Activating the interleukin-6-Gp130-STAT3 pathway ameliorates ventricular electrical stability in myocardial infarction rats by modulating neurotransmitters in the paraventricular nucleus

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Research article

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Abstract

Background: Malignant ventricular arrhythmia is one of the main reason of death in acute myocardial infarction. In recent years, more and more attention has been paid to the mechanism of its pathogenesis. In this study we investigated the changes of inflammatory factors in the paraventricular nucleus during acute myocardial infarction and its effect on ventricular stability. Methods : The rats were divided into control group, myocardial infarction group and drug-administered group to observe how interleukin-6 and its downstream GP130-STAT3 pathway in paraventricular nucleus effect the ventricular stability . All data are expressed as the mean ± SEM. One-way ANOVA was used for comparison between groups, and the LSD test was used for comparison between two groups. $p<0.05$ was considered statistically significant. Results : After myocardial infarction (MI), the concentration of inflammatory factor interleukin-6 and the downstream Gp130-STAT3 pathway increased in the PVN. After anti-interleukin-6 antibody and Gp130 inhibitor (SC144) injection into the PVN in MI rats, glutamate increased and GABA decreased in the PVN. We also observed a higher plasma norepinephrine concentration, which increased the vulnerability to ventricular arrhythmias. Conclusions : Interleukin-6 in PVN plays as protective way in MI .and the Gp130-STAT3 pathway plays a key role in this process. We anticipate that our findings will provide new ideas for the prevention and treatment of arrhythmia after MI.

Background

Acute myocardial infarction (AMI) is myocardial necrosis caused by acute, persistent ischaemia and hypoxia in the coronary arteries. Arrhythmia is one of the major complications of AMI, especially ventricular arrhythmia, which is one of the main reasons for sudden death [1]. In AMI, there two peak incidences of ventricular arrhythmia: 1 hour and 24 hours, respectively. After 24 hours, the susceptibility to ventricular arrhythmia is significantly reduced. The mechanism of ventricular arrhythmia in myocardial infarction (MI) within 2 hours may be due to reentry and injury current, while the mechanism after 2 hours may be reentry and autonomic abnormalities [2]. The autonomic nervous system comprises sympathetic and para-sympathetic nerves. The cardiac sympathetic nervous system (SNS) can release norepinephrine (NE) to increase the heart rate and decrease ventricular electrical stability. However, the mechanism of this process is not well understood [3].

The central nervous system may play an important role in this process [4, 5]. Lampert R. et al. have proven that ventricular tachycardia and ventricular fibrillation (VF) can be induced by psychological stress, sudden changes in mental state, brain trauma, and elevated intracranial pressure [6]. In the clinic, some patients with frequent premature ventricular beats do not have organic heart disease but often have anxiety. The static fMRI of patients with idiopathic ventricular arrhythmia reveals the activation of brain zones [7]. Brain tissue regions and nuclei, from the medulla to the cerebral cortex, play an important role in the development of arrhythmia, and there are complex and variable interconnections. Stimulating different brain regions and nerve nuclei can lead to different types of arrhythmias. The nucleus mostly commonly associated with ventricular arrhythmia is the hypothalamic paraventricular nucleus (PVN). The

hypothalamus is a subcortical higher-level centre that regulates visceral activity, endocrine function, and emotional behaviour. These functional activities induce changes in cardiovascular activity [8]. However, the exact mechanism of the PVN's effect on arrhythmia remains unclear and needs further investigation. Changes in neurochemical factors, such as reactive oxygen species and inflammatory cytokines, in the hypothalamic PVN during MI may be important factors in the increase in sympathetic nerve sensitivity during MI. Yu-Ming Kang has shown that microinjection of pro-inflammatory cytokine inhibitors into the central nervous system can alleviate the symptoms of MI, and the effect is significantly better than that of the peripheral route of administration [9, 10]. The endocrine mechanism may play an important role in this process. For example, glutamate is enhanced and GABA declines in the PVN during MI, thereby affecting sympathetic over-activation and further affecting heart function [11].

