International Journal of Clinical and Experimental Medicine Research, 2023, 7(3), 407-415
https: //www.hillpublisher.com/journals/ijcemr/
ISSN Online: 2575-7970
ISSN Print: 2575-7989

Mechanisms by Which Spinal Cord Stimulation Intervenes in Atrial Fibrillation: The Involvement of the Endothelin-1 and Nerve Growth Factor/P75ntr Pathways

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How to cite this paper: Yiyan Peng, Peng Li, Wei Hu, Qi Shao, Panpan Li, Haiyue Wen. (2023) Mechanisms by Which Spinal Cord Stimulation Intervenes in Atrial Fibrillation: The Involvement of the Endothelin-1 and Nerve Growth Factor/P75ntr Pathways. *International Journal of Clinical and Experimental Medicine Research*, 7(3), 407-415.
DOI: 10.26855/ijcemr.2023.07.021

Received: June 15, 2023
Accepted: July 12, 2023
Published: August 14, 2023

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Abstract

Background: The cardiac autonomic nervous system (CANS) plays an integral role in normal cardiac physiology and the pathogenesis that leads to arrhythmias. CANS consists of complex neural hierarchies in a series of interacting feedback loops that regulate atrial electrophysiology and are inherently susceptible to remodeling of atrial rhythms. In addition to the use of traditional medicines and ablation techniques to treat atrial fibrillation, there is also increasing interest in the use of spinal cord stimulation as an invasive method to modulate the autonomic axis of the heart. **Objective:** Can the spinal cord stimulation regulate the autonomic nerves through the ET-1 and NGF/p75NTR pathways and thus inhibit the occurrence of atrial fibrillation? **Methods:** Sixteen beagles were randomly divided into a RAP group (n=8) and a RAP+SCS group (n=8), and the effective refractory period (ERP), ERP dispersion, atrial fibrillation induction rate, and atrial fibrillation vulnerability window (WOV) at baseline, 6 hours of RAP, 6 hours of RAP+SCS were measured. The atrial tissue was then taken for immunohistochemical analysis to dertermine the localization of endothelin-1 (ET-1), nerve growth factor (NGF), p75NTR, NF-kB p65 and other genes. **Results:** Our results showed that SCS attenuated the shortening of ERP in all parts caused by RAP, and after 6 hours of SCS, the probability of atrial fibrillation in dogs was reduced compared with that in the RAP group. Moreover, the expression of ET-1, NGF and p75NTR in the atrial tissues of dogs in the RAP+SCS group was significantly increased, but the expression of NF-kB p65 was reduced. **Conclusion:** Spinal cord stimulation promotes the positive remodeling of cardiac autonomic nerves by weakening NFκB p65-dependent pathways to interfere with the ET-1 and NGF/p75NTR pathways to resist the original negative remodeling and inhibit the occurrence of atrial fibrillation.

Keywords

Atrial fibrillation, spinal cord stimulation, autonomic nerves, nerve growth factor, endothelin-1, NF-kB p65, p75NTR

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia, and its basic pathophysiology includes electrical remodeling, structural reconstruction, and autonomic remodeling [1]. Previous studies have demonstrated that spinal nerve stimulation (SCS) may inhibit rapid atrial pacing (RAP)-induced atrial fibrillation by inhibiting autonomic remodeling, and the mechanism of its action may be related to the expression of nerve growth factor NGF [2]. Many studies have found that cardiac autonomic nerve growth is closely related to nerve growth factor (NGF), and endothelin-1 (ET-1) can promote the synthesis of nerve growth factor (NGF) by cardiomyocytes, thereby causing cardiac sympathetic abnormalities and altering cardiac autonomic imbalance [3-5], but the exact signaling pathway is unknown. This study aimed to use the spinal cord stimulation of an atrial fibrillation dog model to determine whether the ET-1 and NGF/p75NTR pathways can promote the positive remodeling of cardiac autonomic nerves and affect the changes in atrial myocyte channel proteins, thereby changing the electrophysiological characteristics of the myocardium and promoting positive electrical remodeling of atrial muscle, so as to antagonize the negative effects of antigens, intervene in the triggering and maintenance of atrial fibrillation, and thus treat atrial fibrillation.

