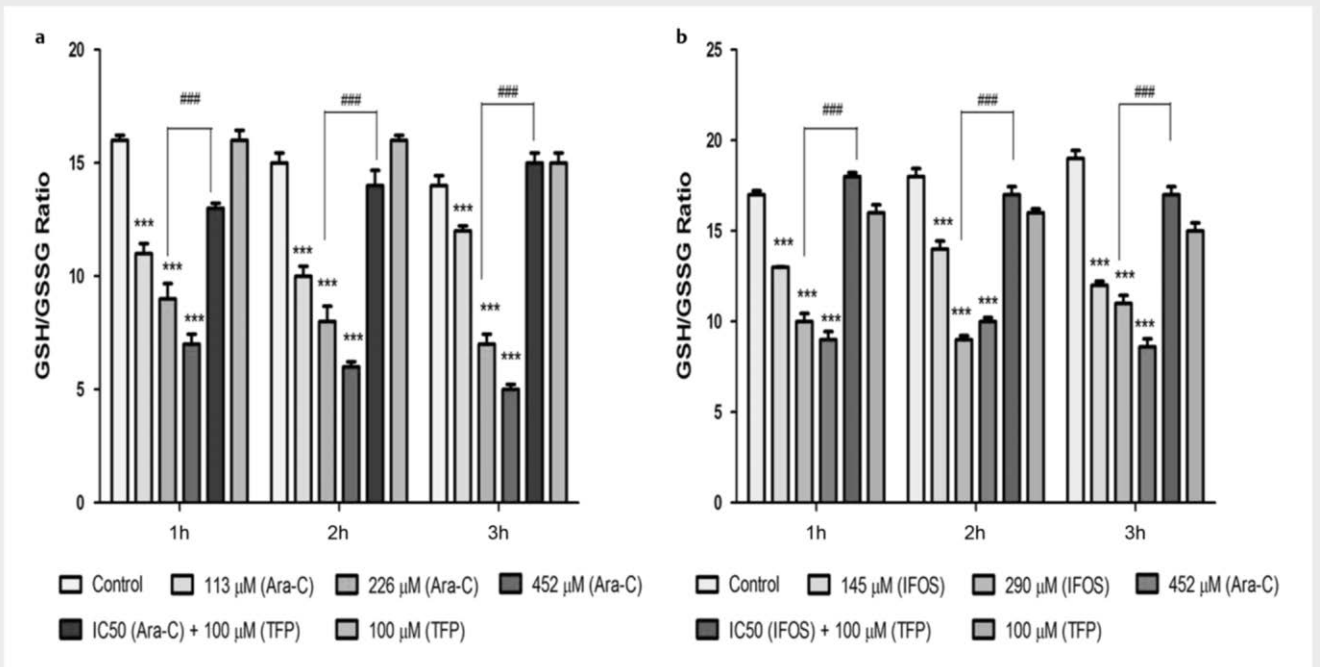
▶ **Fig. 1** Viability of isolated neurons following treatment with Ara-C/IFOS for 3 h (**a** and **b**) and protective effect of TFP against Ara-C/IFOS toxicity (**c** and **d**). Cell viability determined by trypan blue assay after incubation of the cells with different concentration of Ara-C/IFOS. Ara-C and IFOS both decrease neuron viability in a dose-dependent manner and this decrease is significant at concentration higher than 100 µM. (*** $p<0.001$ vs. control) (**a** and **b**). Protective effect of TFP (100 µM) are tested against cytotoxicity induced Ara-C/IFOS (**c** and **d**). Presented data showed these agents significantly decreased cell death compared to treated groups with Ara-C/IFOS alone. (*** $p<0.001$ vs. control, ### $p<0.001$ vs. treated groups with Ara-C/IFOS).