Shigeaki Suzuki et al. have demonstrated that unlike other inflammatory factors, IL-6 plays a protective role in the early stage of injury. Intracerebroventricular injection of rhIL-6 dramatically reduced ischaemic brain damage when measured 24 hours after middle cerebral artery occlusion [12, 13, 14]. Glycoprotein 130 (Gp130) is the receptor of IL-6 and is the main signalling molecule for intracellular signal transduction. After binding, phosphorylation activates the cytoplasmic region of Gp130. Phosphorylated Gp130 exposes a binding site to STAT3 to induce STAT3 phosphorylation and then enters the nucleus to initiate transcription [15, 16, 17]. Shigeaki Suzuki has proven that STAT3 is markedly phosphorylated after focal ischaemia in the peri-ischaemic region. Beth A. Habecker et al. have confirmed that Gp130 mediates the conversion of peripheral sympathetic neurons to cholinergic neurons after MI [18]. The sympathetic co-release of Ach and NE impairs adaptation to high heart rates and increases arrhythmia susceptibility. In the central nervous system, the Gp130 pathway promotes the differentiation and growth of nerves [19, 20]. However, the effect of Gp130 on hormone conversion in the PVN has not been studied.

Glutamate is one of the most important excitatory amino acids in the central nervous system, and it regulates sympathetic nerve activity and cardiovascular function through the NMDA receptor. Yu-Ming Kang et al. observed that glutamate in the hypothalamic PVN was greatly elevated in heart failure rats, and NMDA receptor activity in the periventricular nucleus was enhanced. Stimulation of NMDA receptors in the PVN can increase sympathetic discharge. GABA is the main inhibitory neurotransmitter in the PVN of the hypothalamus. Injecting GABA into the PVN of the hypothalamus can reduce heart rate and reduce arrhythmia. GAD67 is a rate-limiting enzyme of GABA and a marker for the recognition of GABAergic neurons. Its distribution is parallel to GABA.

The aim of this study was to investigate whether IL-6 in the hypothalamus PVN plays a protective role in the incidence of ventricular arrhythmia after MI and whether the Gp130-STAT3 pathway plays a key role in this process.

Methods

Animals

Adult male Sprague Dawley rats (200-250 g) were purchased from the Animal Experimental Center of Second Affiliated Hospital of Harbin Medical University. Housing conditions included 8 rats per cage, 12 hours light, freely available food and water, temperature 23±2°C, and relative humidity 40%-50%.

Coronary ligation and paraventricular nucleus injection (PNI) [21]

Rats underwent sterile surgery under anaesthesia (20% Ulatan, 0.75 ml/100 g) for induction of MI by ligation of the left anterior descending coronary artery or the same surgery without ligation of the vessel (sham). The hypothalamic PVN in each rat was injected with artificial cerebrospinal fluid (ACSF), anti-IL-6 antibody or Gp130 antagonist (SC144) according to the rat stereotaxic atlas coordinates [22, 23, 24].(n=12)

Cardiac electrophysiological appraisal and method of animal euthanasia

After the surgery, we recorded the arrhythmia occurrence in rats within 24 hours using a single-lead dynamic electrocardiogram. Twenty-four hours after coronary artery ligation or sham operation, rats were anesthetized by intraperitoneal injection Ulatan (20%, 0.75 ml/100 g). Then the rats' VF threshold and induced VF were masured. Attempts were also made to induce VF using a 10-s burst of 40–60 ms cycle length (CL) pacing. VF episodes longer than 1 s were regarded as a successful VF induction. S1–S1 stimulation (60 ms) was repeatedly applied to the right ventricle with an increase in stimulation intensity by 0.5 V each time until VF/VT was induced. Each stimulation lasted for 10 s and was followed by a 30-s rest period before the next round of stimulation. The minimum stimulation voltage that can induce VF was regarded as the threshold of VF. After electrophysiological appraisal, animals were sacrificed by rapid excision of heart to confirmation of permanent cessation of the circulation when they were still unconscious.

Immunohistochemistry

After electrophysiological examination, 4% paraformaldehyde was inserted into the left ventricle and the ascending aorta to fix the brain tissue. After the brain tissue was fixed, the part between the optic chiasm and mammillary body was resected in the rostral to caudal direction. The tissue underwent serial sectioning on a paraffin slicer, and sections that were approximately 1.50 mm from the bregma were obtained [25, 26]. Immunohistochemical labelling was performed in sections to identify IL-6 (Bioss, China, 1:100), Gp130 (1:20, Santa, Amercia), pSTAT3 (1:50, Bioss, China), and NMDA (Bioss, China, 1:50). For each rat, the positive neurons within the bilateral borders of the PVN were manually counted in three consecutive sections, and an average value was reported.