2. Materials and Methods

Sixteen beagles ranging from 15 to 20 kg were used in this experiment. All procedures were performed under 3% sodium pentobarbital anesthesia with an initial dose of 1 ml/kg and a maintenance dose of 2ml/h. The depth of anesthesia was monitored throughout the experiment by examining heart rate, respiratory rate, and toe crush responses. All dogs were endotracheally intubated and ventilated on a ventilator (MAO01746, Harvard Apparatus, Holliston, USA). A catheter was introduced into the left femoral artery to monitor the systemic arterial pressure, and the body surface electrocardiogram and blood pressure were recorded throughout the experiment with a computer laboratory system (Lead 2000B, Jingjiang Inc., Wuhan, China). Intravenous fluids were injected into the left femoral vein to maintain fluid loss. Dogs maintained the body nuclear temperature at 36.5 ± 1.5℃ with open thoracotomy in the left and right thoracic fourth intercostal space.

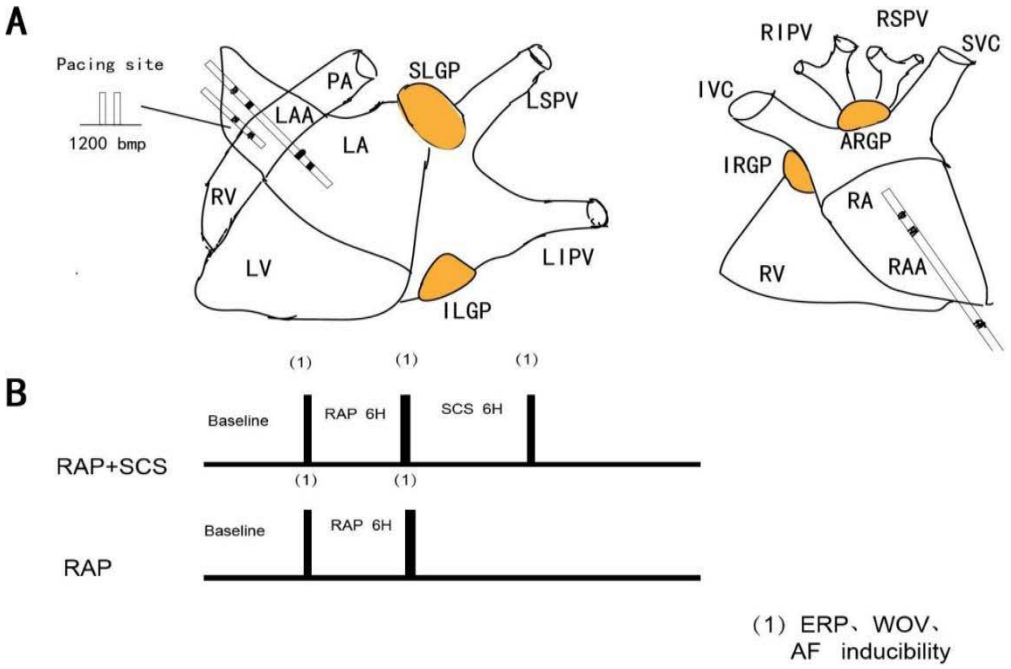

Figure 1. Schematic diagram of electrodes (A) and flow chart of experiments (B).

Atrial fibrillation = atrial fibrillation; ARGP = the right anterior ganglionic plexus; BH= baseline; ERP = effective refractory period; ILGP = the left lower ganglionic plexus; IRGP = what was found in the lower right ganglionic plexus; IVC = inferior vena cava LA = left atrium LAA = left atrial appendage left lower pulmonary vein LIPV = left pulmonary vein left upper pulmonary vein left ventricle PA = pulmonary artery RA = right atrium; RAA = R

A P in the right atrial appendage = 6 h rapid atrial pacing; RIPV = the right lower pulmonary vein; RSPV = the right upper pulmonary vein; Right ventricle = right ventricle; SCS = spinal cord stimulation; SLGP = the left upper ganglionic plexus; SVC = superior vena cava; WOV, weak window.

