Biochemical and Biophysical Research Communications 392 (2010) 551–556

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

MMP-mediated cleavage of β-dystroglycan in myelin sheath is involved in autoimmune neuritis

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ARTICLE INFO

Article history:
Received 13 January 2010
Available online 25 January 2010

Keywords:
Dystroglycan
Demyelination
Autoimmune neuritis
Matrix metalloproteinases
Captopril

ABSTRACT

α-/β-Dystroglycans (DG) located at the outmost layer of myelin sheath play a critical role in its formation and stability in the peripheral nerve system. The demyelination of nerve fibers is present in autoimmune neuritis, however, it is not known about the molecular mechanisms underlying this pathological process. In an animal model of experimental autoimmune neuritis, we observed that β-DG cleavage was associated with the demyelination of peripheral nerves. The neuritis and β-DG cleavage were accompanied by matrix metalloproteinase (MMP)-2/-9 over-expressions and attenuated by captopril, a MMP inhibitor. The blockade of MMPs also improves clinical signs. Our results reveal a crucial role of MMP-mediated β-DG cleavage in autoimmune neuritis, such as Guillain–Barre' syndrome, and bring insights into therapeutic strategies for autoimmune diseases.

Introduction

In the peripheral nerves, dystroglycan (DG) complex is restricted to Schwann cell outer membrane apposing endoneural basal lamina [1]. The membrane-spanning complex including α- and β-DG is encoded by a single gene, and cleaved into two proteins during posttranslation [2]. α-DG as a cell surface peripheral protein interacts with laminin in extracellular matrix (ECM). β-DG as an integral membrane protein anchors α-DG to cell membrane through the N-terminus of extracellular domain and binds to the dystrophin through the C-terminal of cytoplasmic domain [3–7]. Therefore, DG complex plays a unique role in myelin formation and stability, and its absence may cause the dysmyelination in peripheral nerve system (PNS) [8–11].

The proteolysis of β-DG has been observed under various pathological conditions [12–18], in which matrix metalloproteases (MMP) disrupt DG complex by cleaving the extracellular domain of β-DG into β-DG_{30} in the peripheral tissues [17] as well as on astrocyte end-feet in experimental autoimmune encephalomyelitis [18]. β-DG was selectively cleaved by MMP-2 and MMP-9 [19–21]. A specific question is whether β-DG in Schwann cell outer membrane is a target of MMP-2 and MMP-9, and its cleavage leads to autoimmune neuritis. This issue will be addressed by using experimental autoimmune neuritis (EAN), since it shows pathological changes similar to autoimmune neuritis, such as inflammatory demyelination, myelin sheath breakdown, leukocyte infiltration and MMP activation [22–26].

With the multidisciplinary approaches including clinical score evaluation, Western blot, immunohistochemistry, and pharmacology, we found that both MMP-2 and MMP-9 disrupted β-DG in the outmost layer of myelin sheath, and in turn led to inflammatory cell infiltration demyelination in the peripheral nerves. Captopril, an inhibitor of MMPs, improved these pathological changes and clinical signs.

Materials and methods

The induction of EAN and the administration of captopril. Thirty-six female Lewis rats (160–180 g, Vital River Laboratory Animal Ltd., Beijing, China) were randomly divided into three groups (12 in each group), i.e., control, EAN and captopril treatment. All rats were bred and housed in non-SPF animal facility at Harbin Medical University in accordance with IACUC guidelines. Rats in two experimental groups were immunized in both hind footpads with 200 μl

Abbreviations: DG, dystroglycan; EAN, experimental autoimmune neuritis; MMP, matrix metalloproteinase; PNS, peripheral nerve system; PMSF, phenylmethanesulfonyl fluoride; SDS–PAGE, sodium dodecyl sulfate–polyacrylamide gel electrophoresis.

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doi:10.1016/j.bbrc.2010.01.062

of inoculum containing 230 μg P2 peptide of peripheral myelin-amino acids 53–78 (TESPFKNTEISFKLGQEFEETTADNR) (GL Biochem Ltd., Shanghai, China) and 2 mg *Mycobacterium Tuberculosis* (strain H37RA; Difco, Detroit, MI, USA) emulsified in 100 μl of saline and 100 μl of Freund's incomplete adjuvant (FIA; Sigma). Control rats were injected in the same way without P2 peptide. Captopril (Genmed Scientifics Inc., Arlington, MA, USA; 5 mg/kg body weight in 1 ml saline) was intraperitoneally injected once daily into the rats of captopril treatment group immediately after immunization, whereas 1 ml saline was used in other two groups.

