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Paclitaxel induces neurotoxicity through endoplasmic reticulum stress

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ABSTRACT

Due to chemotherapy, the majority of breast cancer patients survive, but frequently complain of chemotherapy-associated cognitive impairment. This phenomenon is termed "chemobrain" or "chemofog" in the literature. However, its mechanisms are unclear. The objective of this study was to investigate the mechanisms of paclitaxel (Px)-induced neurotoxicity, with a focus on endoplasmic reticulum (ER) stress.

To investigate Px-induced neurotoxicity and ER stress induction, SK-N-SH cells were treated with 1, 10, 50, and 100 μM Px for 24 h. Neurotoxicity was assessed using MTS viability assays, and ER stress was assessed by evaluating the expression of phosphorylated eIF2α (phospho-eIF2α), C/EBP homologous protein (CHOP), and cleaved caspase 4 and caspase 3 (the active form of each caspase). Furthermore, to investigate whether immunoglobulin heavy-chain binding protein (BiP) inducer X (BIX), which induces the molecular chaperone BiP, could attenuate Px-induced neurotoxicity, SK-N-SH cells were pre-treated for 12 h with 3.5 μM BIX before Px treatment.

Neurotoxicity was observed in SK-N-SH cells treated with Px in a dose-dependent manner compared with vehicle control. Furthermore, phospho-eIF2α, CHOP, and activated caspase 4 and caspase 3 were significantly induced in Px-treated cells. In addition, pre-treatment with BIX significantly attenuated the induction of CHOP and activated caspase 4 and caspase 3. The viability of BIX pre-treated cells prior to Px treatment was significantly increased compared with cells that were not treated with BIX. Our results suggest that Px induces neurotoxicity in part through activating the ER stress response. Our findings should contribute to novel approaches regarding the mechanism of Px-induced neurotoxicity, including chemobrain.

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1. Introduction

The development of new chemotherapeutic agents and treatment regimens for breast cancer has reduced the risk of recurrence and prolonged patient survival. However, mild to moderate cognitive impairment following adjuvant chemotherapy for breast cancer, also known as "chemofog" or "chemobrain", are reported in 15–75% of breast cancer survivors [1–5]. The impaired domains are diverse, and include memory, processing speed, attention, and executive function impairments [6,7]. These deficits impair daily living activities of cancer patients, and are likely associated with impaired function in the hippocampal and frontal lobe regions of the human brain [8–11]. There are multiple hypotheses regarding chemotherapy associated cognitive impairments (CACI), including disruption of hippocampal cell proliferation and neurogenesis [12], chronic increases in inflammation [13,14], increased oxidative stress [13], white matter disruption [15,16], and long-term changes in cerebral blood flow and metabolism [17]. However the detailed mechanism and interventions for CACI have not yet been established.

Paclitaxel (Px) is one of the taxane agents, which binds microtubules, stabilizes microtubule dynamics, and arrests the cell at the mitotic phase [18]. It is broadly used for breast, gynecological, lung, and gastric cancer. Thornton et al. recently reported that taxane-based chemotherapy causes arthralgia/myalgia and ataxia, as well as more pronounced emotional distress and reduced mental quality of life throughout adjuvant treatment [19]. Generally, it is believed that Px is prevented from penetrating into the brain via the blood brain barrier (BBB). However, a study using positron emission tomography (PET) found detectable levels of radiolabeled Px in the brain after intravenous administration [20], indicating that Px crosses the BBB.

Recently, it has been reported that endoplasmic reticulum (ER) stress is involved in various human neurological diseases, such as

Abbreviations: BBB, blood brain barrier; BiP, immunoglobulin heavy-chain binding protein; BIX, BiP inducer X; CACI, chemotherapy associated cognitive impairments; CHOP, C/EBP homologous protein; ER, endoplasmic reticulum; PET, positron emission tomography; JNK, c-Jun NH2-terminal kinase; Px, paclitaxel.

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Parkinson's disease [21,22], Alzheimer's disease [23–25], and causes cognitive dysfunction. The ER stress response, also called the unfolded protein response, is a defense system that deals with the accumulation of unfolded proteins in the ER lumen. However, when ER stress is very severe, cells induce and/or activate C/EBP homologous protein (CHOP), the c-Jun NH2-terminal kinase (JNK) pathway, and caspase 4, thus leading to apoptosis. Therefore, we hypothesized that Px may cause severe ER stress that is related to neuronal apoptosis in the brain, thereby causing brain dysfunction.

