Injury 54 (2023) 1065–1070

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Antioxidant and neuroprotective effects of dexpanthenol in rats induced with traumatic brain injury☆

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ARTICLE INFO

Article history:
Accepted 10 February 2023

Keywords:
Antiapoptotic
Anti-inflammatory
Antioxidant
Dexpanthenol
Neuroprotection
Traumatic brain injury

ABSTRACT

Trauma-induced primary damage is followed by secondary damage, exacerbating traumatic brain injury (TBI). Dexpanthenol has been shown to protect tissues against oxidative damage in various inflammation models. This study aimed to investigate possible antioxidant and neuroprotective effects of dexpanthenol in TBI.

Wistar albino male rats were randomly assigned to control (n = 16), trauma (n = 16) and dexpanthenol (500 mg/kg; n = 14) groups. TBI was induced under anesthesia by dropping a 300 g weight from 70-cm height onto the skulls of the rats. Twenty-four hours after the trauma, the rats were decapitated and myeloperoxidase (MPO) levels, luminol- and lucigenin-enhanced chemiluminescence (CL), malondialdehyde (MDA) levels, superoxide dismutase (SOD) levels, and catalase (CAT) and caspase-3 activities were measured in brain tissues. Following transcardiac paraformaldehyde perfusion, histopathological damage was graded on hematoxylin-eosin-stained brain tissues.

In the trauma group, MPO level, caspase-3 activity and luminol-lucigenin CL levels were elevated ($p < 0.05$–0.001) when compared to controls; meanwhile in the dexpanthenol group these increases were not seen ($p < 0.05$–0.001) and MDA levels were decreased ($p < 0.05$). Decreased SOD and CAT activities ($p < 0.01$) in the vehicle-treated TBI group were increased above control levels in the dexpanthenol group ($p < 0.05$–0.001). in the dexpanthenol group there was relatively less neuronal damage observed microscopically in the cortices after TBI.

Dexpanthenol reduced oxidative damage, suppressed apoptosis by stimulating antioxidant systems and alleviated brain damage caused by TBI. Further experimental and clinical investigations are needed to confirm that dexpanthenol can be administered in the early stages of TBI.

Introduction

Mild traumatic brain injury (mTBI) is the most common TBI encountered in clinical settings [1]. Neurologic deficits, behavioral alterations and cognitive problems dramatically affect quality of life of TBI patients [2]. In TBI pathophysiology, trauma-induced primary injury is followed by secondary injury, exacerbating TBI [2,3]. Secondary injury mainly includes disruption of energy metabolism, oxidative stress, lipid peroxidation, inflammation and apoptosis [4,5]. Pharmacological studies aim to ameliorate the effects of secondary injury-related cascades [6–8]. To date, only a few agents have proven to effectively reduce symptom burden in mTBI; thereby high-quality and clinically reliable further studies are still needed [9].

Dexpanthenol (D-panthenol; (+)-2,4-dihydroxy-N-(3-hydroxypropil)-3,3 dimethilbutiramide), also known as provitamin B5, is a biologically active alcohol form of panthotenic acid [10].

☆ This study was presented as a poster at the 16th National Neuroscience Meeting, 20–23 May 2018, Istanbul, Turkey and as an oral presentation at the World Federation of Neurosurgical Societies 2019 International Meeting, March 21–24 2019, Belgrade, Serbia.

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https://doi.org/10.1016/j.injury.2023.02.025
0020-1383/

It is water soluble [11] and has antioxidant, anti-inflammatory, antiapoptotic, and neuroprotective activities [11–14]. Dexpanthenol has been shown to protect brain tissue against oxidative damage and apoptosis in a neuroinflammation model [15] and to protect against streptozotocin-induced neuronal damage [16]. In a cerebral ischemia and reperfusion model, dexpanthenol has exerted potent antioxidant activity and was found to be neuroprotective [14]. The current study was aimed to investigate possible anti-inflammatory, antioxidant and neuroprotective effects of dexpanthenol in a mTBI model.