2.1 Program stimulation

Acute atrial remodeling induced by 6 h RAP was performed at 1200 beats/min (2 threshold) in the left atrial ventricle. The ERP in the atrial and pulmonary veins was determined by reducing S1- S2 with programmed stimulation of a S1=330 ms, a 10-diastolic threshold. The S1 – S2 interval was reduced by 10 ms from the initial 180 ms, followed by a 2 ms reduction when near the ERP. WOV was used as a quantitative measure of AF induction rate and was defined as the difference between the longest and shortest S1-S2 interval (ms) at AF induction. AF was induced by the S1S1 (a procedure of 120ms, 100ms and 75ms cycle length for 5s each and repeated three times for each frequency) (Figure 1). AF was defined as an irregular atrial rate> 500bpmlasting> 5s [6].

2.2 Spinal cord stimulation (SCS)

A small incision was made in the dorsal thoracic spine (T1~T2 level), and the thoracic epidural cavity was punctured with a Tuohy needle until the loss of resistance. The electrode was then introduced into the epidural cavity through this cannula, with the electrode tip oriented to the level of the T1-T2 spinal cord, slightly to the left of the midline. The end of the electrode was connected to a stimulator (S88, Grass Instruments, Quincy, MA) and to generate 50 Hz pulses with a 0.2 ms duration. Continuous stimulation occurred for 6 hours.

2.3 Histological staining

At the end of the experiment, the atrial tissue was rapidly excised and fixed in 4% paraformaldehyde at room temperature. Paraffin-embedded tissue was cut into 5 μm sections. Immunofluorescence staining was used to determine the expression and localization of endothelin-1 (ET-1), nerve growth factor (NGF), p75NTR, NF- κB p65, and tyrosine hydroxylase (TH) in tissues. Sections were incubated in PBS containing 10% FBS for 60 min and incubated overnight with the primary antibody at 4 ℃, including anti-ET-1 (ABclonal, China), anti-NGF (Abcam, Cambridge, England), anti-p75ntr (Abcam, Cambridge, England), anti-NF- κB p65 (Abcam, Cambridge, England) and anti-TH (Abcam, Cambridge, England). Sections were washed with PBS and incubated with secondary antibodies for 1 h at 37℃. After the sections were washed, they were visualized using the DAB reagent. Hematoxylin was counterstained with cores dehydrated with ethanol and sealed with glycerol gelatin. Blinded analysis was performed using Image-Pro Plus 6.0 (Media Cybernetics).

2.4 mRNA analysis

Total RNA was obtained from atrial tissue using TRIzol reagent (Service bio) and then reverse transcribed to cDNA. Finally, the PCR assay was performed. The primers are shown in Table1. The relative expression level was calculated using the 2- ΔΔ Ct method.

Table 1. Primer sequences of the genes that were verified by RT-PCR

Primer name	Forward sequence (5 ′ -3 ′)	Reverse sequence (5 ′ -3 ′)
ET-1	CTGCTCCTGCTCTTCCCTGAT	TGTGGTCTGTTGCCTTTGTGAT
TrkA	GCTGTCTTTGCCTGCCTCTT	GACAAGGAACTGCCACCTAATG
NGF	TCCTTCCTGGGCATGGAATC	ACAGCACTGTGTTGGCATAGA
P75NTR	TGGACAGCGTGACGTTCTCC	GATCTCCTCGCACTCGGCGT
NF-KB p65	GTGCAGAAAGAAGACATTGA	AGGCTAGGGTCAGCGTATGG

2.5 Experimental scheme

The 16 beagles were randomly divided into two groups: RAP + SCS (n = 8) and RAP (n =8) for 6 hours of RAP and RAP + SCS for SCS at the T1-T2 spinal cord level (delivered at 50 Hz, 0.1-ms pulse width, by approximately 90% of the motion threshold). Atrial electrophysiological parameters (ERP, ERP dispersion, WOV) were measured at three time points: baseline, 6-h RAP, and 6-h RAP + 6-h SCS. Finally, the removed atrial tissue was used for

protein blotting and messenger RNA (mRNA) analysis.

2.6 Data analysis

Measurement data of the study data were expressed using the mean ± standard deviation and analyzed by paired t tests, with P <0.05 considered statistically significant. Data analysis and plotting were performed using the Graph pad Prism software.