In this study, we investigated whether Px caused an ER stress response and subsequently, ER stress-related neuronal apoptosis.

2. Materials and methods

2.1. Cell culture

SK-N-SH neuroblastoma cells were grown in Dulbecco's Modified Eagle's media (DMEM; GIBCO/Invitrogen Life Technologies, Paisley, UK) with 10% fetal bovine serum (FBS; JRH, Woodland, CA, USA). MCF-7 breast cancer cells were purchased from American Type Culture Collection (ATCC, Rockville, MD, USA). MCF-7 cells were cultured in Minimum Essential Medium Eagle (MEM; ATCC) with 0.01 mg/ml bovine insulin (Sigma, St. Louis, MO, USA) and 10% FBS.

Cells were maintained at 37 °C in an incubator with an atmosphere of 5% carbon dioxide (CO_2). Cells were routinely passaged using trypsin (0.25%)–EDTA (0.1%) solution in Hank's Balanced Salt Solution (HBSS; Himedia Laboratories Pvt. Ltd., Mumbai, India).

2.2. Paclitaxel treatment

Px was purchased from Sigma and dissolved in dimethyl sulfoxide (DMSO). SK-N-SH cells and MCF-7 cells were treated for 24 h at 37 °C with 1, 10, 50, or 100 μM, respectively. DMSO was used as a vehicle control.

2.3. BIX treatment

Immunoglobulin heavy-chain binding protein (BiP) inducer X (BIX) [26] was dissolved in DMSO. SK-N-SH cells were treated for 12 h at 37 °C with 0.5, 1, 2, 3.5, 5, or 10 μM BIX prior to Px treatment. DMSO was used as a vehicle control. The media was replaced with fresh media containing each dose of Px without BIX for 24 h.

2.4. MTS cell viability assays

Cellular viability was assessed using CellTiter 96 Aqueous One Solution Cell Proliferation Assays (Promega, Madison, WI, USA). Briefly, SK-N-SH cells or MCF-7 cells were seeded in 96-well plates. Cells were allowed to attach for 24 h, followed by incubation with Px or vehicle control for 24 h. For BIX experiments, cells were treated with or without BIX before Px treatment and incubated for 12 h. Next, 20 μl of MTS reagent was added to each well and cells were incubated for 2 h. Optical density was measured at 490 nm using a Micro Plate Reader (Bio-Rad, Hercules, CA, USA).

2.5. Microscopic observation and cell viability assays

To observe morphological changes in SK-N-SH cells after Px treatment, we used phase-contrast microscopy.

2.6. Western blots

Cells were washed in Tris-buffered saline (TBS), harvested, and lysed in RIPA buffer (Thermo Fisher Scientific Inc, Rockford, IL, USA) with protease inhibitor cocktail (Roche, Mannheim, Germany), and phosphatase inhibitor cocktail (Roche). Lysates were sonicated on ice three times for 5 s each, and then incubated for 15 min. After centrifugation for 20 min at 13,000*g*, supernatants were retained and boiled in SDS sample buffer. Lysates (10 μg) were separated on SDS–polyacrylamide gels and transferred to polyvinylidene fluoride (PVDF) membranes (Bio-Rad, Hercules, CA, USA). Non-specific protein binding was blocked by incubating membranes for 1 h at room temperature in 5% w/v non-fat milk powder in TBS-T [50 mM Tris–HCl (pH 7.6), 150 mM NaCl, and 0.1% v/v Tween-20]. The membranes were incubated overnight at 4 °C with the following primary antibodies: anti-KDEL (1:1000; Santa Cruz Biotechnology, Santa Cruz, CA, USA) that detects BiP, anti-phospho-eIF2α (1:300; Cell Signaling Technology, Boston, MA, USA), anti-CHOP (1:1000; Santa Cruz Biotechnology), anti-caspase 4 (1:500; Medical and Biological laboratories, Nagoya, Japan), anti-caspase 3 (1:1000; Cell Signaling), and anti-GAPDH (1:1000; Thermo Fisher Scientific, Waltham, MA, USA). The membranes were then washed three times in TBS-T for 5 min. Finally, the membranes were incubated for 60 min at room temperature with HRP-conjugated anti-rabbit or anti-mouse antibodies (Promega, Madison, WI, USA). Protein bands were detected using the ECL Plus kit (GE Healthcare, Buckinghamshire, UK). The intensity of each band was quantified using NIH image J software.

