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Valproate Attenuates Nitroglycerin-Induced Trigeminovascular Activation by Preserving Mitochondrial Function in a Rat Model of Migraine

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Migraine is a chronic disease that interferes with life quality and work productivity. Valproate shows protective effects against migraine, yet the underlying mechanisms are unclear. This study aimed to evaluate the potential effect of valproate on migraine using a rat model of nitroglycerin-induced trigeminovascular activation, as well as to explore the underlying mechanism.

Material/Methods: Intraperitoneal injection of nitroglycerin was conducted to induce trigeminovascular activation in rats. To explore the protective effect of valproate, a low dose (100 mg/kg) or a high dose (200 mg/kg) of valproate was intraperitoneally injected into rats, and then the levels of 5-hydroxytryptamine and nitric oxide in the peripheral blood were examined. The mtDNA copy number and the protein levels of peroxisome proliferator-activated receptor-γ coactivator 1α, mitochondrial transcription factor A, and peroxisome proliferator-activated receptor-γ in the spinal trigeminal nucleus were detected to evaluate the biogenesis of mitochondria. The mitochondrial energy metabolism was determined by the mitochondrial membrane potential and the levels of adenosine triphosphate, cytochrome C oxidase, and reactive oxygen species.

Results: Valproate attenuated nitroglycerin-induced trigeminovascular activation in rats, with reduced scratching behavior and restored 5-hydroxytryptamine and nitric oxide levels. Moreover, the mitochondrial energy metabolism and the biogenesis of mitochondria were preserved by valproate in nitroglycerin-treated rats.

Conclusions: The protective effect of valproate against migraine may be achieved through the modulation of mitochondrial biogenesis and function. Our study provides evidence for the potential use of valproate in the treatment of migraine.

MeSH Keywords: Energy Metabolism • Migraine Disorders • Mitochondrial Turnover • Valproic Acid

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Background

Migraine is a chronic nerve vascular disease that is commonly seen in clinical settings. The major clinical symptoms of migraine include moderate-to-severe pulsatile headaches, often accompanied by nausea and vomiting [1]. Migraine seriously interferes with quality of life and work productivity. Optical and acoustic stimuli, as well as some daily activities, are known to exacerbate migraine headaches, whereas a quiet environment and plenty of rest can relieve the headaches.

Valproate is a broad-spectrum antiepileptic drug that is used to over one-third of epileptic patients [2]. Valproate has also been approved by the FDA for the treatment of neuralgia and bipolar disorders. Valproate can exert a neuroprotective effect and modulates neuronal differentiation and survival, as well as long-term neuroplasticity [3,4]. In addition, valproate can protect the cortical neurons from spontaneous cell death and improve the behavioral outcomes [5]. Valproate is effective in relieving headaches and is proposed to be a potential anti-migraine drug [6–9]. Valproate can also be used in the treatment of headaches from medication overuse [10] and as a prophylaxis of episodic migraine [9].

Mitochondria are important sites of energy metabolism, especially in the high energy-consuming organs. Mitochondrial dysfunction is associated with a variety of nervous system diseases [11]. It has been reported that mitochondrial function is often impaired in patients with migraine [12], and mitochondrial dysfunction is thus implicated in the pathophysiology of migraine [11,13].

Valproate can be used to prevent and mitigate migraine, but the underlying mechanism remains unclear. In the present study, we explored the effect of valproate on migraine and the underlying mechanism in a rat model of nitroglycerin-induced trigeminovascular activation. Valproate was found to attenuate nitroglycerin-induced trigeminovascular activation in rats by preserving the mitochondrial function.

Material and Methods

Animals

Male Sprague-Dawley rats (8 weeks old, weighing around 200 g) were obtained from Liaoning Changsheng Biotechnology Co., Ltd. (Benxi, China) and housed in a controlled environment (23±2°C, 50±5% relative humidity, and 12 h: 12 h light: dark cycles).

Forty rats were randomly divided into 4 groups (Control, Model, Model+VP-L, and Model+VP-H). Rats in the Model+VP-L group and Model+VP-H group received a low dose of valproate (100 mg/kg in saline) (Dalian Meilun Biotech Co., Ltd., Dalian, China) or a high dose of valproate (200 mg/kg in saline) every day by intraperitoneal injection for 5 days. Rats in the Control and Model groups received an equal volume of saline. On the sixth day, rats in the Model, Model+VP-L, and Model+VP-H groups received an intraperitoneal injection of nitroglycerin (10 mg/kg in saline) (Beijing Yimin Pharmaceutical Co., Ltd., Beijing, China), and rats in the Control group received an equal volume of saline. After administration of nitroglycerin, the number of scratching behaviors was recorded. Four hours after nitroglycerin injection, the peripheral blood was collected and the levels of 5-hydroxytryptamine (5-HT) and nitric oxide (NO) were measured using a 5-HT ELISA kit (USCN, Wuhan, China) and a total NO assay kit (Beyotime, Haimen, China) respectively. The rats were then sacrificed, and the spinal trigeminal nucleus was obtained for subsequent experiments. The care and treatment of the animals was approved by the Animal Ethics Committee of the First Affiliated Hospital of Harbin Medical University.