3. Results

3.1 Effect of S C S on ERP, Σ WOV, and AF inducible properties

Figure 2.At baseline, ERP was measured at any tissue site. SCS attenuated the shortening of the ERP at all sites caused by the RAP (2A-2D). SCS caused an increase in Σ WOV (2E). After 6 h of RAP, AF was observed in 3 of 8 dogs in the RAP group and 2 of 8 dogs in the SCS + RAP group with AF (37.5% vs. 25%, P> 0.05) (2F). (P<0.05 Compared with RAP group)

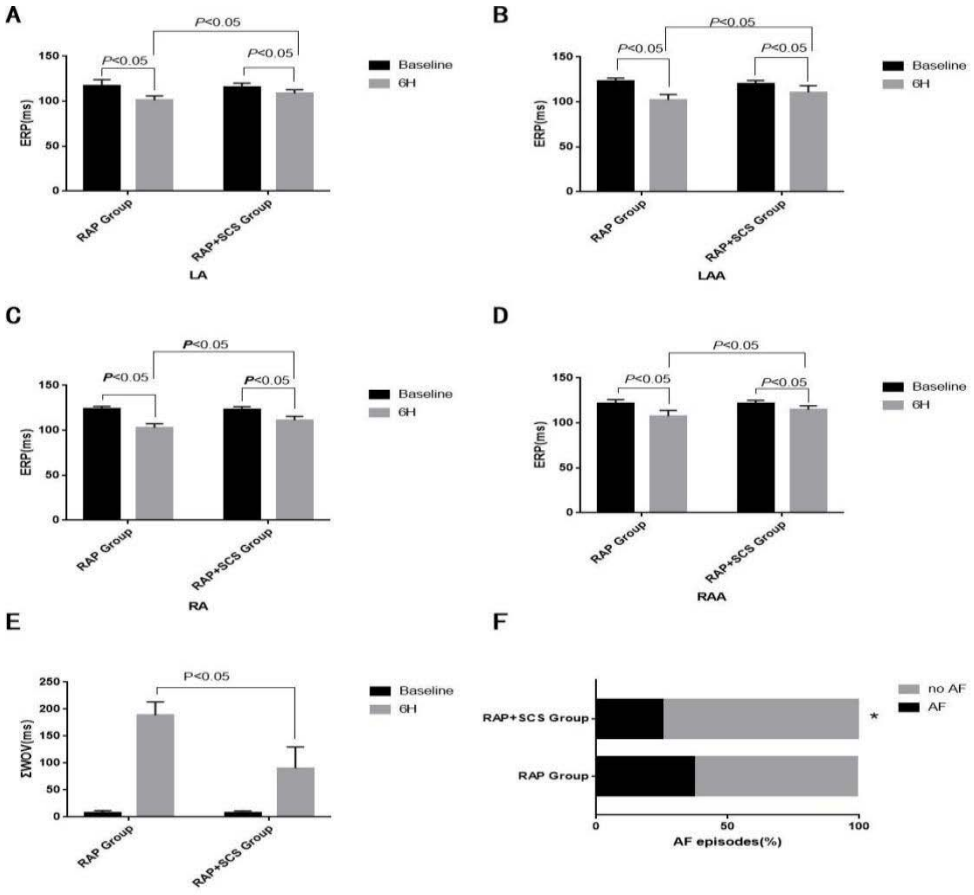

Figure 2. Effect of SCS on ERP, ΣWOV, AF episodes at all sites of the atrium.

3.2 Effect of S C S on the molecules associated with the ET-1 signaling pathway

3.2.1 Localization and expression of E T-1, NGF, p75NTR, NF- κB p65, and TH in atrial tissue

The localization of ET-1, NGF, p75NTR, NF- κB p65, and TH in atrial tissue was determined by immunohistochemistry (Figure 3). Atrial tissue expression of ET-1 (3A, 3B), p75NTR (3C, 3D), NF- κB p65 (3E, 3F), NGF (3G, 3H), and TH (3I, 3J) in the RAP + SCS and RAP groups was found. The scale bar represents 50 μm. The figure shows the average optical density (mean density) data for various target proteins expressed as the mean ± SD (Figure 4). The expression of ET-1, NGF, and p75NTR was higher in the RAP + SCS group than in the RAP group, and NF- κB p65 and TH expression were lower than thoes in the RAP group (P<0.05 Compared with RAP group).