Western blot analysis

Brain tissue was quickly extracted in a low temperature environment, and Palkovits's microdissection procedure was used to isolate the PVN. The tissue was homogenized in RIPA buffer containing protease inhibitor cocktail (Beyotime Biotechnology). A BCA protein assay (Beyotime Biotechnology) was used to determine protein concentrations. Equal amounts of protein were separated by SDS-PAGE electrophoresis

and then transferred electrophoretically to a polyvinylidene fluoride membrane (Bio-Rad)[27, 28]. The membranes were incubated with the following primary antibodies for 2 hours at room temperature: IL-6 (1:1000, Abcam, England), Gp130 (1:1000, Santa, Amercia), pSTAT3 (1:1000, Bioss, China), and NMDA (1:1000, Bioss, China). Goat anti-mouse IgG or goat anti-rabbit IgG was used as a secondary antibody for a 2-hour incubation at room temperature. Finally, the membrane was placed in a gel imaging analysis system for exposure and analysis (AlphaView-fluorChemFC3).

Measurement of glutamate and GABA in PVN tissues

Brain tissue was separated as previously described. Perchloric acid (0.1 mol/L, Sigma) was added to the brain tissue. Then, the tissue was dissolved on an ice pack or crushed ice, fully mashed and homogenized, and sonicated for five minutes. Finally, the samples were centrifuged at 12,000 r/min for 10 min at 4°C. The supernatant was aspirated, diluted and filtered through a filtration membrane. The concentrations of glutamate and GABA were measured using a liquid chromatography mass spectrometer (Singapore, Xevo).

Measurement of circulating catecholamine levels

The supernatant was obtained after the blood was centrifuged. Plasma NE was measured using ELISA (Bioss).

Statistical analysis

All data are expressed as the mean ± SEM. One-way ANOVA was used for comparison between groups, and the LSD test was used for comparison between two groups. $p<0.05$ was considered statistically significant.

Results

Electrophysiological study

After coronary artery ligation or sham operation, rats were assigned to treatment with anti-IL-6 antibody or SC144, and the occurrence of ventricular arrhythmia within 24 hours was recorded using a small animal dynamic electrocardiogram. Compared to sham rats, MI rats showed an increased incidence of spontaneous ventricular arrhythmias. The incidence of spontaneous ventricular arrhythmias in paraventricular nucleus injection (PNI) anti-IL-6 antibody-treated rats or PNI SC144-treated rats was higher than that in sham rats and MI rats. To further study the changes in cardiac electrophysiology, we measured cardiac-induced VF and VF threshold in each group of rats. The induced VF of MI rats was higher than that of sham rats, and PNI rats had higher induced VF than did MI rats. Compared to sham rats, MI rats and PNI rats showed a decreased VF threshold, and the VF threshold was lower in PNI rats than in MI rats. (Figure 1)

IL-6, Gp130 and pSTAT3 expression in the PVN

The immune system was activated when the left anterior descending coronary artery was ligated. As shown in Figure 2, in MI rats, the IL-6 concentration in the PVN increased significantly, which then activated the Gp130 receptor and its downstream mediator pSTAT3. With the reduction in IL-6 content by injection of anti-IL-6 antibody, Gp130-pSTAT3 activation was blunted. Gp130-STAT3 activation was blunted by SC144, which could bind to Gp130 and eventually abrogate STAT3 phosphorylation and nuclear translocation. (Figure 2)

NMDA and GAD67 expression in the PVN

Immunohistochemistry and Western blotting showed that MI rats had higher NMDA levels and lower GAD67 levels in the PVN than did sham rats. PVN injections of anti-IL-6 antibody and SC144 promoted increases in NMDA and decreases in GAD67 within the PVN of MI rats (Figure 3)

Neurotransmitters in the PVN

We observed significant changes in excitatory neurotransmitters and inhibitory neurotransmitters in the PVN in MI and PNI rats compared to those in sham rats. Compared to sham rats, MI rats had higher levels of glutamate and lower levels of GABA in the PVN. Furthermore, PNI rats had more glutamate and less GABA in the PVN than MI rats did. (Figure 4)

Plasma humoural factors

To determine the sympathoexcitation effect of MI and PVN infusion, we measured plasma NE levels in blood using ELISA. As expected, compared with sham rats, MI rats had higher plasma NE. Additionally, PNI rats had higher levels of plasma NE than MI rats did. (Figure 4)

Discussion

The novel findings of our present study are listed as follows. (i) A cytokine (IL-6) induces an imbalance between excitatory and inhibitory neurotransmitters in the PVN of MI rats, attenuating sympathoexcitation. (ii) The Gp130-pSTAT3 signalling pathway plays a key role in the process of neurotransmission.

