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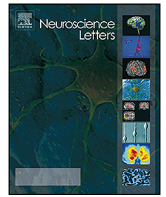

Research article

The neuroprotective effects of taurine against nickel by reducing oxidative stress and maintaining mitochondrial function in cortical neurons

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HIGHLIGHTS

- Taurine diminished nickel-induced cytotoxicity in primary cultured neurons.
- Taurine attenuated the oxidative stress and mitochondrial dysfunction of neurons exposed to nickel.
- Taurine may have pharmacological potential in treating the adverse effects of neurotoxins that target the mitochondria.

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ABSTRACT

Previous studies have indicated that oxidative stress and mitochondrial dysfunction are involved in the toxicity of nickel. Taurine is recognized as an efficient antioxidant and is essential for mitochondrial function. To investigate whether taurine could protect against the neurotoxicity of nickel, we exposed primary cultured cortical neurons to various concentrations of nickel chloride ($NiCl_2$; 0.5 mM, 1 mM and 2 mM) for 24 h or to 1 mM $NiCl_2$ for various periods (0 h, 12 h, 24 h and 48 h). Our results showed that taurine efficiently reduced lactate dehydrogenase (LDH) release induced by $NiCl_2$. Along with this protective effect, taurine pretreatment not only significantly reversed the increase of ROS production and mitochondrial superoxide concentration, but also attenuated the decrease of superoxide dismutase (SOD) activity and glutathione (GSH) concentration in neurons exposed to $NiCl_2$ for 24 h. Moreover, nickel exposure reduced ATP production, disrupted the mitochondrial membrane potential and decreased mtDNA content. These types of oxidative damage in the mitochondria were efficiently ameliorated by taurine pretreatment. Taken together, our results indicate that the neuroprotective effects of taurine against the toxicity of nickel might largely depend on its roles in reducing oxidative stress and improving mitochondrial function. Taurine may have great pharmacological potential in treating the adverse effects of nickel in the nervous system.

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1. Introduction

The high consumption levels of nickel-containing products in modern society have raised considerable concerns about their potential hazardous effects on human health. Nickel proves to be a potential carcinogenic agent and has multiple toxic effects in various systems [6,7]. The nervous system is one of the main target organs of nickel toxicity. Previous evidence showed that nickel exposure resulted in a variety of neurological symptoms, including headaches, giddiness, tiredness, lethargy and ataxia [6]. In different types of nerve cells in vitro studies, nickel

Abbreviations: ATP, adenosine-5′-triphosphate; LDH, lactate dehydrogenase; MDA, malondialdehyde; SOD, superoxide dismutase; GSH, glutathione; GSSG, glutathione oxide; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; $\Delta\Psi m$, mitochondrial membrane potential.

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exposure decreased mitochondrial activity, inhibited cell proliferation, disturbed neuronal calcium homeostasis and displayed developmental neurotoxicity through changing the gene expression of the glutamate receptors [21,26,34]. Among the many mechanisms involved in nickel-mediated neurotoxicity, oxidative stress has been proposed to play a pivotal role [6,23]. Substantial recent attention has focused on the use of various antioxidants to prevent the adverse effects of nickel on the nervous system.

Mitochondria are the major sites that produce reactive oxygen species (ROS). Excess ROS induce oxidative damage to unsaturated fatty acids, proteins and DNA in the mitochondria [20,30]. With unique structural and functional characteristics, mitochondria are often the targets of a number of environmental toxins, especially those that cause mitochondrial oxidative stress [10]. Mitochondrial dysfunction induced by oxidative stress could disturb the electron transferring and amplify the ROS generation, which exacerbate the oxidative stress and form a vicious cycle. Thus, oxidative damage to the mitochondria is typically considered as the primary or secondary etiology of toxicity of various environmental toxins including nickel [2]. Indeed, our previous study indicated that the nickel exposure induced obvious oxidative stress and mitochondrial dysfunction both in vitro and in vivo [17,33,34].

Taurine, a sulfur-containing amino acid, presents at high concentrations in the mammalian brain. Taurine plays significant roles in neurotransmission, neuromodulation, osmoregulation, detoxification and calcium homeostasis [9,11]. As a type of antioxidant, taurine has been found to be neuroprotective against oxidative damage under various pathological conditions including hypoxia, hypoglycemia, ischemia, excitotoxicity, metabolic poisons and β-amyloid-induced neurotoxicity [14,24]. Particularly, taurine could interact with mitochondria and maintain mitochondrial homeostasis. In the mitochondria, taurine could reduce oxidative stress, stimulate mitochondrial anti-oxidative enzymes (Mn-SOD), regulate mitochondrial calcium homeostasis and preserve mitochondrial function [9,31]. Because oxidative stress and mitochondrial dysfunction are recognized as an adverse effects of nickel exposure, the purpose of our study was to investigate the neuroprotective roles of taurine against the neurotoxicity of nickel.