2.7. Statistical analyses

Data are expressed as mean values ± standard deviation (SD). Unpaired Student's *t*-tests were used to determine the levels of significance between sample means. All results are representative of at least three independent experiments.

3. Results

3.1. Neuronal toxicity induced by Px

Px toxicity was examined using MTS assays. We used 1, 10, 50, 100 μM Px to treat SK-N-SH cells and MCF-7 cells. MCF-7 cells treated with Px showed 92% (1 μM), 90% (10 μM), 55% (50 μM), and 49% (100 μM) viability compared with control cells (Fig. 1a). SK-N-SH cells treated with Px showed 37% (1 μM), 37% (10 μM), 20% (50 μM), and 19% (100 μM) viability compared with control cells (Fig. 1a). We also observed apparent morphological changes in SK-N-SH cells after Px treatment (Fig. 1b). Based on these data, we used 1 μM Px in all subsequent experiments.

3.2. Px induces ER stress and ER stress-related apoptosis in SK-N-SH cells

We used Western blot analyses to investigate whether Px induced ER stress in SK-N-SH cells. Phospho-eIF2α was elevated in Px-treated SK-N-SH cells after 24 h compared with control cells (Fig. 2a and b). Furthermore, CHOP, activated caspase 4, and caspase 3 were significantly induced in Px-treated SK-N-SH cells compared with control cells (Fig. 2c–h). Because caspase 4, which is located in the ER, is known to be specifically activated by excessive ER stress [27], these results indicate that Px induced ER stress and ER stress-related neuronal apoptosis in SK-N-SH cells.

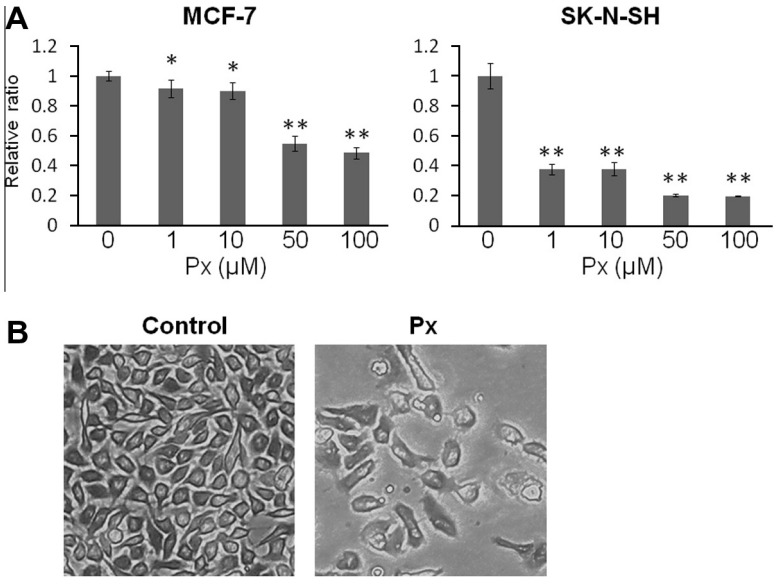

Fig. 1. Px toxicity in SK-N-SH and MCF-7 cells. (a) Px was added to MCF-7 cells (left) and SK-N-SH cells (right) at the indicated dose. Cell toxicity was assessed using MTS assays 24 h later. DMSO was applied as the vehicle control. The relative ratio compared with the absorbance of vehicle control (0 μM) is indicated. Histograms indicate the mean ± SD from six independent experiments. Asterisks (*) indicate significantly different from the vehicle treated group. $^{*}P < 0.05$, $^{**}P < 0.01$ (Student's *t*-test). (b) Phase-contrast microscopy images of SK-N-SH cells after treatment with 1 μM Px.