Neuroanatomical studies have shown that the PVN sends direct projections to spinal preganglionic neurons of sympathetic ganglia. Stimulation of cell bodies in the PVN causes an increase in blood pressure, heart rate and circulating NE concentrations [29]. Injecting glutamate or GABA antagonist into the PVN resulted in an increase in renal nerve activity and circulating NE concentration, suggesting that a sympathoadrenal component to cardiovascular responses was associated with PVN stimulation [30]. Recent research demonstrated that pathophysiological changes in the PVN are undoubtedly critical to the elevated sympathetic nerve activity in MI. In response to MI, microglia in PVN become activated and secrete cytokines. In this study, we observed an increase in the expression of IL-6 in PVN neurons of MI rats. Interestingly, while previous studies demonstrated that other cytokines, such as TNF-α and IL-1, play

a devastating role [31], IL-6 plays a protective role. When MI rats were treated with IL-6 antagonist, the sympathetic outflow increased. The role of IL-6 is complicated during the inflammation process, which contributes to both injury and repair processes. However, the peak in IL-6 (24 hours) expression is associated with neuroprotection [12]. Many studies have shown that IL-6 dose-dependently protects neurons against NMDA toxicity. Activation of NMDA receptors can increase sympathetic discharge. In our study, we observed that blocking IL-6 induced the increased expression of NMDA in the PVN [32].

Moreover, the Gp130-STAT3 pathway plays a key role in this process. When we treated MI rats with a Gp130 antagonist (SC144), the sympathetic outflow also increased. As common signal transducing receptor subunit, Gp130 acts in association with ligand-specific receptors of IL-6. The intracellular signal transduction induced by IL-6 involves the activation of JAK tyrosine kinase family members, leading to the activation of transcription factors of the STAT family. STAT3 is an important element in the JAK-STAT pathway. The phosphorylation of STAT3 at Tyr705 in response to Gp130-stimulating cytokines leads to the formation of STAT3 dimers, followed by the translocation of these dimers to the nucleus where they regulate the transcription of target genes [33]. Increases in cholinergic genes within the stellate ganglion and widespread co-expression of ChAT protein in TH**+** neurons have been detected in MI rats. The acquisition of cholinergic function requires the expression of the Gp130 cytokine receptor in sympathetic neurons. Removal of Gp130 from sympathetic neurons also prevents the local expression of noradrenergic transmission in the left ventricle after acute MI. In this study, Gp130 played the same role in the PVN by transforming glutamate into GABA and inducing an imbalance between excitatory and inhibitory neurotransmitters, thereby further affecting the outflow of sympathetic activity [34, 35].

In summary, the present study demonstrates that MI rats have higher concentrations of IL-6 and Gp130-STAT3 in the PVN, thereby contributing to sympathetic nerve inhibition and higher ventricular electrical stability. Our findings provide new insights into the treatment of ventricular arrhythmias in MI rats. Preservation of IL-6-Gp130-STAT3 in the PVN can reduce the occurrence of ventricular arrhythmia in the acute phase of MI.

Declarations

Ethics approval and consent to participate

All experimental protocols were approved by local animal care and use committee (Animal Experimental Ethics Association Of the First Affiliated Hospital of Harbin Medical University). The methods were carried out in accordance with the revised Animals (Scientific Procedures) Act 1986.

Consent to publish

Not Applicable

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors have read and approved the manuscript. Conceptualization, MG, DCYand XFQ; Data curation, MG; Formal analysis, MG; Funding acquisition, DCY and XFQ; Investigation, MG; Methodology, MG and JGC; Project administration, XFQ; Resources, XFQ; Software, JGC; Supervision, DCY and XFQ; Writing–original draft, MG; Writing–review and editing, DCY, and XFQ.