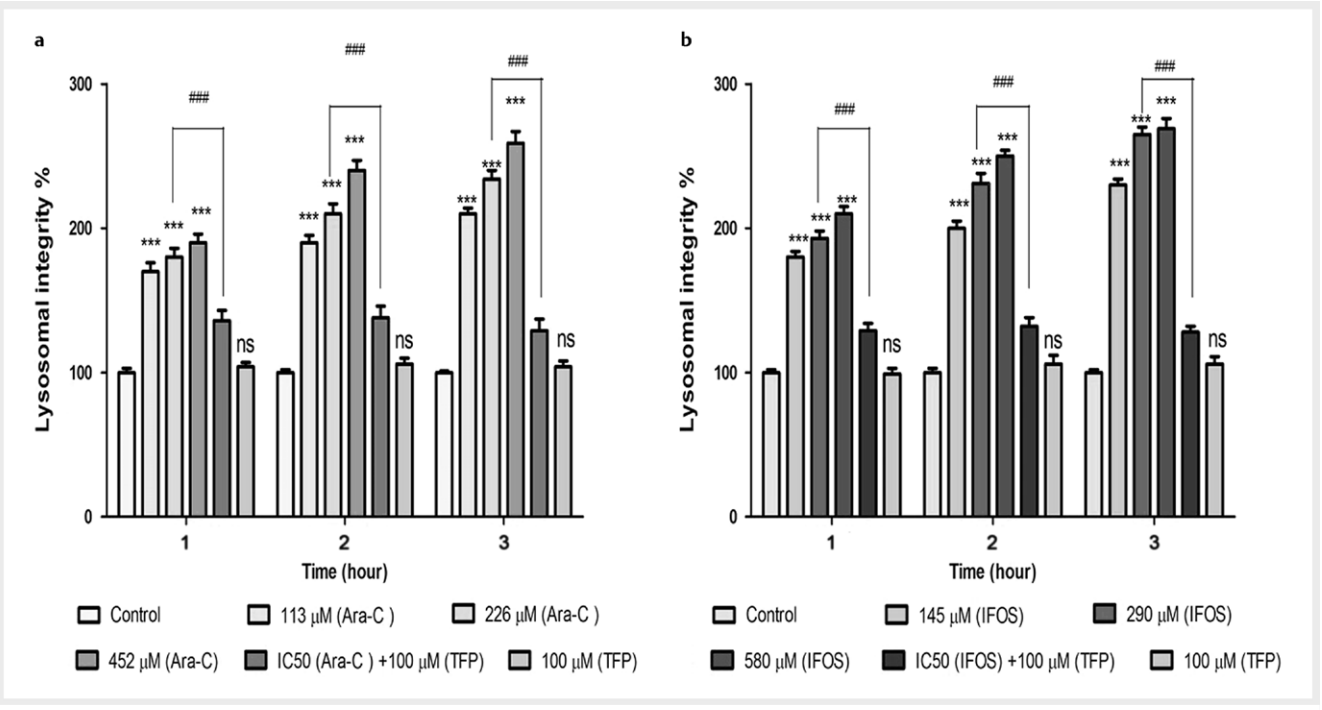
▶ **Fig. 2** ROS Generation in isolated neurons after incubation with Ara-C/IFOS for different concentrations and time (1, 2 and 3 h) intervals and protective effect of TFP against Ara-C/IFOS induced ROS formation (**a**-**b**). Ara-C/IFOS has induced dose and time dependent ROS production (**a**-**b**). TFP, inhibited Ara-C/IFOS -induced generation of ROS in isolated neurons. (*** $p<0.001$ vs. control, ### $p<0.001$ vs. treated groups with Ara-C/IFOS).