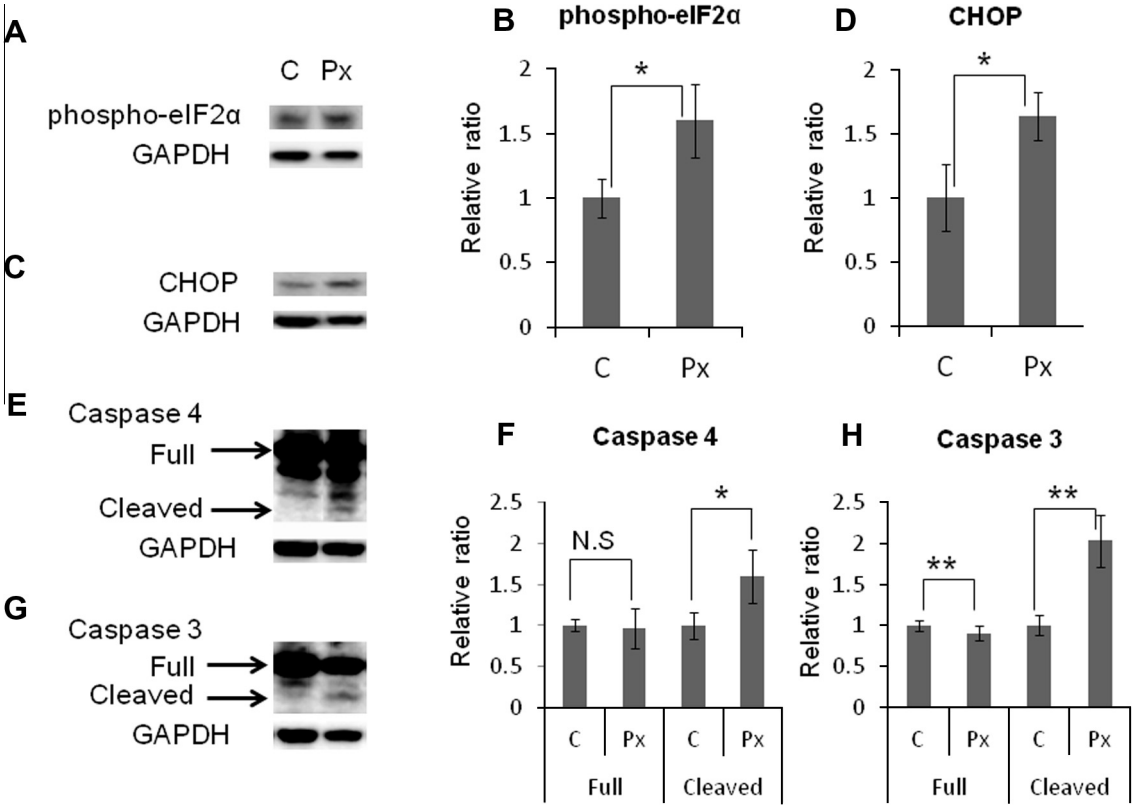

Fig. 2. Px induces ER stress and ER stress related apoptosis in SK-N-SH cells. (a, c, e, and g) SK-N-SH cells were treated with 1 μM of Px for 24 h and detected for Phospho-eIF2α, CHOP, caspase 4, and caspase 3 by Western blotting. GAPDH was used as an internal control. (b, d, f, and h) Densitometric analyses of Western blot experiments were normalized with GAPDH. The relative ratio compared with each control is demonstrated. Mean ± SD of each group are shown. Asterisks (*) indicate significantly different from the vehicle treated group. $^{*}P < 0.05$, $^{**}P < 0.01$ (Student's *t*-test).

3.3. Induction of BiP by BIX attenuates the ER stress response in SK-N-SH cells

Previously, we reported that BIX induced an ER molecular chaperone, BiP, and could prevent or attenuate neuronal death induced by ER stress [26,28,29]. We investigated whether BIX could attenuate Px-induced neurotoxicity in SK-N-SH cells. Similar to our previous report [26], significant toxicity of BIX was not detected at concentrations from 0.5 μM to 10 μM in SK-N-SH cells (data not shown). Therefore, we used 3.5 μM BIX for all subsequent experiments.

We pre-treated SK-N-SH cells with 3.5 μM BIX for 12 h, and then changed to fresh media containing 1 μM Px and incubated for another 24 h. Cell lysates were collected and used for Western blot experiments. BiP expression was up-regulated in BIX-treated cells compared with that in untreated control cells. The expression of BiP in BIX (−)/Px (+) treated cells was also up-regulated compared with BIX (−)/Px (−) treated cells (Fig. 3a and b). Increased phopho-eIF2α expression mediated by Px was significantly reduced upon the addition of BIX (Fig. 3c and d). Similarly, the expression of CHOP, activated caspase 4, and caspase 3 in BIX (+)/Px (+) treated cells was reduced compared with the expression levels in BIX (−)/Px (+) treated cells (Fig. 3e–j). These data confirm the involvement of Px in the ER stress response, and indicate that BIX could attenuate Px-induced neuronal cell death via the BiP induction.