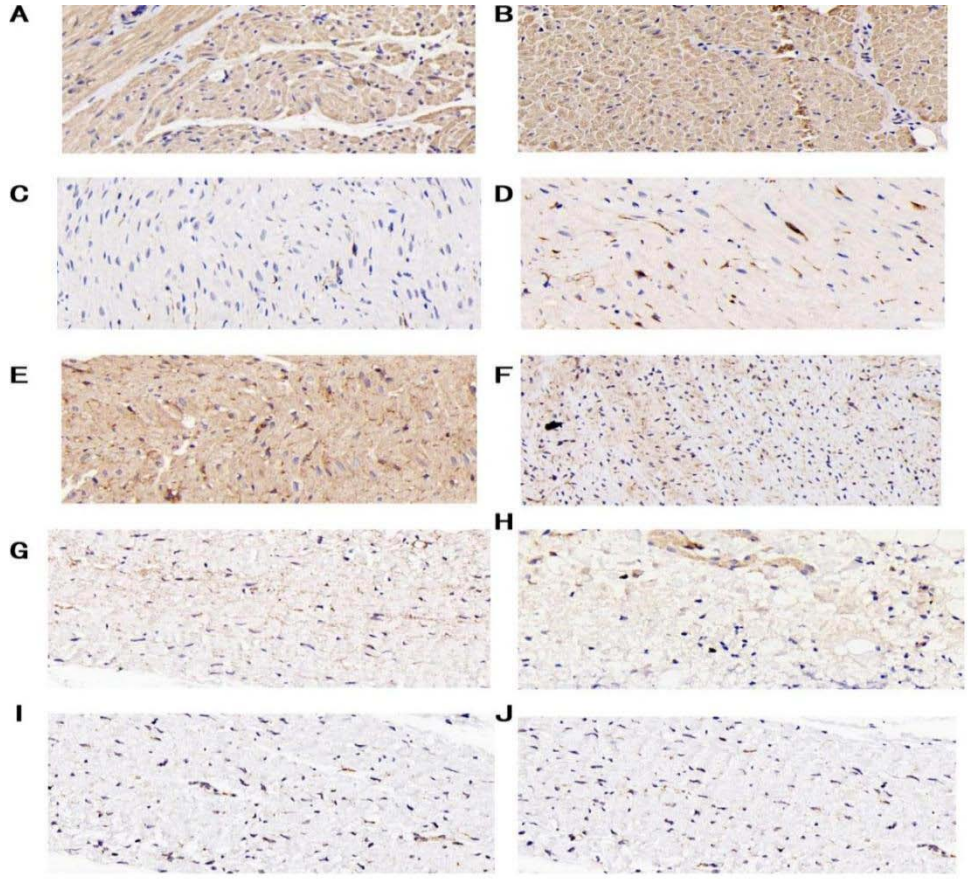

Figure 3. The localization of ET-1, NGF, p75NTR, NF- κB p65, and TH in the atrial tissue was determined by immunohistochemistry. Scale bar represents 50 μm.

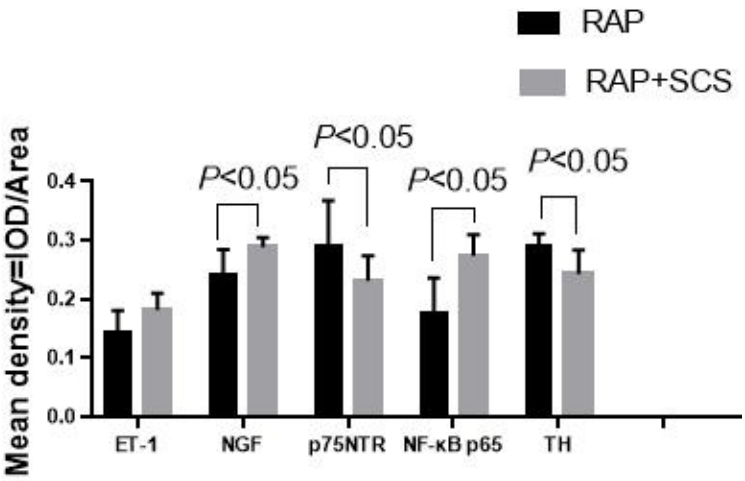

Figure 4. Average optical density of the various target proteins in the atrial tissue.