Clinical signs and scores. An observer blindly in the regimen treatment weighted rats daily to examine a presence of clinical deficit, and scored them every day for paresis severity of based on the followings: 0, no illness; 1, flaccid tail; 2, paraparesis or ataxia; 3, tetraparesis or hind-limb paralysis; 4, tetraparesis and difficult breath; and 0.5, intermediate symptoms.

The collection of tissues. Rats were deeply anaesthetized with ether, and sciatic nerve segments excised close to the lumber spinal cord were removed from eight rats in each group twelve days after immunization. Sciatic nerves were either snap-frozen in liquid nitrogen for Western blot or were fixed in 4% paraformaldehyde/embedded in paraffin for immunohistochemistry.

HE and LFB staining. Paraffin sections of sciatic nerve were stained with haematoxylin (HE), and replicate sections were stained with luxol fast blue (LFB) violet for the evaluation of cell infiltration and demyelination. The images of these sections were taken under an optic microscopy (100×) by digital camera and measured by using Image Pro Plus software (Media Cybernetics, Silver Springs, MD, USA). The results expressed as cells/2 mm. The severity of demyelination in peripheral nerves was scored by using semi-quantitative grading system: 0, normal; 1, less than 25% demyelinated fibers; 2, 25–50%; 3, 50–75%; and 4, more than 75%.

Immunohistochemistry. The paraffin sections (5 μm) of sciatic nerve were deparaffined, rehydrated and then boiled for 15 min in citrate buffer (pH 6.0). Endogenous peroxidases were inhibited with 3% H_2O_2 for 15 min in all sections and nonspecific binding sites were blocked with 10% goat serum (Beyotime, Beijing, China) except for MMP-9 sections. These sections were incubated overnight at 4 °C with β-DG antibody (dilution 1:200), MMP-2 antibody, or MMP-9 antibody (1:100, Santa Cruz, USA). Immunoreactions were visualized with avidin- biotin peroxidase complex (ZSGB-BIO, Beijing, China). Peroxidase reaction was developed by using a diaminobenzidine substrate kit (ZSGB-BIO, Beijing, China). Finally, the sections were counterstained with haematoxylin. In negative control, primary antibodies were omitted.

Western blot. Sciatic nerves from three groups of rats were homogenized in RIPA lysis buffer (Beyotime, Beijing, China) containing protease inhibitor PMSF. Homogenates were centrifuged at 12,000 rpm for 10 min at 4 °C, and supernatant was harvested. The supernatant was frozen in aliquots at −70 °C for Western blot analysis. Partial supernatant extracted from control rats was incubated with 0.2 ng/μL recombinant rat MMP-2 (rMMP-2) or recombinant rat MMP-9 (rMMP-9) (R&D systems, Inc., Minneapolis, MN, USA) at 37 °C for an hour in reaction buffer (50 mM Tris, 10 mM $CaCl_2$, 1 μM $ZnCl_2$, 150 mM NaCl, and 0.05% Brij-35, pH 7.5), also in the presence of 2 mM captopril. Before the use, rMMP-2 and rMMP-9 were activated with 1 mM 4-aminophenylmercuric acetate (APMA; Genmed Scientifics Inc., Arlington, USA) for 2 h at 37 °C.

The protein samples mixed with SDS sample loading buffer plus β-mercaptoethanol were electrophoresed on a 10% SDS–PAGE gel and transferred onto a nitrocellulose membrane (Promega, Madison, USA). Membranes were exposed to β-DG antibody (Santa Cruz Biotech., USA) and GAPDH antibody (ZSGB-BIO, Beijing, China), and then exposed to anti-mouse secondary antibodies conjugated with alkaline phosphatase (AP). Immunoreactive bands were visualized by using AP substrate reagent (Thermo scientific, Waltham, MA, USA or Promega). The band density was quantified by using Image Pro Plus software (Media Cybernetics, Silver Springs, MD, USA). All of them were normalized to GAPDH for the relative values.