Measurement of mtDNA copy number

DNA was extracted from rat spinal trigeminal nucleus using a DNA extraction kit (Tiangen, Beijing, China) according to the manufacturer's instructions. The mtDNA copy number was measured by quantitative real-time PCR according to the methods described previously [14–17], with the following primers: DN1 forward primer: 5'-TTATCCTCTTATCCGTCCTC-3'; DN1 reverse primer: 5'-TGTTAAGTCGAAGGGAGC-3'; β-actin forward primer: 5'-AGGGAAATCGTGCGTGAC-3'; β-actin reverse primer: 5'-AGGAAGGAAGGCTGGAAG-3'. The relative mtDNA copy number was calculated using the $2^{-\Delta\Delta Ct}$ method.

Western blot analysis

Proteins in the spinal trigeminal nucleus were extracted using a total protein extraction kit (Wanleibio, Shenyang, China). After measurement of the protein concentration with a BCA protein assay kit (Wanleibio), an equal amount of proteins from each group was subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis. Subsequently, the separated proteins were transferred onto polyvinylidene fluoride membranes (Millipore, Bedford, MA), followed by blocking with 5% skim milk. After washing with TBST, the membranes were incubated overnight at 4°C with primary antibodies against peroxisome proliferator-activated receptor-γ (PPARG) (1:400, Bioss, Beijing, China), peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) (1:1000, Abcam, Cambridge, UK), mitochondrial transcription factor A (TFAM) (1:2000, Abcam), B-cell lymphoma-2 (Bcl-2), Bcl-2-associated X protein (Bax) (1:400, Boster, Wuhan, China), and β-actin (1:1000, Santa Cruz, Dallas, TX). Thereafter, the membranes were washed with TBST and then incubated with the corresponding horseradish peroxidase-labeled

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secondary antibody (1:5000, Wanleibio) at 37°C for 45 min. The membranes were washed with TBST again and the signals were detected with an ECL detection system (Wanleibio). The gray intensity of the target proteins was analyzed with Gel-Pro-Analyzer software, and the relative protein level was calculated using β-actin as the internal reference.

Determination of adenosine triphosphate (ATP) level

The spinal trigeminal nucleus was homogenized in 9 volumes of PBS. After freezing and thawing 3 times, the homogenate was centrifuged and the supernatant was harvested. The protein concentration in the supernatant was measured with a BCA protein assay kit, and the ATP level was determined with an ATP assay kit (JianchengBio, Nanjing, China) according to the manufacturer's protocol.

Cytochrome C oxidase activity assay

The protein concentration in the supernatant of spinal trigeminal nucleus homogenate was determined, and the activity of cytochrome C oxidase in the supernatant was detected with a rat cytochrome C oxidase assay kit (WHB, Shanghai, China) according to the manufacturer's instructions.

Measurement of reactive oxygen species (ROS)

After measurement of protein concentration, the supernatant of tissue homogenate was used for determining the ROS level using an ROS assay kit (JianchengBio) according to the protocol.

Determination of mitochondrial membrane potential

The mitochondrial membrane potential was assessed by staining with the JC-1 probe, followed by fluorescence microscopy or flow cytometry. The spinal trigeminal nucleus was made into single-cell suspension. The cells were incubated with the JC-1 working solution from the JC-1 kit (KeyGen, Nanjing, China) at 37°C for 20 min. The cells were then washed twice and resuspended in the incubation buffer. The cell images were captured under a fluorescence microscope (Olympus, Tokyo, Japan), and the fluorescence signals were quantitated by flow cytometry (BD, Franklin Lakes, NJ).

Statistical analysis

The results are presented as mean ± standard deviation (SD). The differences between the Control group and the Model group were analyzed using Student's *t* test, and differences between the Model group, Model+VP-L group, and Model+VP-H group were analyzed using one-way analysis of variance followed by Bonferroni's multiple comparison test. $p<0.05$ was considered to be statistically significant.