Materials and methods

Experimental groups

In this study, all experimental procedures were reviewed and approved by the Marmara University Animal Care and Use Committee (12.2017.mar). All experiments and animal care were conducted in accordance with the European Communities Council Directive for experimentation, September 22, 2010 (2010/63/EU) and the ARRIVE guidelines were applied. Forty-six adult male Wistar albino rats weighing 250–400 g were housed in an air-conditioned room with 12-h light and dark cycles, maintained at constant temperature (22 ± 2 °C) and relative humidity (65%–70%). They were fed standard laboratory chow and had free access to water.

The rats were randomly assigned to one of the three groups:

1. Control group (n = 16): Rats underwent only a skin incision and received a single intraperitoneal dose of saline (0.9% NaCl, 0.1 ml/100 g) immediately after surgery. Nontraumatized brain samples were obtained 24 h after surgery; some samples were used for biochemical analysis (n = 10), whereas others were stored in formaldehyde solution for histopathological analysis (n = 6).
2. Trauma group (n = 16): Rats underwent TBI as described below and received a single intraperitoneal dose of saline immediately after TBI. Brain samples were removed 24 h after injury and used for biochemical (n = 10) or histopathological (n = 6) analysis.
3. Dexpanthenol group (n = 14): Rats received a single intraperitoneal dose of dexpanthenol (500 mg/kg; Bepanthen, Bayer Türk Kimya, Turkey) immediately after TBI. The selected dose of dexpanthenol was based on that used in previous studies [13,17]. Brain samples were used for biochemical (n = 8) and histopathological (n = 6) analysis 24 h after TBI.

Anesthesia and induction of TBI

The animals were anesthetized by an intraperitoneal injection of a combination of 10 mg/kg xylazine (Rompun, Bayer, Turkey) and 50 mg/kg ketamine (Ketalar, Parke Davis, Turkey) and were allowed to breathe spontaneously. A moderate brain injury model, described by Marmarou et al. [18] and modified by Ucar et al. [19], was applied for head trauma. Rats were placed in prone position on the table and supported on a 10-cm foam bed that provided deceleration after impact. A midline incision was made on the head, and the coronal and lambdoid sutures were identified. A metallic disk of 10 mm diameter and 3 mm thickness was fixed to the cranium using bone wax between the two cranial sutures and the midline. Trauma was applied at the point where the disk was placed on the midline. A lead object weighing 300 g was allowed to fall freely from a height of 70 cm through a copper tube on to the metal disk over the skull of the rat [6]. After the induction of injury, the metallic disk was removed, the surgical area was cleaned, and the skin was sutured.

All the animals were decapitated 24 h after the trauma following anesthesia, and the brains were carefully removed. Samples of forebrain tissues were obtained in a standardized manner by excising the same parts of the brain for the analysis of each parameter.

Biochemical analyses

Measurement of myeloperoxidase activity in brain tissue

Myeloperoxidase (MPO), an enzyme that is mainly located in the azurophilic granules of polymorphonuclear leukocytes, is commonly used to demonstrate the accumulation of neutrophils in tissues [20]. Tissue MPO activity was evaluated by measuring the hydrogen peroxide-dependent oxidation of o-dianizidine dihydrochloride. One unit alteration of enzyme activity measured at 460 nm and 37 °C was determined to be the amount of the MPO present per gram of tissue [21].

Chemiluminescence measurements in brain tissue

Chemiluminescence (CL) is a direct, noninvasive method of measuring the activity of reactive oxygen radicals using luminol and lucigenin as enhancer probes. When added to in vitro biological systems, luminol and lucigenin produce high levels of excited products. Excited electrons from these compounds generate radiating light energy or CL that can be detected by a luminometer. Luminol detects radicals such as hydroxyl ions, hydrogen peroxide, and hydrochloric acid, whereas lucigenin is selective to superoxide anions [22,23]. Results were expressed as relative light units/mg tissue (rlu/mg). The detailed protocol was previously published [6].

Determination of tissue malondialdehyde levels

Homogenized brain samples (in 10% trichloracetic acid) were centrifuged (4 °C, 3000 rpm, 15 min) and the supernatants recentrifuged (4 °C, 15,000 rpm, 8 min). The lipid peroxide levels were determined by spectrophotometry at 535 nm wave-length and expressed as nanomoles of MDA per gram tissue. The detailed protocol was previously published [6].