3.4. BIX attenuates Px-induced neurotoxicity

To evaluate the effect of BIX in the attenuation of Px-induced neurotoxicity, we compared the viability of BIX (−)/Px (+) treated cells with BIX (+)/Px (+) treated cells using MTS assays. The viability of BIX (+)/Px (+) treated cells was significantly increased compared with that of BIX (−)/Px (+) treated cells ($P < 0.01$) (Fig. 4).

4. Discussion

Px is one of the most effective chemotherapeutic agents for the treatment of breast cancer. It is known to stabilize microtubules and cause G2/M cell cycle blockade, mitochondrial damage, and p53-independent apoptosis. At present, the molecular mechanisms involved in Px-induced apoptosis have generally focused on mitochondria-mediated signaling pathways. In this study, we found that Px caused ER stress related apoptosis in SK-N-SH cells by inducing CHOP and activating caspase 4. Recently, Liao et al. also reported that Px induced ER stress in leukemic U937 cells [30]. However, these authors used a much higher dose (100 μM) of Px in their study. In contrast, we demonstrated 1 μM Px was sufficient to induce ER stress-related neuronal apoptosis. Thus, we suggest that neuronal cells are more vulnerable to Px-induced ER stress than other cell types. In fact, less than 1 μM Px is sufficient to induce appreciable morphological changes, including neurite retraction, inhibition of axonal elongation, interference with axonal transport, and apoptosis in primary cortical or hippocampal neurons [31,32]. This is the first report regarding the involvement of ER stress-related apoptosis in neuronal cells treated with Px.

Px has generally been hypothesized not to pass the BBB. However, using PET studies, Gangloff et al. recently reported detectable levels of radiolabeled Px were found in the brain after intravenous administration [20]. According to this report, the biodistribution of ^{18}F-FPAC in the brain, which exhibits a very similar biodistribution to Px, was approximately 1/10 of that in tumors in mice bearing MCF-7 tumors. Interestingly, our results showed that SK-N-SH cells were more sensitive to Px than MCF-7 cells (Fig 1a). In addition, the dose of Px we used was extremely low compared to the doses used clinically for breast cancer adjuvant chemotherapy. Based on these data, it is possible that even very low doses of Px can reach the brain and potentially induce ER stress-related neuronal apoptosis. Because ER stress is involved in several neurological diseases and causes cognitive dysfunction [33,34], Px could also cause cognitive dysfunction. Further *in vivo* studies, including behavioral evaluation in Px-injected mice, are needed to support our study.

We reported previously that BIX prevented or attenuated ER stress-related neuronal toxicity, including ischemic insult, via BiP