Results

Valproate attenuated nitroglycerin-induced trigeminovascular activation

After induction of trigeminovascular activation with nitroglycerin, the number of scratching behaviors was recorded. As shown in Figure 1A, the number of scratching behaviors in the Model group was significantly higher than that in the Control group. Compared with the Model group, the number of scratching behaviors was decreased in the Model group rats with valproate pre-treatment. The levels of 5-HT and NO in the peripheral blood were also measured. Consistent with the number of scratching behaviors, the 5-HT level was decreased and the NO level was increased in the Model group compared with the Control group, and the nitroglycerin-induced changes were minimized by valproate (Figure 1B, 1C). These results demonstrate that treatment with valproate attenuates nitroglycerin-induced trigeminovascular activation in rats.

Valproate modulated mitochondrial biogenesis

The mtDNA copy number was measured in the rat model with or without valproate treatment. Compared with the Control group, the mtDNA copy number in the Model group was decreased (Figure 2A). A low dose of valproate significantly attenuated nitroglycerin-induced reduction of mtDNA copy number, and a high dose of valproate preserved the mtDNA copy number to nearly normal level (Figure 2A). To investigate the effect of valproate on the biogenesis of mitochondria, the protein levels of PGC-1α, TFAM, and PPARG were detected by Western blot analysis. As shown in Figure 2, the protein levels of PGC-1α, TFAM, and PPARG were lower in the Model group in comparison with the Control group (Figure 2B–2D), but nitroglycerin-induced reduction in the expression of PGC-1α, TFAM, and PPARG was inhibited by valproate. These results indicate that valproate maintains mitochondrial biogenesis that was disrupted by nitroglycerin.

Mitochondrial energy metabolism was preserved by valproate

ATP is an important product of energy metabolism. The level of ATP in the spinal trigeminal nucleus was measured in the nitroglycerin-induced trigeminovascular activation rat models with or without valproate treatment. The ATP level was lowered in the Model group, indicating the dysfunction of mitochondrial energy metabolism. Compared with the Model group, a low dose of valproate elevated the ATP level, which was further increased by a high dose of valproate (Figure 3A). These results suggest that nitroglycerin-induced dysfunction of mitochondrial energy metabolism in the spinal trigeminal nucleus is alleviated by valproate.

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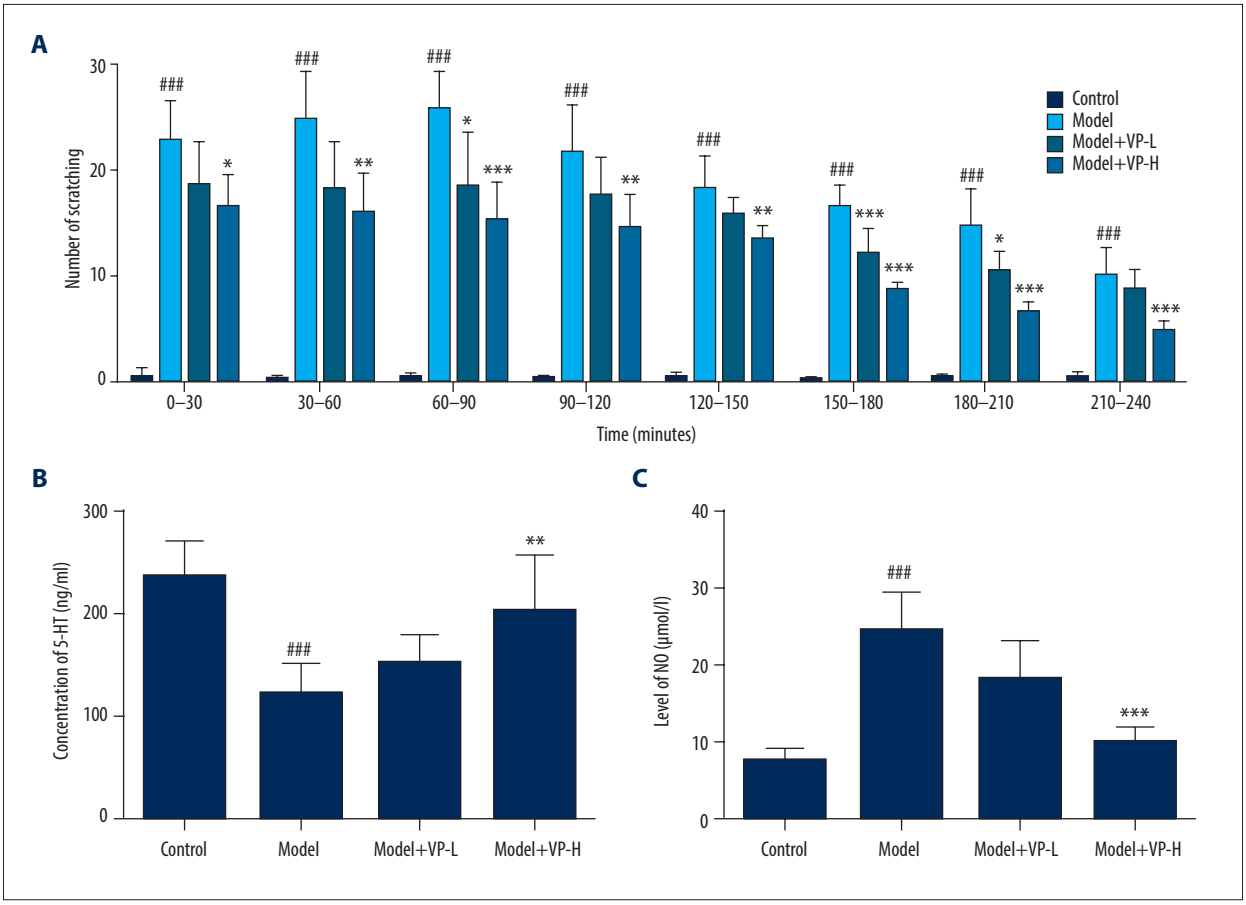