Statistical analysis. Differences between groups were tested by an one-way ANOVA test. Differences between pairs of groups were tested by Student's *t*-test. Differences of evaluation for clinical and neuropathological data were assessed by a Mann–Whitney *U*-test. Data are presented as mean ± SE and *P*-value < 0.05 was defined as significance.

Results

Sciatic nerves in the animal model of experimental autoimmune neuritis (EAN) typically show inflammatory demyelination and cell filtration (Fig. 1A–C). These changes are similar to pathological changes of autoimmune neuritis in patients, such as inflammatory demyelination, leukocyte infiltration, and myelin sheath breakdown [22–26]. In the elucidation of the role of MMP-mediated β-DG cleavage in the autoimmune neuritis, our strategies include to examine whether MMPs expression and β-DG cleavage are associated with EAN and whether MMP inhibitor improves pathological changes and clinical signs in EAN.

β-DG cleavage and MMP-2/9 expression are associated with EAN

To examine β-DG cleavage in myelin sheath, we used immunohistochemistry to sciatic nerve sections with antibody against β-DG C terminal as well as Western blot to $β\text{-}DG_{30}$ and $β\text{-}DG_{43}$. Normally, the cytoplasmic domains of β-DG are localized in Schwann cell cytoplasm underlying outer membrane apposing basal lamina. If $β\text{-}DG_{43}$ is cleaved into small pieces, such as $β\text{-}DG_{30}$, during the demyelination of neuritis, β-DG C terminal will disappear from myelin sheath and $β\text{-}DG_{30}$ will be high.

Compared with controls (top panel in Fig. 1D), β-DG appears a decrease in EAN sciatic nerves as showed by low immunoactivity in Fig. 1D, bottom panel. Statistical analysis in Fig. 1E shows that the mean score of β-DG is significantly lower in EAN than control ($P < 0.01$, $n = 8$). We further examined whether the decrease of β-DG in EAN sciatic nerves is caused by β-DG cleavage with Western blot to tissues from control and EAN rats. Fig. 1F showed the presences of $β\text{-}DG_{43}$ and $β\text{-}DG_{30}$ in control and EAN, however, the level of $β\text{-}DG_{30}$ appeared higher in EAN group (top panel in Fig. 1F). Statistical analysis in the bottom panel of Fig. 1F shows the semi-quantified results of $β\text{-}DG_{43}$ and $β\text{-}DG_{30}$ by imaging their intensities relative to GAPDH. $β\text{-}DG_{43}$ decreases and $β\text{-}DG_{30}$ increases in EAN rats significantly compared with controls ($P < 0.01$). These results indicate that β-DG cleavage is associated with EAN.

We then examined whether the expressions of MMP-2 and MMP-9 are high in EAN rats for β-DG cleavage and sciatic nerve demyelination. Immunohistochemistry and Western blot analyses were done to determine the distribution and levels of MMP-2 and MMP-9 in control and EAN sciatic nerves. Immunohistochemistry in Fig. 2A shows that MMP-2 (left panels) and MMP-9 (right panels) are present in Schwann cells and endothelial cells. Compared with control (top panels), MMP-2 and MMP-9 appear increased in EAN sciatic nerves (bottoms). Statistical analysis in Fig. 2B show that the relative values of MMP-2 and MMP-9 increase in EAN sciatic nerves (gray bars) significantly ($P < 0.01$, $n = 8$). Moreover, we tested this result by using Western blot to quantify MMP proteins in control and EAN rats. Fig. 2C shows that the levels of MMP-2 and MMP-9 appear higher in EAN group (top panel). Bottom panel shows that the relative values of MMP-2 and MMP-9 in EAN rats are significantly higher compared with controls ($P < 0.01$, $n = 8$). These results indicate that the over-expressions of MMP-2 and MMP-9 are associated with EAN.