3.2.2 The mRNA expression of E T-1, NGF, TrkA, p75NTR, and NF-κB p65

As shown in left atrium (Figure 5) and right atrium (Figure 6), the mRNA expression of ET-1, NGF and p75NTR was higher in the RAP + SCS group than in the RAP group (P <0.05), and the mRNA expression of NF- κB p65 and trkA was lower in the RAP + SCS group than in the RAP group (P <0.05). (P<0.05 Compared with RAP group)

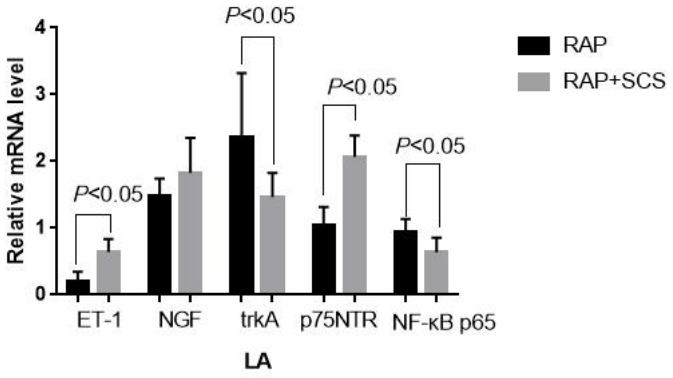

Figure 5. The mRNA levels of ET-1, NGF, p75NTR, NF- κB p65, and trkA, respectively, in the left atrium tissue.

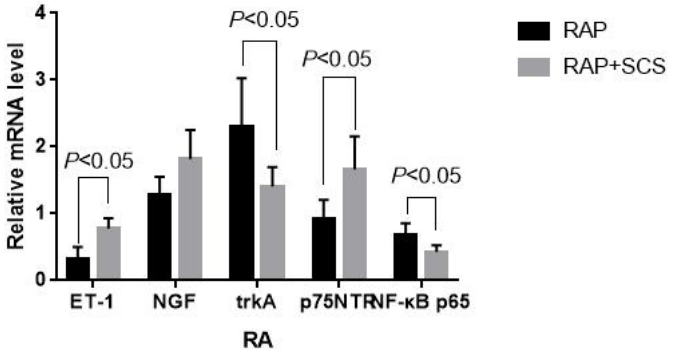

Figure 6. The mRNA levels of ET-1, NGF, p75NTR, NF- κB p65, and trkA, respectively, in the right atrium tissue.

4. Discussion

Autonomic nervous system (ANS) imbalance is one of the important mechanisms by which atrial arrhythmias occur [7]. Although pulmonary venous isolation is widely used for AF ablation, it is an invasive procedure with potentially serious complications. Spinal cord stimulation (SCS) is the delivery of electrical stimulation to spinal cord segments through implanted electrodes to treat a variety of painful conditions, including chronic back pain and intractable angina [8, 9]. Recent studies have shown that spinal cord stimulation can be used to prevent the development of atrial fibrillation after cardiac surgery [10]. We controlled the development of atrial fibrillation by using a spinal cord-stimulating canine animal model to modulate the ANS imbalance. Previous studies have demonstrated that spinal cord stimulation has a direct effect on cardiac electrophysiology [11, 12]. This study also confirmed that spinal cord stimulation breaks the vicious cycle of autonomic electrical remodeling and structural remodeling by inhibiting the shortening of atrial ERP and the expansion of WOV, thereby inhibiting negative autonomic remodeling and inhibiting the occurrence of atrial fibrillation.