Determination of tissue superoxide dismutase and catalase activity

Superoxide dismutase (SOD) activity in the brain samples was measured as previously described [24]. Absorbance was measured at 460 nm with a Shimadzu UV-02 model spectrophotometer. A standard curve was prepared using bovine SOD (Sigma–Aldrich; S-2515–3000 U, USA) as a reference. Absorbance readings were obtained prior to and 8 min after illumination, and the net absorbance was calculated.

The method for measuring catalase (CAT) activity is based on the catalytic activity of the enzyme in the decomposition reaction of H_2O_2 yielding H_2O and O_2 [25]. The detailed protocol for these measurements was previously published [6].

Measurement of tissue caspase-3 activity

To determine the levels of caspase-3 activity in the brain tissue, a commercial kit (Rat Caspase 3, Casp-3 ELISA Kit, Kat.No: SL0152Ra, Sunlong Biotech Co. Ltd., China) was used; as per the manufacturer's instructions. Supernatants of tissue homogenates were used for measuring the activity of the apoptotic marker caspase-3.

Histopathological examination

Animals were anesthetized with ketamine and xylazine as described previously and 4% paraformaldehyde in phosphate buffer (pH 7.4) was perfused through the aorta. After decapitation, the brains of the animals were removed from the skull and immersed in the same fixative for 24 h at 4 °C. Tissues were then embedded in paraffin and 5-µm-thick coronal sections were created using a rotary microtome. The sections were stained with hematoxylin

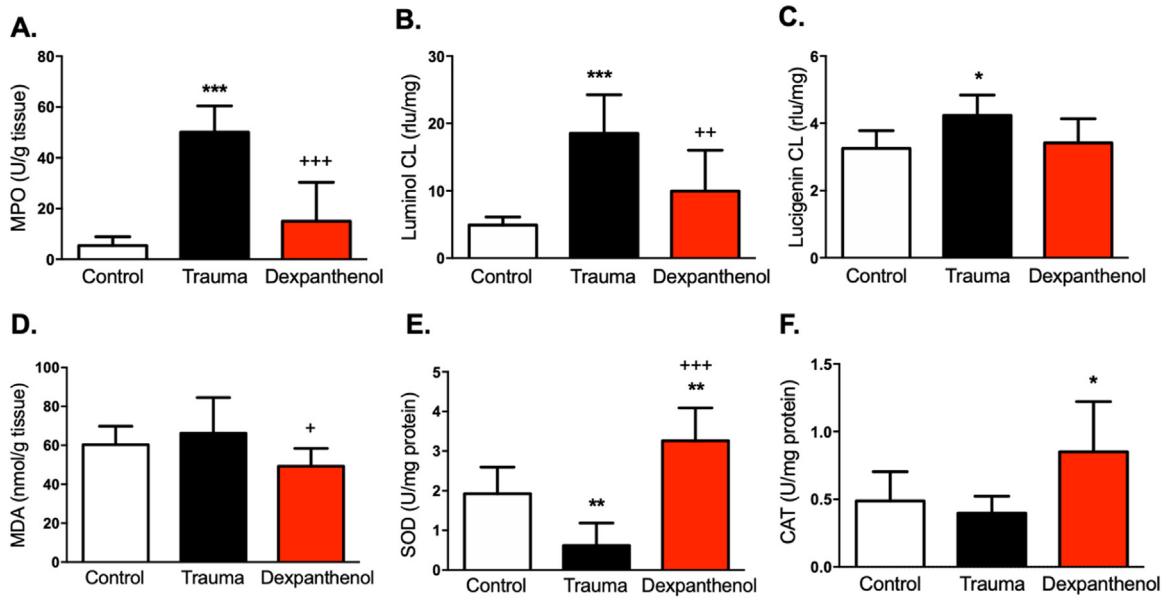

Fig. 1. Bar graphs showing tissue myeloperoxidase (MPO) activity (A), luminol levels (B), lucigenin levels (C), malondialdehyde (MDA) activity (D), superoxide dismutase (SOD) activity (E), catalase (CAT) activity (F) of the study groups. Values are expressed as mean ± SD. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with the control group; ++$p < 0.01$, +++$p < 0.001$ compared with the trauma group).