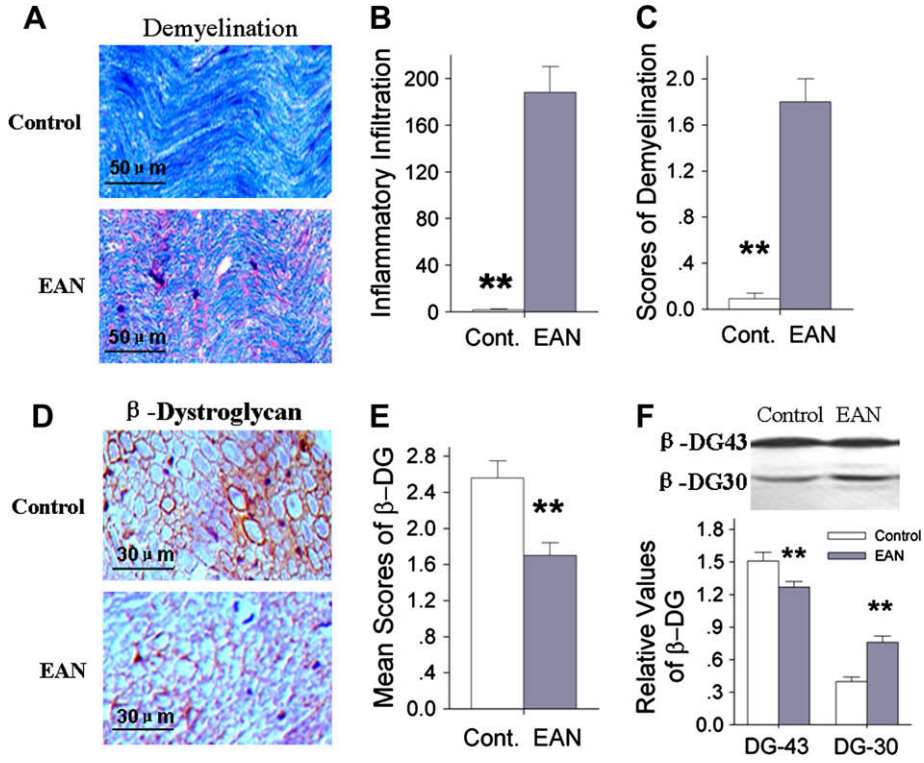

Fig. 1. β-DG cleavage is associated with experimental autoimmune neuritis (EAN). (A) The comparisons of sciatic nerves under control (top panel) and EAN (bottom). (B) Analytic data shows inflammatory cell filtration under control (white bar) and EAN (gray). (C) Bar graph shows the scores of demyelination under control (white) and EAN (gray). (D) The comparisons of β-DG expression in sciatic nerves under control (top panel) and EAN (bottom). (E) Analytic data shows the mean score of β-DG under control (white bar) and EAN (gray). (F) The levels of β-DG_{43} and β-DG_{30}, detected by Western blot, under the conditions of control and EAN. The level of β-DG_{30} is higher and the level of β-DG_{43} is lower under the condition of EAN, compared to control. Asterisks: $^{**}P < 0.01$. *Abbreviation:* Cont., control; EAN, experimental autoimmune neuritis; and DG, dystroglycan.

Furthermore, the experiment for β-DG cleavage by MMPs was conducted by incubating sciatic nerve extracts in recombinant rat MMP-2 or MMP-9 (Methods for detail). The level of β-DG_{30} was elevated after the treatment of rMMP-2 or rMMP-9, and β-DG degradation was suppressed in the presence of captopril, MMP-2/-9 inhibitor (Fig. 2D). Together the results above, we suggest that MMP-mediated β-DG cleavage is involved in autoimmune neuritis. If it is a case, we expect to see that the inhibition of MMPs improves β-DG cleavage and nerves' demyelination in autoimmune neuritis. As captopril inhibited MMP-mediated β-DG cleavage (Fig. 2D), we used captopril as an inhibitor of MMPs.

MMP inhibition improves pathological changes and clinical signs in EAN

The analyses of immunohistochemistry and Western blot were conducted in the groups of EAN and captopril-to-EAN where captopril was treated immediately after auto-immunization (Methods for detail). Panels from left to right in Fig. 3 show the comparisons in the changes of inflammatory demyelination as well as in the expressions of β-DG, MMP-2, and MMP-9 from these two groups. The use of captopril-to-EAN rats appeared to improve demyelination and β-DG cleavage as well as to reduce MMPs' expressions in sciatic nerves (Fig. 3A). The statistical analyses in Fig. 3B from left to right panels indicate that captopril significantly reduces inflammatory cell filtration ($n = 8$), mean demyelination scores ($n = 8$), β-DG cleavage ($n = 8$) and MMP-2/MMP-9 expressions ($n = 8$, $P < 0.01$). Thus, an inhibition of MMPs improves pathological changes in autoimmune neuritis.