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Figures

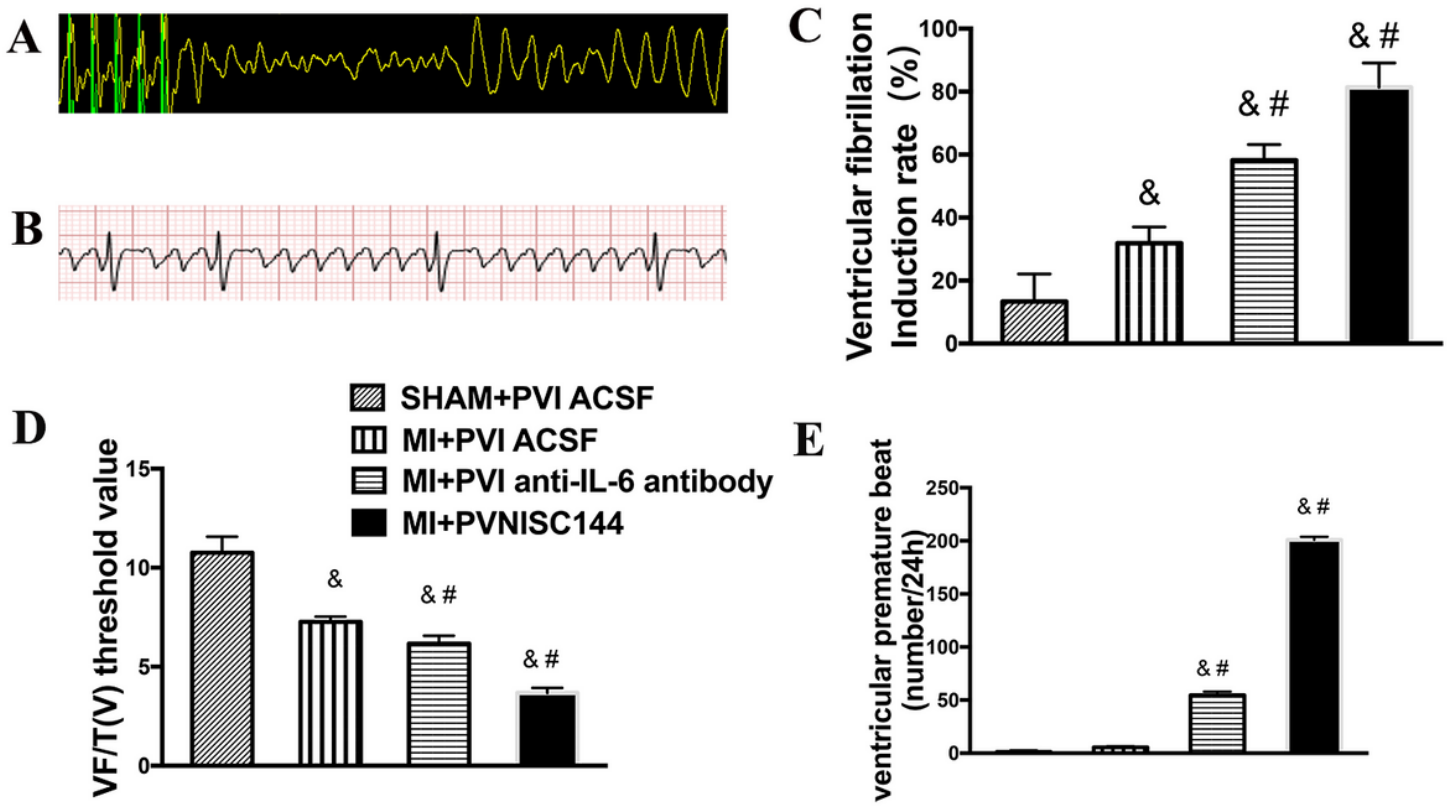

Figure 1

Effects of PVN infusion of anti-IL-6-antibody or SC144 on ventricular electrophysiological activity in MI rats. (A) Recordings of typical inducible ventricular arrhythmias by programmed electrical stimulation; (B) the ventricular premature beat within 24 hours recording by the small animal dynamic electrocardiogram; (C) a quantitate analysis of induced ventricular fibrillation; (D) A quantitate analysis of ventricular

fibrillation threshold; (E) A quantitative analysis of premature ventricular beats in 24 hours. Values are mean±SE. &p<0.05 vs sham rats, #p<0.05 vs MI rats.