and eosin stain and examined under a photomicroscope (Olympus BX51, Japan). The severity of neuronal damage in the cortex was scored semiquantitatively as: 0 = no, 1 = mild, 2 = moderate, and 3 = severe damage. Pyknotic nuclei and intense staining of the shrunken neuronal perikarya were considered in scoring the degree of neuronal degeneration. Histopathology was scored on a 9-point scale that included subscores for neuronal degeneration, pericellular and vascular edema (0–3 points each) [6–8].

Statistical analysis

Data were analyzed using GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA) and expressed as means ± SEM. Analysis of biochemical data was performed using one-way variance analysis. Values of $p < 0.05$ were considered to be statistically significant.

Results

Biochemical evaluation

Myeloperoxidase activity (U/g tissue)

MPO activity was significantly higher in the brain samples of trauma group than that of the control group ($p < 0.001$), revealing that cerebral MPO activity was increased after TBI. However, in the dexpanthenol group cerebral MPO activity was significantly lower than that in the trauma group ($p < 0.001$) (Fig. 1A).

Chemiluminescence measurement (rlu/mg)

Both luminol- and lucigenin-enhanced chemiluminescence levels were higher in the trauma group those in the control group ($p < 0.001$ and $p < 0.05$, respectively). Dexpanthenol treatment prevented the elevation of luminol-enhanced CL levels ($p < 0.01$ Fig. 1B). Lucigenin-enhanced CL values tended to decrease in the dexpanthenol group, but did not reach statistical significance (Fig. 1C).

Malondialdehyde levels

MDA levels showed a tendency to increase in the trauma group as compared to controls ($p > 0.05$). However, in the dexpanthenol-treated group, a significant decrease in MDA was observed as compared to trauma group ($p < 0.05$; Fig. 1D).

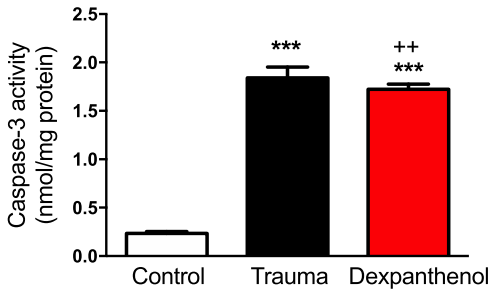

Fig. 2. Bar graphs showing tissue caspase-3 activity of the study groups. Values are expressed as mean ± SD. (***$p < 0.001$ compared with the control group; ++$p < 0.01$ compared with the trauma group).

Superoxide dismutase and catalase activity (U/mg protein)

Compared with the control group, cerebral SOD activity was decreased following TBI ($p < 0.01$), while dexpanthenol treatment totally abolished this reduction ($p < 0.001$; Fig. 1E). When we evaluated CAT activity, there was a tendency to decrease in CAT activity in the trauma group, but this decrease was not significant. In the dexpanthenol group, the CAT activity was even greater than that of the control group ($p < 0.05$; Fig. 1F).

Caspase-3 activity (nmol/mg protein)

Caspase-3 activity was significantly higher in the trauma group than in the control group ($p < 0.001$), while treatment with dexpanthenol significantly inhibited the TBI-induced increase in caspase-3 activity ($p < 0.01$; Fig. 2).