Figure 1. Valproate attenuates nitroglycerin-induced trigeminovascular activation in rats. (**A**) After treatment with nitroglycerin and valproate, the number of scratching behaviors in each group was recorded. (**B**) The level of 5-HT in the peripheral blood were measured. (**C**) Level of NO in each group. The results are presented as mean ±SD. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared with the Model group. ### $p<0.001$ compared with the Control group. VP-L – low dose of valproate (100 mg/kg); VP-H – high dose of valproate (200 mg/kg); 5-HT – 5-hydroxytryptamine; NO – nitric oxide.

The mitochondrial membrane potential is crucial for energy metabolism in the mitochondria. In this study, the mitochondrial membrane potential was detected by JC-1 probe. As shown in Figure 3B, almost all the JC-1 probes in the Control group showed red fluorescence, which indicated a high mitochondrial membrane potential. In contrast, the JC-1 probes in the Model group showed green fluorescence, indicating a low mitochondrial membrane potential in the nitroglycerin-induced trigeminovascular activation rat model. After treatment with a low dose of valproate, the JC-1 probes showed more red fluorescence and less green fluorescence, while the JC-1 probes in the Model+VP-H group showed almost full red fluorescence (Figure 3B). These results indicate that valproate treatment maintains the mitochondrial membrane potential in nitroglycerin-induced trigeminovascular activation. Further, the mitochondrial membrane potential was quantitated by flow cytometry. Consistent with the observations by fluorescence microscopy, the mitochondrial membrane potential in the Model group was significantly decreased compared with the Control group. However, treatment with valproate prevented nitroglycerin-induced reduction of mitochondrial membrane potential (Figure 3C, 3D). These results demonstrate that valproate preserves the mitochondrial membrane potential in the spinal trigeminal nucleus during nitroglycerin-induced trigeminovascular activation.

Bax and Bcl-2 have close relationships with the opening of the mitochondrial permeability transition pore. Here, the protein levels of Bax and Bcl-2 were detected by Western blot. In the Model group, the protein level of Bax was higher than that in the Control group (Figure 4A), and the protein level of Bcl-2 was lower than that in the Control group (Figure 4B). In contrast, treatment with valproate decreased the level of Bax and increased the level of Bcl-2 in the nitroglycerin-treated rats (Figure 4A, 4B). These results provide molecular evidence for the hypothesis that valproate modulates the mitochondria energy metabolism in subjects with migraine.