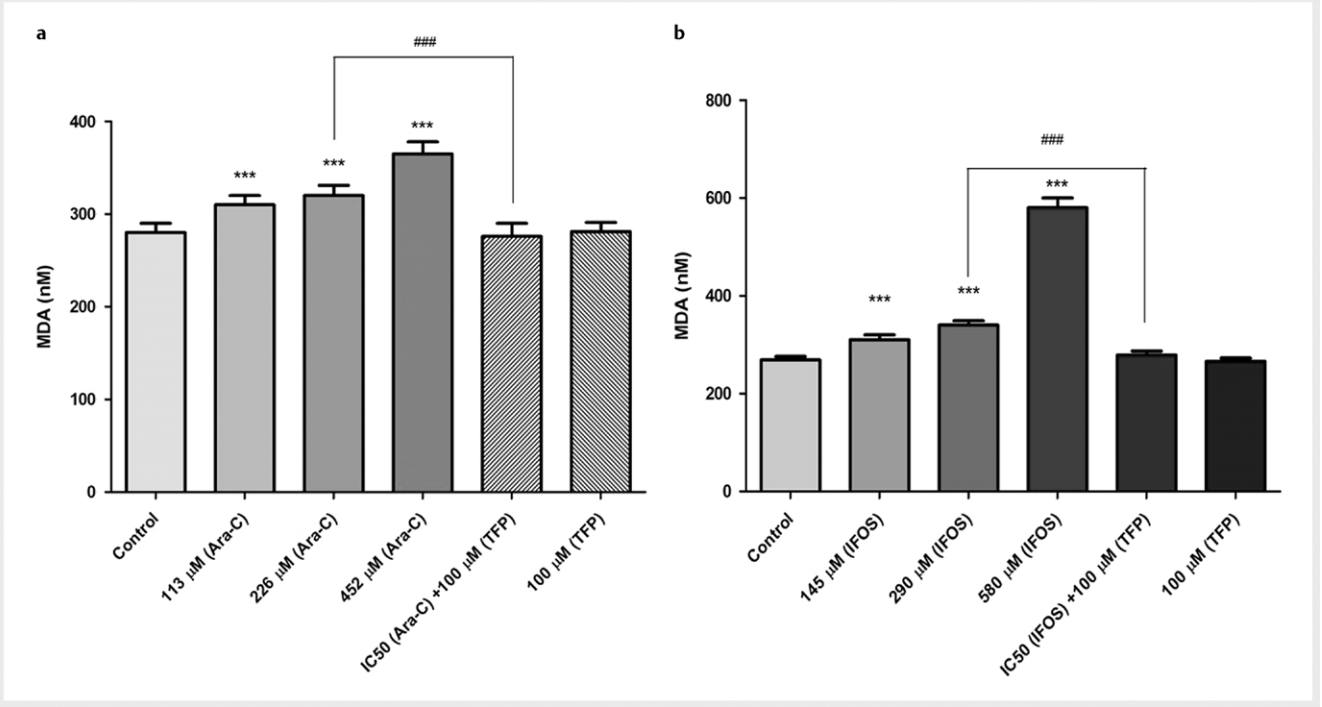
▶ **Fig. 3** Collapse of mitochondrial membrane potential (MMP) in isolated neurons following incubation with Ara-C/IFOS for 1, 2 and 3 h and protective effect of TFP against Ara-C/IFOS induced mitochondrial damages (**a**-**b**). Collapse in mitochondrial membrane potential started 1 h after treatment of isolated neurons with Ara-C/IFOS at three concentrations. Ara-C/IFOS-induced mitochondrial membrane potential collapse was time and concentration dependent (P < 0.001) (**a**). TFP prevented Ara-C/IFOS-induced collapse in isolated neurons. (*** p < 0.001 vs. control, ### p < 0.001 vs. treated groups with Ara-C/IFOS).



▶ **Fig. 4** Lysosomal membrane destabilization in isolated neurons after incubation with Ara-C/IFOS and protective effect of TFP against Ara-C/IFOS-induced lysosomal damages (**a**-**b**). After 1, 2 and 3 h treatment, Ara-C/IFOS caused significant (P < 0.001) lysosomal membrane leakage (**a**). TFP prevented Ara-C/IFOS-induced lysosomal membrane leakage. (*** p < 0.001 vs. control, ### p < 0.001 vs. treated groups with Ara-C/IFOS).



▶ **Fig. 5** Induction of lipid peroxidation in isolated neurons and after incubation with Ara-C/IFOS and protective effect of TFP against Ara-C/IFOS-induced oxidative damages (**a**-**b**). Lipid peroxidation significantly increased when isolated neurons were incubated with Ara-C/IFOS (**a**). TFP prevented Ara-C/IFOS-induced lipid peroxidation. (*** p<0.001 vs. control, ###p<0.001 vs. treated groups with Ara-C/IFOS).



▶ **Fig. 6** Effect of Ara-C/IFOS on GSH/GSSG ratio and protective effect of TFP against Ara-C/IFOS-induced GSH depletion (**a**-**b**). As demonstrated, significant (P<0.001) GSH/GSSG ratio decrease was found after treatment with Ara-C/IFOS. TFP prevented depletion of GSH (*** p<0.001 vs. control, ###p<0.001 vs. treated groups with Ara-C/IFOS).

ratio significantly ($P < 0.05$) increased at 1,2 and 3 h following co-treatment with Ara-C/IFOS + TFP in isolated neurons.