To test the improvement of clinical signs by captopril, saline (EAN group) or captopril (EAN plus captopril) was injected once daily from days of post-immunization (DPI) 0–30. Rats with EAN showed a progressive weight loss from DPI 9–16, whereas captopril-treated EAN rats showed no weight loss (Fig. 4A). In addition, EAN rats signed floppy tails at DPI 8 (clinical score: 0.1 ± 0.2), progressive hind-limb paralysis at DPI 12 (clinical score: 2.3 ± 0.5) and an incomplete recovery equivalent to persistent weakness of the tail by DPI 30 (clinical score: 0.30 ± 0.30). In captopril-treated EAN rats, clinical signs were seen at DPI 10 (clinical score: 0.10 ± 0.20), reached to the maximal level at DPI 12 (clinical score: 0.90 ± 0.20) and disappeared at DPI 22 (Fig. 4B). Mann–Whitney *U*-test shows the significant differences in clinical score and weight body between EAN and EAN plus captopril groups ($P < 0.05$). These results indicate that the inhibition of MMPs by captopril reduced the severity of neurological deficits and weight loss of EAN rats.

Discussion

In the study of the mechanisms underlying autoimmune neuritis, our findings are below. MMPs' over-expression and β-DG degradation are associated with experimental autoimmune neuritis in sciatic nerves (Figs. 1 and 2). Recombinant MMP-2 and MMP-9 cleave β-DG (Fig. 2D). MMP-2/9 inhibitor, captopril improve these pathological changes and clinical signs in EAN (Figs. 3 and 4). These data indicate that MMP-mediated β-DG cleavage plays a critical role in the autoimmune neuritis of peripheral nerve system, and the inhibition of MMPs' activity by captopril is a therapeutic option for autoimmune neuritis.

The pathological changes in autoimmune neuritis include inflammatory cell filtration and demyelination in peripheral nerves [22,26–27]. It remains unclear how the demyelination and inflammation occur. In peripheral nerves, DG is produced by Schwann