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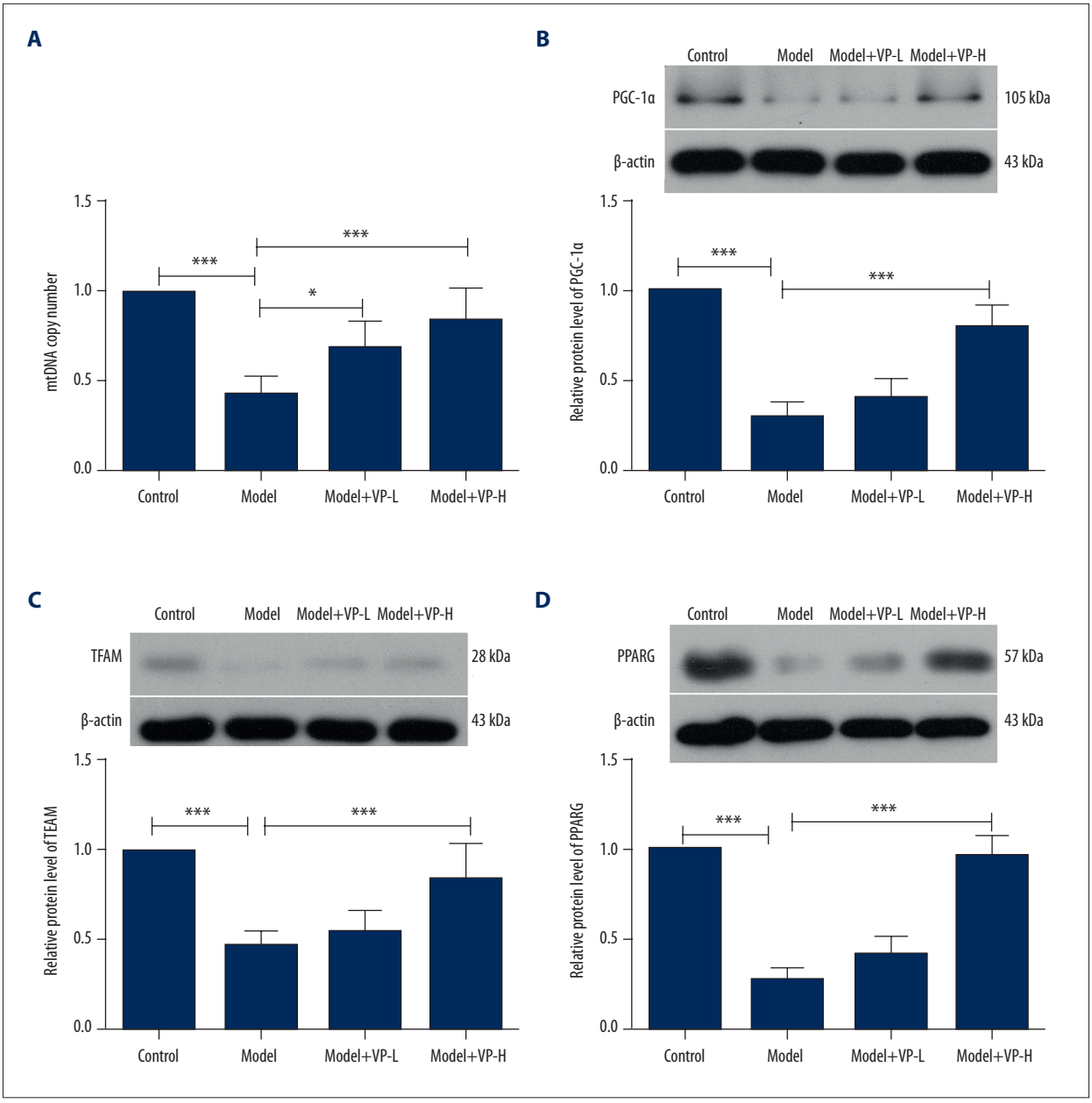

Figure 2. Valproate preserves the biogenesis of mitochondria in a rat model of nitroglycerin-induced trigeminovascular activation. (**A**) The mtDNA copy number in the spinal trigeminal nucleus was measured. (**B**) The protein level of PGC-1α was detected by Western blot analysis with β-actin as the internal reference. (**C**) Western blot was used to detect the protein level of TFAM. β-actin was used as the internal reference when the relative protein level was calculated. (**D**) Western blot was used to detect the protein level of PPARG. Each experiment was repeated 3 times and the results are presented as mean ±SD. * $p<0.05$, *** $p<0.001$. VP-L – low dose of valproate (100 mg/kg); VP-H – high dose of valproate (200 mg/kg); PGC-1α – peroxisome proliferator-activated receptor-γ coactivator-1α; TFAM – mitochondrial transcription factor A; PPARG – peroxisome proliferator-activated receptor-γ.

Cytochrome C oxidase is a key enzyme in the respiratory chain. The activity of cytochrome C oxidase was also examined in our study. As shown in Figure 4C, the cytochrome C oxidase activity in the Model group was decreased significantly as compared with the Control group. This was consistent with the decreased ATP level in the Model group. Compared with the Model group, valproate dose-dependently increased the activity of cytochrome C oxidase in the nitroglycerin-treated rats (Figure 4C).