Figure 2

Effects of PVN infusion of anti-IL-6 antibody or SC144 on IL-6, Gp130 and pSTAT3 levels within the PVN in MI rats: (A) A representative immunohistochemical image of IL-6; (B) densitometric analysis of IL-6 staining; (C) a representative immunohistochemical image of Gp130; (D) densitometric analysis of Gp130 staining; (E) a representative immunohistochemical image of pSTAT3; (F) densitometric analysis of pSTAT3 staining. (G) A representative immunoblot image of IL-6, Gp130 and pSTAT3. (H-J) Densitometric analysis of protein expression of IL-6, Gp130 and pSTAT3. Values are the mean ± SE. &p<0.05 vs SHAM, #P<0.05 vs MI rats.

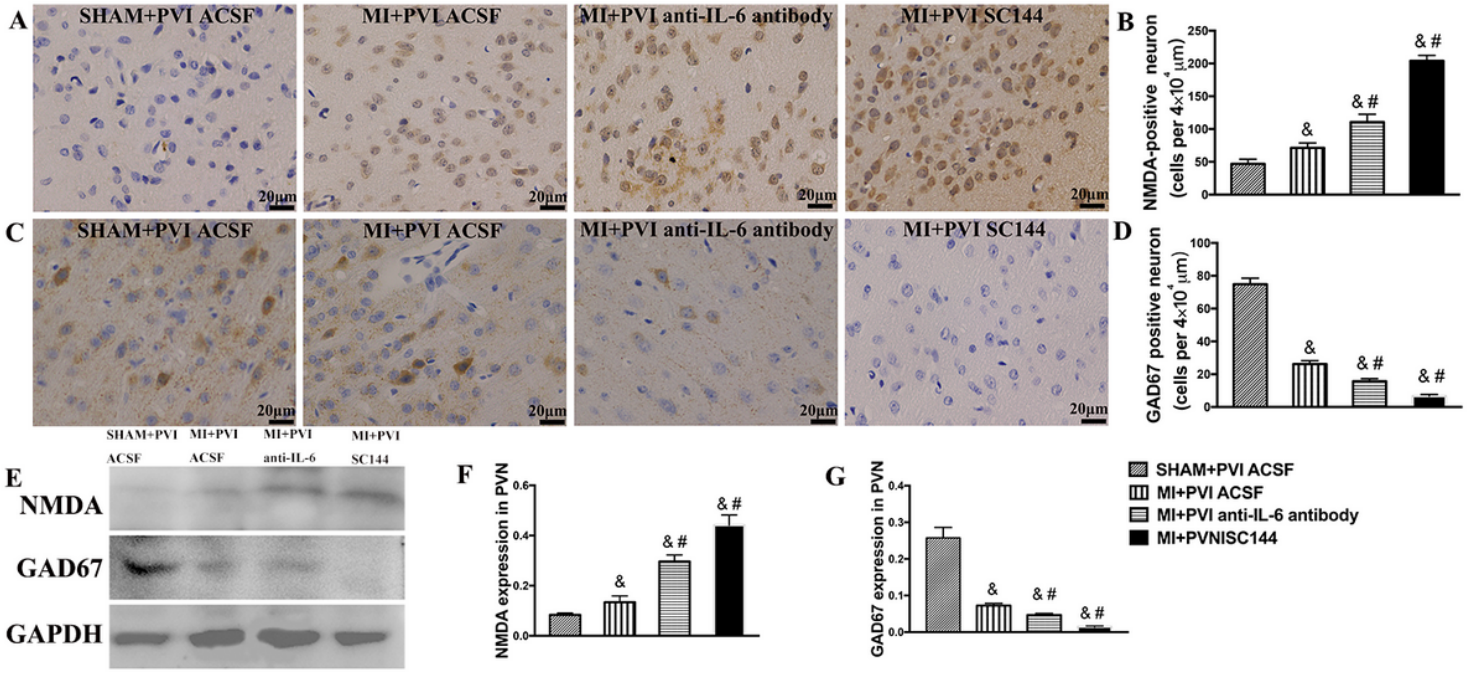

Figure 3

Effects of PVN infusion of anti-IL-6 antibody or SC144 on NMDA and GAD67 within the PVN in MI rats: (A) a representative immunohistochemical image of NMDA; (B) densitometric analysis of NMDA staining; (C) a representative immunohistochemical image of GAD67; (D) densitometric analysis of GAD67 staining; (E) a representative immunoblot image of NMDA and GAD67; (F) densitometric analysis of protein expression of NMDA and GAD67. Values are the mean ± SE. &p<0.05 vs SHAM, #P<0.05 vs MI rats.