Histopathological evaluation

Normal neuropil structure and neurons with uniform morphology, large nuclei, and distinct nucleoli were prominent in the cortices of control rats (Fig. 3A). Compared with the controls, neuronal damage with pyknotic cell nuclei were detected in the traumatized

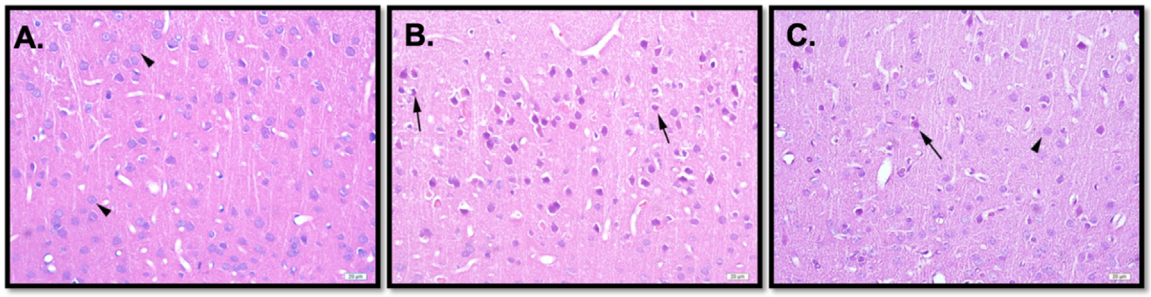

Fig. 3. Photomicrographs showing hematoxylin and eosin staining in the cortices of experimental groups. Control group (A) showed regular neuronal morphology and neuropil structure. Evident degeneration of neurons was observed in the trauma group (B). In the dexpanthenol group (C), degenerated neurons were decreased. Arrowhead: neurons with normal morphology; arrow: degenerated neurons, bars: 20 µm.

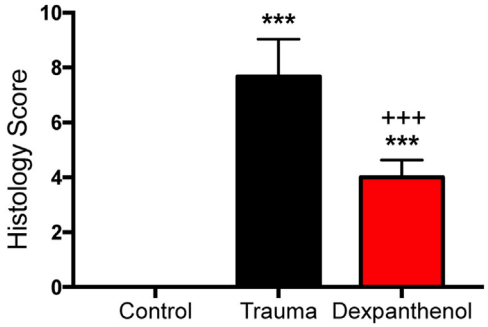

Fig. 4. Bar graphs showing tissue histological scores of the study groups. Values are expressed as mean ± SD. (***$p < 0.001$ compared with the control group; +++$p < 0.001$ compared with the trauma group).

rats (Fig. 3B). The histological score of the trauma group showed a significant increase when compared with that of the control group ($p < 0.001$; Fig. 4). Following dexpanthenol treatment, less neuronal damage was observed with less prominent effects of trauma on neuropil structure (Fig. 3C). Compared with the trauma group, the dexpanthenol group had a significantly lower histological score ($p < 0.001$; Fig. 1F).

Discussion

Traumatic brain injury (TBI) is a leading cause of disability and death [26]. Primary injury is directly caused by trauma, while secondary injury results from ionic imbalance due to lack of energy, excitotoxicity, oxidative stress, lipid peroxidation, and apoptosis [27]. Pharmacologic studies have attempted to reverse the effects of secondary injury, but to date there is lack of evidence for effectiveness of the candidate agents in TBI.

Dexpanthenol is renowned for its effects on skin and is commonly used in wound healing [28]. The alcohol analog of pantothenic acid (also known as vitamin B5) [29], dexpanthenol has been shown in previous studies to protect tissues from oxidative damage [17,30]; in addition, dexpanthenol's anti-inflammatory and antiapoptotic activity has been long recognized [11]. Dexpanthenol has an important role in the health and function of the brain [31,32]. It takes part in the synthesis of several neurotransmitters [33,34] and has been reported to show potential antioxidant and neuroprotective activity in a cerebral ischemia-reperfusion injury model [14]. Similarly, dexpanthenol treatment ameliorated brain damage in gamma irradiated rats. Dexpanthenol's antioxidant activity has been associated with improved levels of amino acid neurotransmitters which play significant roles in energy metabolism [35]. Dexpanthenol treatment given after streptozotocin-induced memory deficit was shown to ameliorate inflammation, and to preserve cognitive functions by restoring cholinergic system neurons [16]. Dexpanthenol's recently-discovered neuroprotective activity gives hope for its use in clinical practice as an easily accessible and affordable treatment for neuroinflammation.