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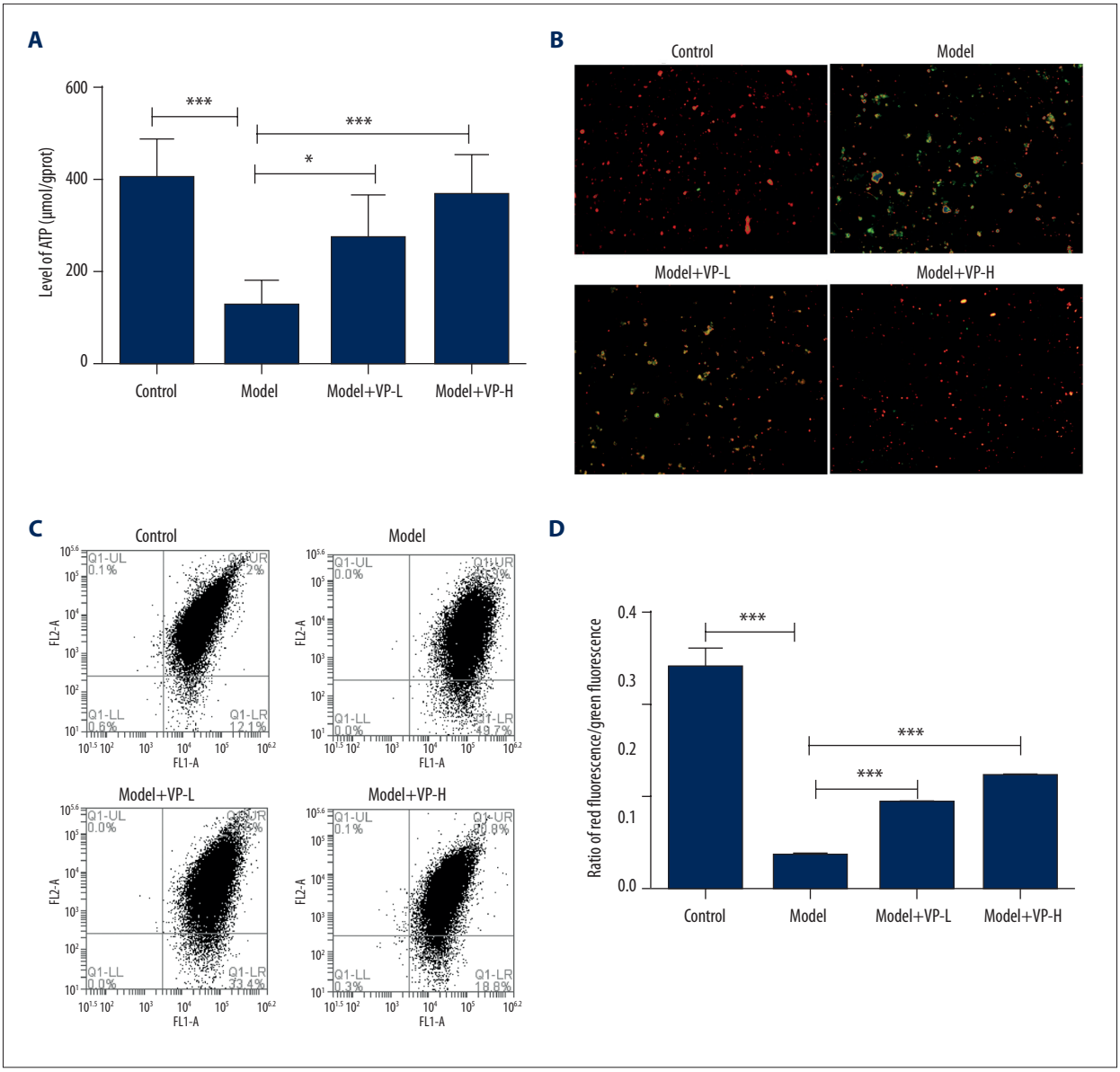

Figure 3. Valproate maintains mitochondrial energy metabolism in a rat model of nitroglycerin-induced trigeminovascular activation. (**A**) The ATP level in the spinal trigeminal nucleus was measured. (**B**) The mitochondrial membrane potential was detected with JC-1. The images were captured under a fluorescence microscope. Green fluorescence indicates a low mitochondrial membrane potentia and red fluorescence indicates a high mitochondrial membrane potential. (**C, D**) The mitochondrial membrane potential was detected by flow cytometry, and the ratio of red fluorescence/green fluorescence was calculated. The results are presented as mean ±SD. * $p<0.05$, *** $p<0.001$. VP-L – low dose of valproate (100 mg/kg); VP-H – high dose of valproate (200 mg/kg); ATP – adenosine triphosphate.

ROS is a byproduct of disordered mitochondrial energy metabolism. Consistent with the disrupted mitochondrial energy metabolism in nitroglycerin-treated rats, a significantly increased ROS level was observed in the Model group (Figure 4D). Treatment with valproate significantly attenuated nitroglycerin-induced ROS elevation in the spinal trigeminal nucleus.