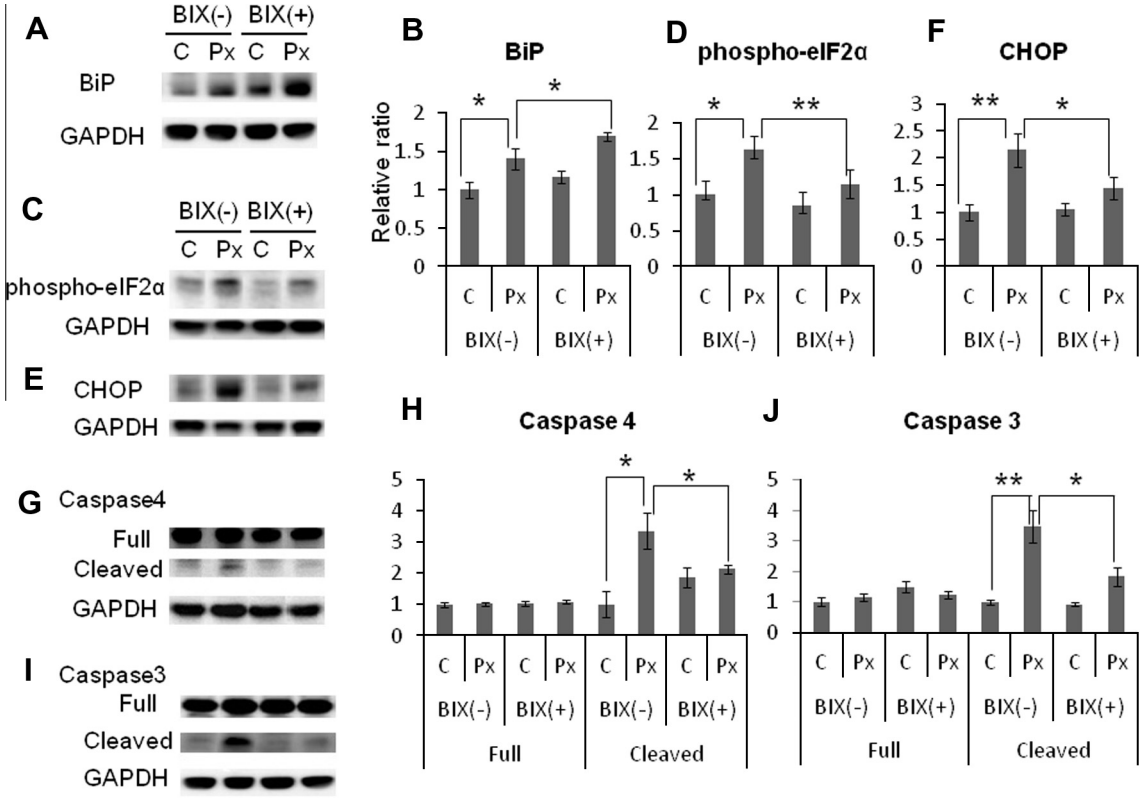

Fig. 3. Induction of BiP by BIX attenuates ER stress response in SK-N-SH cells. (a, c, e, g, and i) SK-N-SH cells were pre-treated with or without 3.5 μM of BIX for 12 h before 1 μM of Px treatment for 24 h and detected for BiP, Phospho-eIF2α, CHOP, caspase 4, and caspase 3 by Western blotting. GAPDH was used as an internal control. (b, d, f, h, and j) Densitometric analyses of Western blotting experiments were normalized with GAPDH. The relative ratio compared with each control is demonstrated. Asterisks (*) indicate significantly different from the vehicle treated group or BIX (−) group. Mean ± SD of each group are shown. *$P < 0.05$, **$P < 0.01$ (Student's *t*-test).

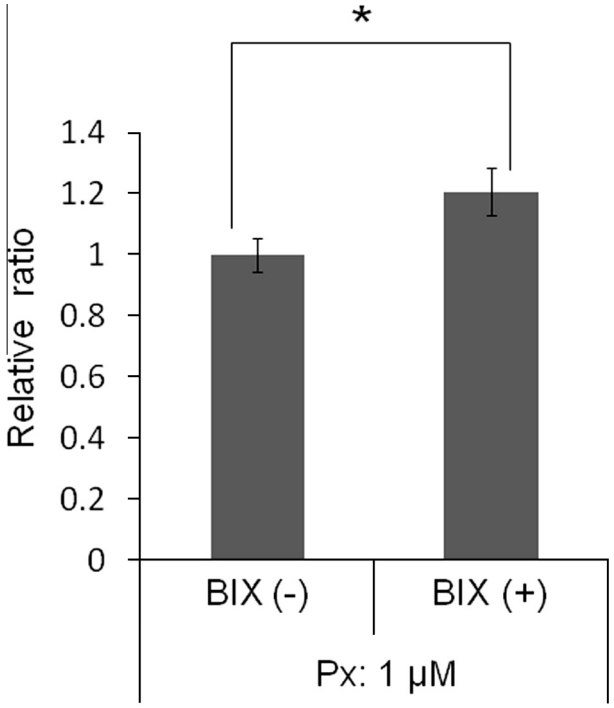

Fig. 4. BIX attenuates the Px induced neurotoxicity. SK-N-SH cells were pre-treated for 12 h with or without 3.5 μM BIX before the addition of 1 μM Px for 24 h. The toxicity of SK-N-SH cells was assessed using MTS assays. Histograms indicate the mean ± SD from six independent experiments. The asterisk (*) indicates a significant difference compared with BIX (−) group. $^{*}P < 0.01$ (Student's *t*-test).

induction [28,29]. In the present study, we demonstrated that BIX attenuated Px-induced neuronal apoptosis (Figs. 3 and 4). Thus, we postulate that BIX might attenuate Px-induced cognitive dysfunction.

The concept of chemobrain is still controversial, and cancer patients suffering from CACI may be underdiagnosed. Here, we demonstrated that Px directly causes neuronal apoptosis through ER stress responses. Our findings should contribute to novel approaches for evaluating the mechanism of Px-induced neurotoxicity, including chemobrain.

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