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Neuroprotective effect of taurine in 3-nitropropionic acid-induced experimental animal model of Huntington's disease phenotype

Mariane G. Tadros [a], Amani E. Khalifa [a,*], Ashraf B. Abdel-Naim [a], Hossam M.M. Arafa [b]

[a] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt*
[b] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt*

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Abstract

An experimental animal model of Huntington's disease (HD) phenotype was induced using the mycotoxin 3-nitopropionic acid (3-NP) and was well characterized behaviorally, neurochemically, morphometrically and histologically. Administration of 3-NP caused a reduction in prepulse inhibition (PPI) of acoustic startle response, locomotor hyper- and/or hypoactivity, bilateral striatal lesions, brain oxidative stress, and decreased striatal γ-aminobutyric acid (GABA) levels. Taurine is a semi-essential β-amino acid that was demonstrated to have both antioxidant and GABA-A agonistic activity. In this study, treatment with taurine (200 mg/kg daily for 3 days) prior to 3-NP administration reversed both reduced PPI response and locomotor hypoactivity caused by 3-NP injection. Taurine pretreatment also caused about 2-fold increase in GABA concentration compared to 3-NP-treated animals. In addition, taurine demonstrated antioxidant activity against oxidative stress induced by 3-NP administration as evidenced by the reduced striatal malondialdehyde (MDA) and elevated striatal glutathione (GSH) levels. Histochemical examination of striatal tissue showed that prior administration of taurine ahead of 3-NP challenge significantly increased succinate dehydrogenase (SDH) activity compared to 3-NP-treated animals. Histopathological examination further affirmed the neuroprotective effect of taurine in 3-NP-induced HD in rats. Taken together, one may conclude that taurine has neuroprotective role in the current HD paradigm due, at least partly, to its indirect antioxidant effect and GABA agonistic action.

Keywords: Taurine; 3-NP; Histochemistry; GABA; Histopathology

1. Introduction

Huntington's disease (HD) is an inherited neurodegenerative disorder, in which progressive widespread neuropathological deficits result in behavioral, histological and neurochemical abnormalities (Ryu et al., 2004). 3-Nitropropionic acid (3-NP) is a mitochondrial toxin that has been found to effectively induce specific behavioral changes and selective striatal lesions in rats and non-human primates mimicking those in HD (Lee and Chang, 2004). The animal model of 3-NP-induced HD in rats was documented to manifest disruption of prepulse inhibition (PPI) of acoustic startle response, locomotor hyper- and/or hypoactivity, bilateral striatal lesions, elevated brain oxidative status, and decreased striatal γ-aminobutyric acid (GABA) levels (Kodsi and Swerdlow, 1997; Schulz et al., 1996; Beal et al., 1993).

The startle reflex is a contraction of the facial and skeletal muscles to sudden, relatively intense stimuli that is usually classified as a defensive response (Swerdlow et al., 1995). PPI is a very robust experimental phenomenon in which there is a normal suppression of the amplitude of startle reflex, when an intense startling stimulus is preceded 30–500 ms by a weak stimulus (Davis et al., 1982). The preceding stimulus "sets up an inhibitory network", which dampens the response to the second stimulus. This sensory gating mechanism is suggested to protect the brain from stimulus inundation, which could otherwise lead to cognitive fragmentation and disturbed thought (Braff and Geyer, 1990). The PPI paradigm thus offers an opportunity to evaluate the effects of 3-NP on a simple quantifiable reflex measure that is known to be abnormal in HD patient.

Many pharmacological agents have been attempted to protect against HD in experimental animals. Though, very

* Corresponding author. Tel.: +20 10 1020600; fax: +20 2 395 3905.
E-mail address: amani@ims.com.eg (A.E. Khalifa).

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few pharmacotherapies have been clinically used for the management of the disease. The most promising therapeutic agent in this setting is minocycline; an antibiotic with anti-inflammatory and antiapoptotic properties. In a 2-year study, minocycline was administered to 14 patients with genetically confirmed HD (Bonelli et al., 2004a). In this study, patients exhibited stabilization in general motor and neuropsychological function at endpoint assessed by the Mini-Mental State Examination, the Total Motor Score, the Total Functional Capacity Scale and the Independence Scale. In another double-blind, randomized, placebo-controlled study in 60 HD patients, tolerability and adverse event frequency were similar between minocycline-treated and placebo groups (Huntington Study Group, 2004). Other clinical data indicate that minocycline was well tolerated in 30 HD patients during 6-month period with no serious adverse events (Thomas et al., 2004). Therefore, long-term, double-blind, placebo-controlled large trials could further help in establishing the value of minocycline in management of HD.