Discussion

In the present study, we evaluated the effect of valproate on migraine in a rat model of nitroglycerin-induced trigeminovascular activation, and further investigated the underlying mechanism. Valproate decreased the number of scratching behaviors and reduced the changes in 5-HT and NO levels in our rat model of nitroglycerin-induced trigeminovascular activation. Moreover, the

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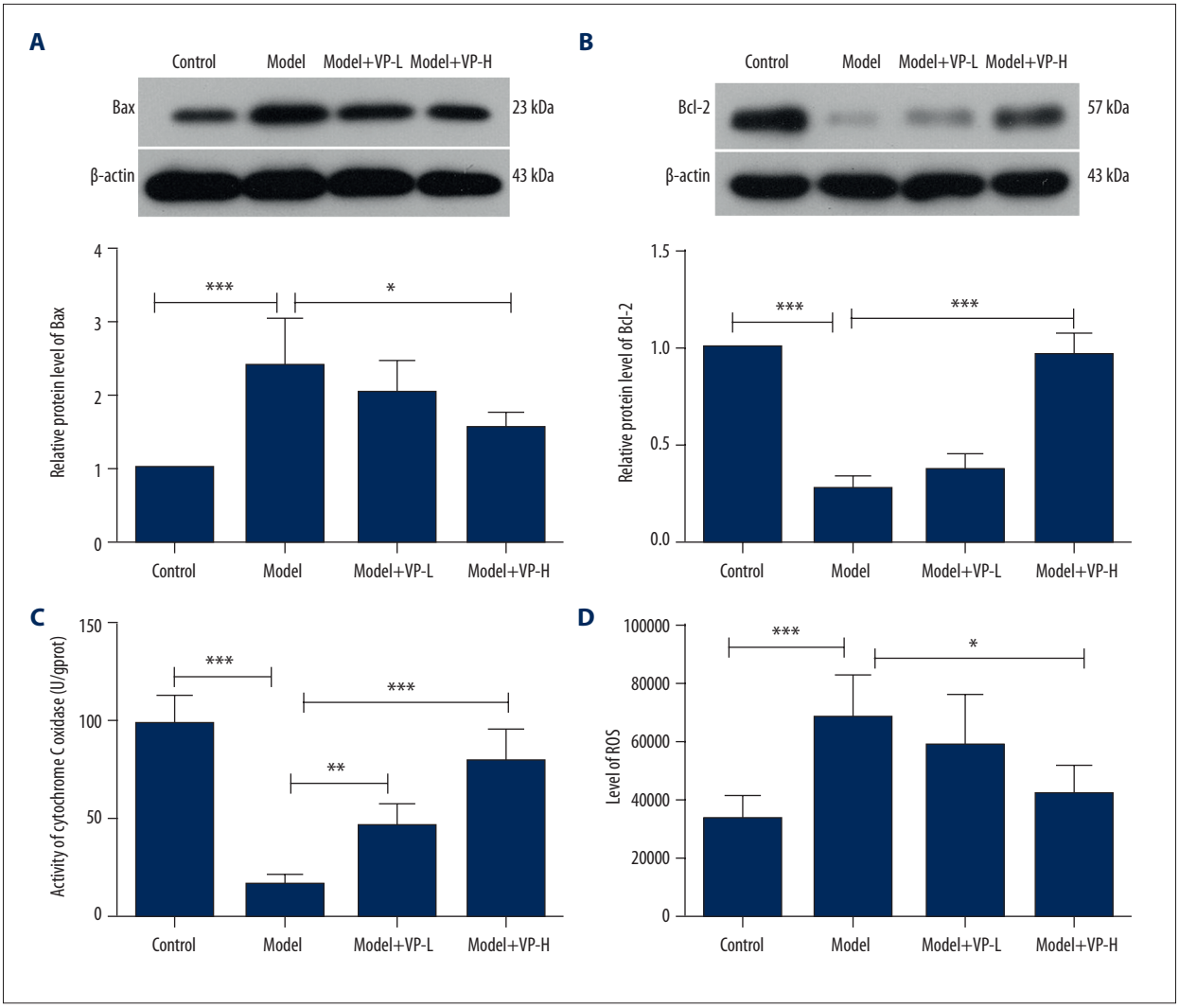

Figure 4. Valproate inhibits nitroglycerin-induced alterations in Bax, Bcl-2, cytochrome C oxidase, and ROS levels. (**A**) The protein level of Bax in each group was detected by Western blot and the relative protein level was calculated using β-actin as the internal reference. (**B**) Bcl-2 level in each group was detected by Western blot. (**C**) The activity of cytochrome C oxidase in each group was measured. (**D**) The ROS level in each group was determined. The results are shown as mean ±SD. * $p<0.05$, ** $p<0.01$, *** $p<0.001$. VP-L – low dose of valproate (100 mg/kg); VP-H – high dose of valproate (200 mg/kg); Bcl-2 – B-cell lymphoma-2; Bax – Bcl-2-associated X protein; ROS – reactive oxygen species.

mitochondrial biogenesis and energy metabolism, which was disrupted in nitroglycerin-treated rats, was stabilized by valproate. These results prompted us to hypothesize that valproate may attenuate migraine by preserving mitochondrial function.