Discussion

The reactive oxygen species are produced in the cell through several pathways. The generated ROS within cells are rapidly removed by various non-enzymatic and enzymatic mechanisms [25]. Disruption of the antioxidant-oxidant equivalence originates oxidative stress and cell damage [25]. The oxidative stress produced by anticancer drugs cause side effects in the treated patients [26]. When the formation of ROS oversteps repair capacities, cellular adaptive biological molecules such as proteins, membrane phospholipids and nucleic acids, become damaged because of oxidative reactions. Finally, oxidative stress leads to the defeat of normal cellular functions and even cell death [27]. Methotrexate, Ara-C, and IFOS are the anticancer drugs that most frequently cause central nervous system (CNS) toxicity. These agents induce central neurotoxic adverse effects [28]. In the current study, we focused on cytotoxicity of Ara-C, and IFOS on isolated brain neurons. Our measured toxicity parameters showed that Ara-C, and IFOS significantly induce ROS formation. Previous studies showed that Ara-C, and IFOS increase the ROS formation and oxidative stress in normal and tumor cells [29, 30]. Also, other examinations showed that both drugs induce lipid peroxidation and decrease GSH in isolated neurons. Our results are consistent with previously published data examining Ara-C, and IFOS-induced oxidative stress in several systems [29, 30].

Drug-induced mitochondrial toxicity has been investigated well for over 50 years in academic settings. Drugs may inhibit mitochondrial function in many different ways [31]. Mitochondrial toxicity has been identified to cause organ toxicity to the central nervous system, kidney, skeletal muscle, heart and liver [32]. Drug classes identified to cause mitochondrial toxicity are anti-diabetic, cholesterol lowering, anti-depressants, pain medications, certain antibiotics, and anti-cancer drugs [33]. Most of drug-induced mitochondrial toxicities were not detected in preclinical animal studies. Most of these effects have been proven through studies in isolated cells and mitochondria [33]. Our results showed that Ara-C, and IFOS significantly induce mitochondrial membrane potential collapse in isolated rat neurons, which is consistent with previously published data examining anticancer drugs-induced mitochondrial toxicity in other tissues.

Lysosomes serve as the cellular recycling center and are filled with numerous hydrolases that can degrade most cellular macromolecules [34]. Lysosomal membrane permeabilization and the consequent leakage of the lysosomal content into the cytosol leads to lysosomal cell death [34]. This form of cell death is mainly carried out by the lysosomal cathepsin proteases and can have apoptotic, apoptosis-like or necrotic features depending on the extent of the leakage and the cellular context [34]. Many lipophilic, weakly basic drugs accumulate in lysosomes and apply complex, pleiotropic effects on organelle structure and function [35]. In the current study we observed lysosomal membrane permeabilization after exposure of isolated neurons with Ara-C, and IFOS. However, this effect may be due to the production of reactive oxygen species or mitochondrial damage caused by these drugs which is known as lysosomal and mitochondrial crosstalk [36].

There are conflicting opinions regarding the administration of antioxidants during cancer therapy [37]. Antioxidants may reduce the effectiveness of chemotherapies, which are based on increasing oxidative stress in tumor cells [37]. For example, Ara-C was toxic to MLH1 and MLH2 deficient tumor cells, but this cytotoxicity was reduced by antioxidants [30]. Also, certain researchers revealed mitochondrial dysfunction and mitotoxicity contribute to amplified oxidative stress [38]. Therefore, mitochondrial protective agents may be a good promising strategy form the inhibition of anticancer drugs toxicity. Mitochondrial permeability transition pore (mPTP) plays a central role in alterations of mitochondrial structure and function leading to neuronal injury [39]. Many anticancer drugs like studied ones in this work, trigger the formation of mPTP, resulting in increased oxidative stress, impaired mitochondrial respiration function, decreased mitochondrial membrane potential and release of cytochrome c [40]. Therefore, mitochondrial membrane permeability inhibitors can block the effects dependent on the opening of the MPT pore. Inhibition of mPTP has appeared as a promising approach for neuroprotection and development of well-tolerated mPT inhibitors with favorable blood-brain barrier penetration is highly warranted [41]. 28 clinically available drugs with a common heterocyclic structure were identified as mPT inhibitors [41]. In the current study we tested neuroprotective effect of TFP as a mPT inhibitor [42] against mitochondrial and oxidative stress induced by Ara-C, and IFOS. Our results showed that TFP as an antipsychotic drug and inhibitor of mPT reversed all the toxicities induced by Ara-C, and IFOS.

In summary our result confirmed that Ara-C, and IFOS induce cytotoxicity through mitochondrial dysfunction, oxidative stress and lysosomal damages in CNS neurons. Also, quite interestingly our data showed that TFP as an antipsychotic drug and inhibitor of mPT with good penetration through blood-brain barrier can reverse Ara-C, and IFOS -induced neurotoxicity in isolated neurons.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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