2. Materials and methods

2.1. Cell culture and treatment

The primary cultured neurons were prepared as previous reported [34]. On day 8, cortical neurons were pre-treated with 10 mM taurine (Sigma, St Louis, MO, USA) for 2 h, a procedure based on the previous study [5] and our pre-experiment. After taurine pretreatment, neurons were exposed to nickel chloride ($NiCl_2$, Sigma, St Louis, MO, USA) for the various experiments. In the LDH release assay, neurons were incubated with various concentrations of $NiCl_2$ (0.5 mM, 1 mM and 2 mM) for 24 h or with 1 mM $NiCl_2$ for various periods (0 h, 12 h, 24 h and 48 h), which was according with our previous study. In other experiments, neurons were incubated with $NiCl_2$ (1 mM and 2 mM) for 24 h.

2.2. Neurotoxicity measurement

Lactate dehydrogenase (LDH) release was evaluated to assess the neurotoxicity of nickel in cortical neurons and was measured with the cytotoxicity detection kit (Roche, Mannheim, Germany). Results were expressed as the percentage of maximum LDH release obtained by lysing the cells in 1% Triton X-100.

2.3. Assay of intracellular reactive oxygen species (ROS)

The determination of intracellular oxidant production was based on the oxidation of DCFH-DA (Beyotime Company, China). Briefly, 1×10^4 cortical neurons were seeded in 96-well plates. After treatment, cells were incubated with DCFH-DA (1:1000) for 1 h. The fluorescence was read at 485 nm for excitation and 530 nm for emission with the Infinite^{TM} M200 Microplate Reader (Tecan, Mannedorf, Switzerland). The experiment was repeated four times and cellular fluorescence intensity was expressed as the fold increase compared to the controls.

2.3.1. Assessment of oxidative stress within mitochondria

Oxidative stress within the mitochondria was determined by using MitoSOX^{TM} Red (Invitrogen Corp., Carlsbad, CA), a mitochondria-targeted fluorescent probe for the highly selective detection of mitochondrial superoxide. After treatment with taurine and nickel, cortical neurons were incubated with culture medium containing 5 μM MitoSOX for 10 min at 37 °C. Fluorescence intensity was analyzed with the microplate reader.

2.3.2. Superoxide-dismutase (SOD) activity determination

The total (Cu–Zn and Mn) superoxide-dismutase activity was determined with the total superoxide dismutase assay kit (Beyotime Company, China) based on the ability of SOD to inhibit xanthine/xanthine oxidase-derived superoxide anion reduction in WST-1 formazan.

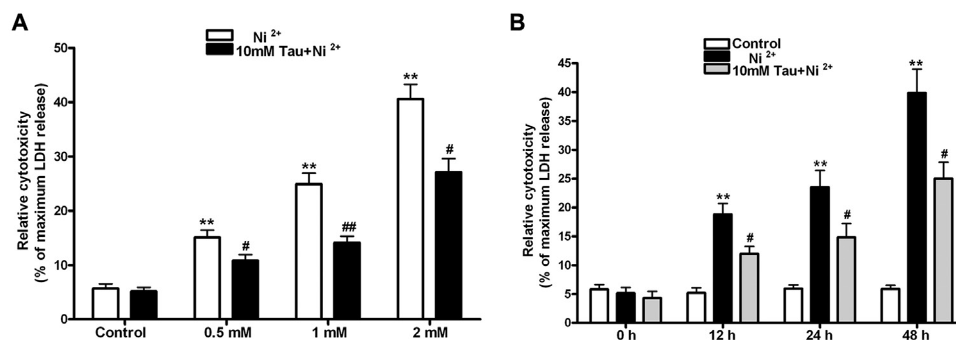

Fig. 1. Taurine protected cortical neurons against nickel-induced cytotoxicity. After cortical neurons were pretreated with 10 mM taurine (Tau) for 2 h, the effects of taurine on LDH release in nickel-treated neurons, were examined by exposing neurons to $NiCl_2$ at the desired concentrations (0.5 mM, 1 mM and 2 mM) for 24 h (A). Time course analysis was performed by incubating the neurons with 1 mM $NiCl_2$ for 0 h, 12 h, 24 h and 48 h (B). After treatment with nickel and taurine, cell-free culture supernatants were collected and incubated with LDH assay solution at 25 °C for 30 min. Optical density was measured at 490 nm and the reference value at 620 nm was subtracted out. Results are expressed as the percentage of maximum LDH release which was obtained by lysing the cells in 1% Triton X-100. $^{**}p < 0.01$ versus sham-exposed control group, $\#p < 0.05$, $\#\#p < 0.01$ versus groups treated with nickel at the same concentration or at the same time point. Values are means ± SE, $n = 4$.

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