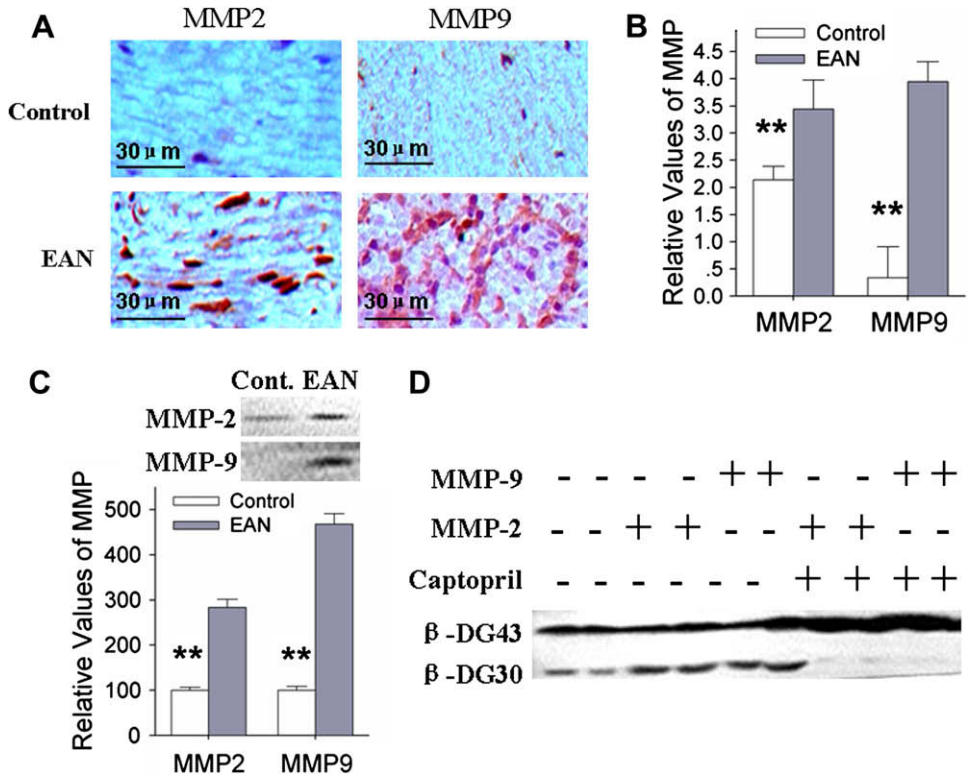

Fig. 2. MMP-2 and MMP-9 are over-expressed during experimental autoimmune neuritis (EAN). (A) The comparisons of MMP-2 (left) and MMP-9 (right) expressions in sciatic nerves under control (top panels) and EAN (bottoms). (B) Analytic data illustrate the relative values of MMP-2 and MMP-9 under control (white bars) and EAN (gray bars). (C) The levels of MMP-2 and MMP-9, detected by Western blot, under the conditions of control and EAN. The levels of MMP-2 and MMP-9 are higher under the condition of EAN, compared with the control. (D) Western blot data show that MMP-2 and MMP-9 cleave β-DG_{43} into β-DG_{30}, which are blocked by captopril. Asterisks: $^{**}P < 0.01$. *Abbreviation:* Cont., control; EAN, experimental autoimmune neuritis; DG, dystroglycan.

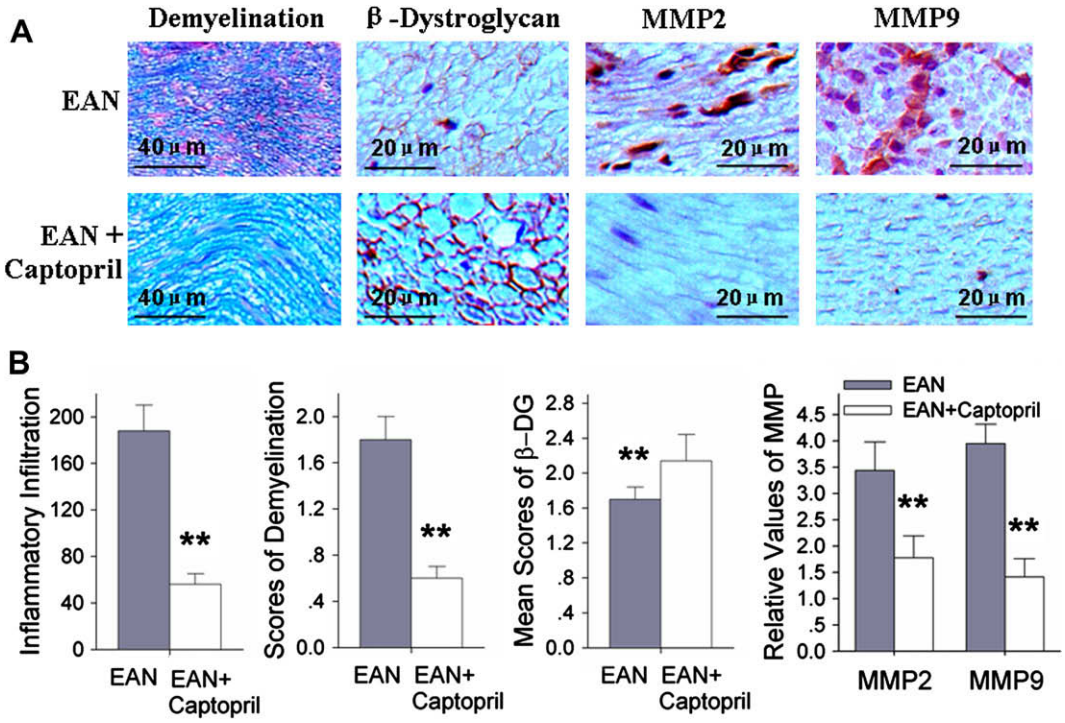

Fig. 3. Captopril blocks inflammatory demyelination, β-DG cleavage as well as MMP-2/-9 expressions during experimental autoimmune neuritis (EAN). (A) The comparisons of inflammatory demyelination and β-DG/MMP-2/-9 expressions in sciatic nerves under EAN (top panels) and EAN plus captopril (bottoms). (B) Bar graphs from left to right illustrate the values of inflammatory filtration, the scores of demyelination the mean score of β-DG and the relative values of MMP-2 and MMP-9 under EAN (gray bars) and EAN plus captopril (white bars), respectively. Asterisks: $^{**}P < 0.01$. *Abbreviation:* Cont., control; EAN, experimental autoimmune neuritis; DG, dystroglycan.