MPO enzyme activity is a marker of neutrophil infiltration to damaged tissues [36]. In previous studies, we have observed that MPO activity is also a reliable indicator of oxidative stress and neuroinflammation in mild TBI [6–8]. In the current study, MPO activity was significantly increased after mTBI, and dexpanthenol treatment depressed the MPO activity significantly. This indicates that dexpanthenol treatment alleviates the damage induced by neutrophil activation and migration. Elevated luminol- and lucigenin-enhanced chemiluminescence levels also indicate oxidative stress in TBI studies and were reported to be significantly increased at 24 h after mTBI [6–8]. In parallel, our recent study also revealed that luminol-enhanced chemiluminescence levels were significantly decreased after dexpanthenol treatment, but lucigenin-enhanced chemiluminescence levels were insignificantly decreased. MPO activity is required for luminol bioluminesce, but lucigenin is independent from MPO and mostly related to chronic inflammation [37]. This biological difference could explain the difference between luminol and lucigenin bioluminescence.

Structural damage seen after TBI promotes calcium influx, resulting in increased reactive oxygen species production [38]. Membrane lipid peroxidation is an indicator of excess oxidative stress and MDA is produced during the peroxidation of membrane polyunsaturated fatty acids [39]. Our study noted a tendency for MDA levels to increase without significance, but also noted dexpanthenol brought about a significant decrease in MDA levels. This proves that TBI related membrane lipid peroxidation is eased with dexpanthenol treatment. Since the tissues produce antioxidant enzymes during excess oxidative stress and the utilization of antioxidant enzymes is much greater during oxidative stress [40], antioxidant therapies are one of the key players in TBI studies [41,42]. A potent antioxidant agent, dexpanthenol was previously shown to be effective in a neuroinflammation model [15]. It has been shown that MDA levels increase and SOD enzyme is consumed within 24 h of TBI [43–46]. CAT, another antioxidant enzyme, is also reportedly consumed within 24 h of TBI [47]. In our study, SOD levels and CAT levels were significantly decreased after TBI but there was no significance. After dexpanthenol treatment both SOD and CAT activities were significantly increased, even above control levels. These findings confirm the potent antioxidant activity of dexpanthenol after mTBI.

Apoptosis is one of the cell death pathways seen following TBI, and caspase-3 is one of the most important indicators of apoptotic cell death [48]. It has been reported that caspase-3 levels are increased following mTBI [6,43–47]. Besides its antioxidant properties, dexpanthenol is also known for its antiapoptotic activities [11,15]. Our study has shown that caspase-3 level was significantly increased in the trauma group and dexpanthenol treatment

provided a significant decrease in caspase-3 level, indicating that dexpanthenol treatment exerts antiapoptotic properties during the early period of mTBI .

Neuroprotective activity of dexpanthenol has been previously reported [14,16]. Following TBI, histopathological changes are important parameters for evaluating the morphological changes and neuroprotection. In our previous study, we have shown that the mTBI model resulted in histological changes in the traumatized brain tissues [6]. Similarly, in the trauma group of the present study, there was prominent hemorrhage, edema, neuronal damage, irregular cell structures, pyknotic cell nuclei, and cytoplasmic deterioration, with prominent perineuronal and perivascular edema. In contrary, the dexpanthenol group showed reductions in neuronal damage and edema, which were correlated with lower histological scores as compared to the score of the trauma group. These findings strengthen our previous findings and it is posssible to conclude that dexpanthenol is a potent neuroprotective agent in mTBI model.

Different TBI models with changing severity and different dosages and treatment times could have been investigated; more diverse and comprehensive biochemical parameters could have been implemented; and ultrastructural analysis with electron microscopic examination could have been introduced to demonstrate pathophysiological changes and behavioral outcomes could have illuminated treatment outcomes. Nevertheless, the current study is the first to report the antioxidant, anti-inflammatory, antiapoptotic and neuroprotective activity of dexpanthenol in a mTBI model.

Conclusion

Dexpanthenol reduced oxidative damage and neuroinflammation and suppressed apoptosis by stimulating antioxidant systems, thereby alleviating brain damage caused by mTBI. Further experimental and clinical investigations are needed to confirm that dexpanthenol can be administered in clinical practice in the early stages of mTBI.

Declarations of Competing Interest

None.

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