Taurine is a semi-essential β-amino acid that is most abundant in brain, heart, retina, skeletal muscle and leukocytes of mammalian species (McCool and Botting, 2000). In a hypoxic rat model, taurine prevented hypoxia-induced lactate accumulation and lipid peroxidation in brain, liver, and heart tissues (Mankovskaya et al., 2000). Beside its reported antioxidant effect, taurine has a GABA-A agonistic activity (El Idrissi et al., 2003). Such pharmacological activities of taurine may suggest a potential therapeutic value in management of HD though yet to be investigated. Therefore, this study aimed at testing the possible protective effect of taurine against 3-NP-induced neurotoxicity in rats. The effect of both taurine and 3-NP alone and in combination was tested on PPI response and locomotor activity of rats. Experiments were also performed to investigate the effect of these treatments on striatal GABA, malondialdehyde (MDA), glutathione (GSH), glutathione peroxidase (GSHPx) and lactate dehydrogenase (LDH) levels/activities. Histochemical determination of striatal succinate dehydrogenase (SDH) activity along with histopathological evaluations was also conducted in this study.

2. Materials and methods

2.1. Animals

Male albino rats of Wistar strain weighing 250–300 g were used. They were housed in plastic cages in a room maintained at constant temperature (21 ± 2 °C) with alternating 12 h light/dark cycle where animal chow and water were provided ad libitum. On the day of the experiment, animals were brought to the experimental room and allowed to habituate to the environmental conditions for a period of approximately 60 min before the beginning of the experiment. All animal treatments adhered strictly to institutional and international ethical guidelines concerning the care and use of laboratory animals and the experimental protocol was approved by Ain Shams University Faculty of Pharmacy Review Committee for the use of animal subjects.

2.2. Drugs and chemicals

Taurine, 3-NP, sodium succinate dibasic hexahydrate, *o*-phosphoric acid, L-glutamic acid, ninhydrin solution, Ellman's reagent [5,5′-dithio-bis-2-nitrobenzoic acid; DTNB], ethylene diaminetetracetic acid disodium (Na_2EDTA), GABA, GSHPx, GSH, thiobarbituric acid (TBA) and 1,1′,3,3′-tetramethoxypropane were all purchased from Sigma-Aldrich, Chemie Gmbh, Germany. NitroBlue Tetrazolium (NBT) was obtained from Fluka AG, Buschs SG, Switzerland. Trifluoroacetic acid (TFA) was purchased from Reidel-de Haën (Germany). Sodium azide (NaN_3) was purchased from Merck-Darmstadt, Germany. Methanol (HPLC grade) was obtained as from Honil Limited, London, UK. Lactate dehydrogenase (LDH) kit was purchased from SGM, Rome, Italy. The rest of the chemicals used in this experimental work were of the highest commercial grade.

Taurine was dissolved in saline and was administered intraperitoneally in a dose of 200 mg/kg daily for three consecutive days (Mankovskaya et al., 2000). 3-NP was dissolved in saline and was administered subcutaneously in a dose of 20 mg/kg daily for five consecutive days (Beal et al., 1993). Drugs or vehicle were administered in a volume of 1 ml/kg body weight. Control animals received respective solvent injections, and they were run concurrently with drug-treated groups.

2.3. Experimental groups

Forty-eight animals were divided into four groups ($n = 12$). The first group received intraperitoneal saline injections once daily for three consecutive days followed at day 4 to 8 by daily injections of 3-NP (20 mg/kg, s.c.). The second group received taurine injections (200 mg/kg, i.p.) once daily for three consecutive days followed at day 4 to 8 by daily injections of 3-NP (20 mg/kg, s.c.). The third group received taurine injections (200 mg/kg, i.p.) once daily for three consecutive days followed at day 4 to 8 by daily subcutaneous injections of saline. The fourth group served as control animals receiving intraperitoneal saline injections once daily for three consecutive days followed at day 4 to 8 by daily subcutaneous saline injections. Locomotor activity was determined for all groups at 3.5 h after drug treatments at days 1, 4, 5, 6, 7 and 8 of the experiment. %PPI of acoustic startle response and startle amplitude were both assessed 215 min after drug treatments at day 5 of the experiment. At day 8 of the experiment, animals were decapitated and skulls were split on ice and salt mixture. Striata were dissected out, homogenized and allocated to two groups for estimation of GABA and oxidative stress indices' levels/activities. Another four groups of rats ($n = 12$) received the same treatment conditions as previously described. On day 8, animals were sacrificed and brains were divided into two groups for conduction of both histochemical and histopathological examinations.

2.4. PPI response measurement

Startle responses were measured using Responder X apparatus (Columbus, Ohio, USA) which consists of Plexiglas