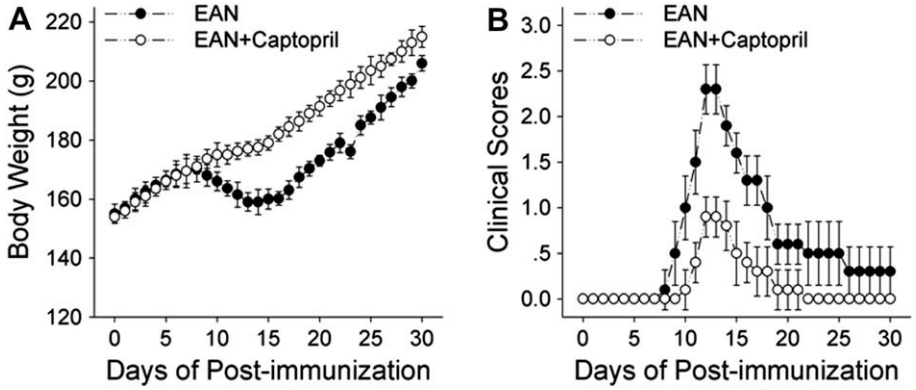

Fig. 4. Captopril improves the loss of body weight and the score of clinical signs in EAN rats. Captopril or saline (5 mg/kg body weight in 1 mL saline, i.p., once daily) was given immediately after an inoculum containing P2 peptide (230 μg) for immunization. (A) Captopril improves the loss of body weight in EAN rats ($P < 0.05$, Mann–Whitney U-test). (B) Captopril improves the clinical scores of EAN rats over time ($P < 0.05$).

cells and located to the outer membrane apposing basal lamina [8]. Our data demonstrate that MMP-mediated β-DG cleavage is parallel with inflammatory cell infiltration and demyelination at the peak of EAN (DPI 12). Therefore, β-DG cleavage may result in nerve demyelination and inflammatory cell infiltration based on the following principles. DG complex stabilizes the plasma membrane by acting as an axis to link extracellular matrix to intracellular cytoskeleton, and plays a unique role in myelin formation and stability [11,28]. The disruption of DG complex in autoimmune neuritis impairs the stability of cell membrane, the viability of Schwann cells [17] and the demyelination of peripheral nerves, which may give path for inflammatory cell infiltration.

Autoimmune neuritis with severe demyelination and inflammatory cell infiltration in the peripheral nerves developed severe movement disorder and weight loss [29–32]. Such clinical signs and pathological changes are significantly improved by the treatment of captopril, MMP inhibitor (Figs. 3 and 4). These results indicated that captopril can be considered as a therapeutic option for the treatment of acute autoimmune neuritis, such as Guillain–Barré syndrome.

The proteolysis of β-DG by MMP-2 and MMP-9 has been reported in previous studies [17–20], such as the disruption of DG complex by MMPs in the peripheral tissues, astrocyte end-feet, schwannoma cell line and cultured neurons. We present that MMP-mediated β-DG cleavage causes inflammatory demyelination and cell filtration in autoimmune neuritis, which updates the profile for the roles of MMP-mediated β-DG proteolysis under the pathological conditions. It is noteworthy that mice with the conditional knockout of DG gene show viable, fertile as well as peripheral nerve myelination despite some abnormality [8]. The knockout of a single gene usually alters the expression of other genes, which may compensate the function encoded this knockout gene, such that animals may not demonstrate the obvious changes in phenotype. On the other hand, it is possible that other proteins related to nerves' myelination undergo pathological changes in autoimmune neuritis, which remains to be tested.

Acknowledgments

This work was supported by the Education Department of Heilongjiang Province in China (1152hz25) and the Science and Technology Department of Heilongjiang Province in China (LC06C24).

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