Valproate is an antiepileptic drug. In our study, valproate was found to attenuate nitroglycerin-induced trigeminovascular activation in rats. Consistently, valproate has been reported to show a remission effect on migraine [6], and intravenous injection with valproate can rapidly abort headaches [18]. Similarly, other antiepileptic drugs, such as topiramate and divalproex, have also been demonstrated to be effective prophylactic treatments of migraine [19].

Mitochondria are crucial to mammalian cells because they are the major sites of ATP production, and are also related to apoptosis regulation and Ca^{2+} homeostasis [20]. Dysfunction of mitochondria can lead to a variety of disorders, especially in organs consuming large amounts of energy. Migraine is a complex disease influenced by the interplays between genetic and environmental factors. Recently, increasing evidence suggests that mitochondrial dysfunction is involved in migraine. Phosphorus magnetic resonance spectroscopy studies show that mitochondrial function is impaired in migraine patients. N-acetylaspartate (NAA), which is produced exclusively in neuronal mitochondria, is reported to be reduced in migraine patients [21,22]. Recent reports also show that abnormal

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mitochondrial function leads to intracellular Ca^{2+} penetration, excessive ROS production, and oxidative phosphorylation deficiency, which may ultimately cause energy failure in cells, and trigger migraine [11]. In the present study, we showed that the mitochondrial biogenesis and the mitochondrial energy metabolism were impaired in a rat model of nitroglycerin-induced trigeminovascular activation. Our results supportive the hypothesis that mitochondrial dysfunction is associated with the pathophysiology of migraine.

In our study, the mtDNA copy number was decreased in the nitroglycerin-induced trigeminovascular activation model, whereas treatment with valproate preserved the mtDNA copy number in the spinal trigeminal nucleus. These results suggest that the mitochondrial biogenesis may be influenced by migraine and valproate. The protein levels of PGC-1α, TFAM, and PPARG, which are closely associated with the biogenesis of mitochondria, were reduced in the rat model of nitroglycerin-induced trigeminovascular activation and were maintained by valproate. The changes in these 3 proteins provide additional evidence for our hypothesis that valproate prevents dysregulation of mitochondrial biogenesis. Consistent with our results, Sitarz et al. showed that valproate had positive effects on the maintenance of mtDNA and mitochondrial biogenesis in POLG-deficient fibroblasts [23]. Moreover, valproate also plays an anti-oxidative role and alleviates neuronal damages caused by migraine attacks through NF-κB [24].

Impaired energy metabolism is a common feature of migraine [25,26]. In our study, the mitochondrial energy metabolism was disrupted in a rat model of nitroglycerin-induced trigeminovascular activation, and was rescued by valproate. These results suggest that the effect of valproate on migraine may be associated with its action on mitochondrial function. Consistent with our study results, Bachmann et al. showed that long-term treatment with valproate enhances mitochondrial function and protects against methamphetamine-induced mitochondrial damage [27]. However, Komulainen et al. reported that treatment with valproate inhibits mitochondrial respiration and leads to mitochondrial dysfunction, oxidative stress, and increased cell death of HepG2 cells, which was assumed to be attributed to the hepatotoxicity of valproate [28]. Interestingly, Bachmann et al. also showed that a low dose of valproate enhances cellular respiration, whereas a high dose of valproate inhibits the respiration rate [27]. Thus, the "contradictory" results from Bachmann's and Komulainen's work may be due to the different doses used. Therefore, further investigations are needed to address whether valproate has hepatotoxicity during the treatment of migraine, as well as to determine the optimal dosage of valproate for the treatment of migraine.

The ratio of Bax and Bcl-2 is very important to the opening of the mitochondrial permeability transition pore, which also leads to the release of cytochrome C and the generation of ROS. Migraine attack triggers oxidative stress, resulting in increased production of ROS [29,30]. In our study, nitroglycerin-induced mitochondrial dysfunction was associated with abnormal levels of Bax, Bcl-2, cytochrome C oxidase, and ROS, and these changes were diminished by valproate treatment. As Bax, Bcl-2, and ROS are closely related to cell apoptosis [31], the abnormal levels of Bax, Bcl-2, and ROS in our study suggest that migraine may also have a relationship with apoptosis of neurocytes, but this hypothesis needs to be verified in future studies.

Conclusions

Our study demonstrated that valproate attenuated nitroglycerin-induced trigeminovascular activation in rats. The protective effect of valproate against nitroglycerin-induced trigeminovascular activation was associated with valproate-mediated protection of mitochondrial biogenesis and function. Our study suggests that valproate may attenuate migraine through the maintenance of mitochondrial function, and provides a possible mechanism underlying the effect of valproate on migraine.

Conflict of interest

The authors declare that there is no conflict of interest.

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