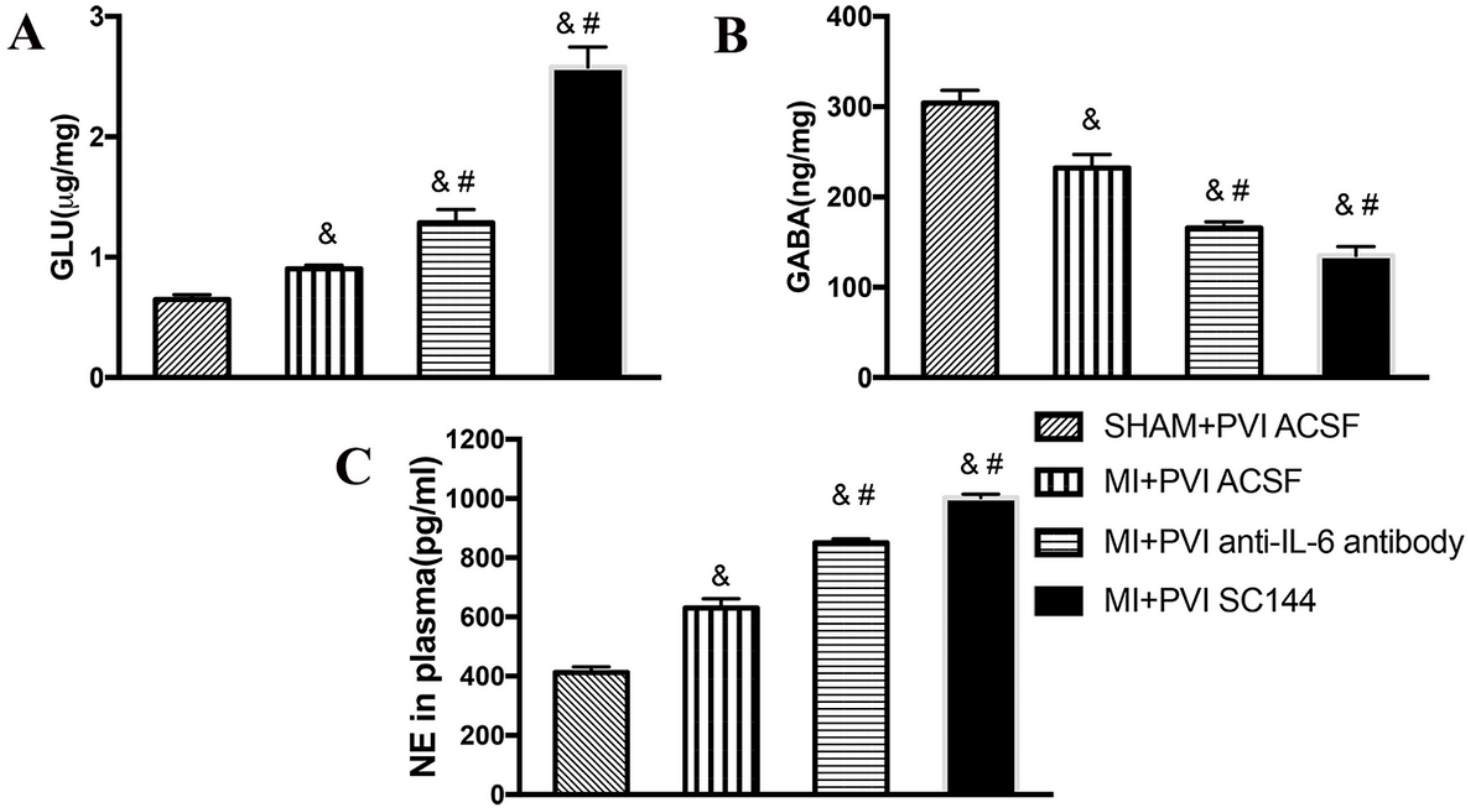

Figure 4

Effects of PVN infusion of anti-IL-6 antibody or SC144 on the PVN glutamate and GABA concentration in MI rats. (A) Glutamate; (B) GABA. Values are the mean ± SE. (C) Quantitative analysis of plasma NE. &P<0.05 vs SHAM rats, #p<0.05 vs MI rats.

Supplementary Files

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- supplement1.pdf