Endothelin-1 (ET-1) is an endogenous vasoconstrictor peptide, and local ET-1 production in the heart is secreted by the endocardium, myocardium, and coronary artery endothelium thereby acting on cardiomyocytes in paracrine and autocrine ways [12, 13]. Previous studies have suggested that ET-1 may play a key role in the regulation of sympathetic activity and is associated with the development of sympathetic neurons [14-17]. NGF is a 118-amino acid glycoprotein composed of three subunits (α, β, and γ complexes), and β-NGF is responsible for its biological activity. NGF is associated with sympathetic distribution, and its increase triggers nerve germination in non-infarcted ventricles and atria [18]. Sympathetic overgermination may be an important factor in sympathetic remodeling leading to arrhythmias [19]. Elevated NGF levels and excessive sympathetic innervation lead to arrhythmias, including AF [21]. ET-1 has been shown to increase nerve growth factor (NGF), mRNA, and protein levels during the development and regeneration of cardiac sympathetic innervation [20, 21]. In this study, we found that the mRNA and protein expression of ET-1 and NGF in the atrial tissue of beagle dogs with spinal cord stimulation RAP for 6 hours was elevated, indicating that spinal cord stimulation can activate the ET-1 and NGF signaling

pathways.

The receptors of cardiac NGF are divided into the high affinity receptor TrkA and the low affinity tumor necrosis factor receptor P75NTR [22], which maintain cardiac sympathetic neuron growth and are closely related to stimulating axon regeneration. NGF/TrkA signaling plays an important role in enhancing normal cardiac calcium circulation and the normal function of the cardiovascular system [23, 24]. Studies have demonstrated that NGF/TrKA signaling is associated with the development of AF [25]. In this study, the expression of p75NTR in the spinal cord stimulation group was higher than that in the RAP group, and the TrkA expression was lower than that in the RAP group, indicating that NGF in the spinal cord stimulation group mainly binds to p75NTR. Therefore, we speculate that the activation of ET-1 and NGF/p75NTR is closely related to the regulation of cardiac autonomic remodeling by spinal cord stimulation.

Nuclear factor kappa B (NF-κB) is a family of dimer transcription factors, and the nuclear factor-κB (NF-κB) transcription factor system plays various roles in nervous system development and postnatal physiological processes [26]. Nuclear factor-κB p65 (NF-κB p65) activation can upregulate cardiac NGF and promote sympathetic innervation [27, 28]. This study showed that the expression of NF- κB p65 was reduced in the spinal cord stimulation group, demonstrating that the activation of NF-κB p65 was inhibited, thus inhibiting the sympathetic nerve growth. The present study also showed that TH expression was significantly reduced in the spinal cord stimulation group, further confirming that sympathetic nerve growth was inhibited. All these results indicate that the ET-1 and NGF/p75NTR signaling pathways in the spinal cord stimulation can attenuate the sympathetic innervation through the NF-κB p65-dependent pathway and promote positive remodeling of the cardiac autonomic nerve to resist the original negative remodeling and inhibit the occurrence of AF.

The clinical significance of this study

This study further explored the mechanism of ET-1 and NGF/p75NTR-dependent pathways in spinal cord stimulation in AF, providing more beneficial effects for future spinal cord stimulation in regulating the cardiac autonomic nervous system.

Research restrictions

This study has some limitations. First, this experiment was performed under general anesthesia, and the anesthesia itself will have some effects on the cardiac electrophysiology. Second, the expression levels of cardiac molecular substances in normal animals (beagle dogs not receiving RAP) were not measured in this study.

Declarations

Ethics approval and consent to participate

The experiments performed in this study were approved by the Animal Ethics Committee of Xiaogan Central Hospital under approval number XGLY2021-06-08. The study is reported in accordance with ARRIVE guidelines. All methods were performed in accordance with the relevant guidelines and regulations.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests, and all authors confirm its accuracy.

Authors' contributions

Yiyan Peng, Peng Li and Wei Hu were responsible for research conception and research design. Yiyan Peng and Qi Shao were responsible for data acquisition. Yiyan Peng and Peng Li were responsible for analysis and interpretation of results. Yiyan Peng, Peng Li and Wei Hu took part in the discussion of the paper. Yiyan Peng wrote the manuscript that was reviewed and revised by Peng Li, Wei Hu, Qi Shao, Panpan Li and Haiyue Wen. All authors have read and approved the manuscript.

Funding

Hubei Province health and family planning scientific research project (WJ2019H155).

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