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Chronic inhibition of the sigma-1 receptor exacerbates atrial fibrillation susceptibility in rats by promoting atrial remodeling

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ABSTRACT

Aims: This study aimed to evaluate the effects of the sigma-1 receptor (S1R) on atrial fibrillation (AF) susceptibility in rats.

Main methods: Rats were randomly assigned into three groups for intraperitoneal treatment with saline (CTL group), BD1047 (an antagonist of the S1R, BD group) or BD1047 plus fluvoxamine (an agonist of the S1R, BD + F group) for 4 weeks. The heart rate variability (HRV) and atrial electrophysiological parameters were measured via the PowerLab system and analyzed by LabChart 8.0 software. Atrial histology was determined with Masson staining. The protein levels of connexin (Cx) 40, Cav1.2, S1R, eNOS, p-eNOS, and p-AKT were detected by western blot assays.

Key findings: Our results showed that BD1047 significantly shortened the atrial effective refractory period (ERP) and action potential duration (APD), increased AF inducibility and duration, augmented sympathetic activity, depressed parasympathetic activity, and reduced heart rate variability (HRV) compared with the CTL group. Masson staining also showed a significant increase in atrial fibrosis in the BD group. Furthermore, the expressions of S1R, Cx40, Cav1.2, p-eNOS, and p-AKT were dramatically reduced in the BD group compared with the CTL group (all $P < 0.01$). However, fluvoxamine administration mitigated most of the abovementioned alterations.

Significance: Our findings indicated that S1R inhibition contributed to atrial electrical remodeling, cardiac autonomic remodeling and atrial fibrosis, which could be attenuated by fluvoxamine, thus providing new insights into the relationship between the S1R and AF.

1. Introduction

Atrial fibrillation (AF), the most common tachyarrhythmia observed clinically, is often associated with cardiovascular comorbidities, such as the increased risk of stroke [1,2]. Current treatment options for AF include control of ventricular rate, anticoagulant therapy, and conversion of sinus rhythm by electrical cardioversion or drugs with modest efficacy and increased risk of adverse events, including proarrhythmic effects [3]. Therefore, it seems necessary to find other safe and effective antiarrhythmic methods to intervene in AF.

The sigma-1 receptor (S1R), mainly localized on the membranes of endoplasmic reticulum, is recognized as a Ca^{2+}-sensitive ligand-operated molecular chaperone and is reported to regulate numerous cellular functions [4]. The S1R combines with the binding immunoglobulin protein (BiP) under basal conditions, and it functions as a chaperone when dissociated with BiP [5]. The S1R agonists promote the dissociation of the S1R/BiP complexes; however, the S1R antagonists inhibit the dissociation, thus resulting in a silent state of the receptor.

Numerous studies have indicated that the S1R plays an important role in neurological diseases, including major depressive disorder and Parkinson's disease [6–8]. Furthermore, emerging studies have demonstrated that the S1R activation is beneficial in various conditions, including bacterial infection [9], cancer [10], and cardiac hemodynamics [11]. The S1R activation could modulate the autonomic neuron

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activity, as well as the ion channels, including the L-type Ca^{2+} current (ICa-L) and the transient outward K^{+} current [4,12], which reveals the potential protective effects of the S1R on arrhythmia. DuP 754, a S1R ligand, was reported to increase the ventricular fibrillation threshold in a post-infarction cardiosclerosis model and a stress-induced model in rats [13]. Fluvoxamine, a selective serotonin reuptake inhibitor, has been reported to yield potent cardioprotection in several rodent models, serving as an S1R agonist [14–16]. BD1047 is a selective S1R antagonist with a high affinity at the S1R [17]. Our recent study indicated that chronic S1R stimulation by intragastric administration of SA4503 for 4 weeks facilitated autonomic nerve dysfunction and atrial fibrillation in depressive rats [18]. That study displayed a beneficial effect of the S1R on cardiac arrhythmia in a rat model of depression, but it remains unknown whether the S1R is directly involved in atrial arrhythmias and whether fluvoxamine elicits the similar effects with SA4503 on AF. In the present study, we aimed to investigate whether S1R inhibition by intraperitoneal treatment of BD1047 affects AF vulnerability in rats and the potential mechanisms. We hypothesized that S1R inhibition will induce atrial electrical remodeling and autonomic remodeling, exacerbate atrial fibrosis, alter the expression of the ion channel, then result in an increased risk of AF vulnerability, which will be attenuated by fluvoxamine.

2. Materials and methods

2.1. Animals

A total of 51 male Sprague Dawley rats (200–240 g) were randomly divided into three groups (n = 17 in each group): (i) CTL group (saline), (ii) BD group (BD1047 0.3 mg/kg, Sigma), and (iii) BD + F group (BD1047 0.3 mg/kg + fluvoxamine 0.3 mg/kg, Sigma). Rats were intraperitoneally injected with drugs or saline once a day at the same time for 28 days. Fluvoxamine and BD1047 serve as the agonist and antagonist of the S1R, respectively. All animal experiments were conducted with approval of the animal experimental administration of Wuhan University and followed the guidelines for the Guide for the Care and Use of Laboratory Animals, which was published by the US National Institutes of Health.

2.2. Electrode measurement of the left atrium

Rats were anesthetized (3%, sodium pentobarbital; Sigma) and heparinized (400 U, heparin sodium; Sigma). Then, the hearts were captured and instantly perfused in accordance with the Langerdorff technique (AD Instruments, Dunedin, New Zealand) according to our previous work [18]. The atrial monophasic action potentials were recorded at the left atrial appendage (LAA) using 2 custom-made Ag–AgCl electrodes (n = 10 in each group). The PowerLab system and LabChart 8.0 software (4/35, AD Instruments, Australia) were used to measure and analyze all the signals.

2.3. Effective refractory period measurement

The atrial effective refractory period (ERP) was measured via an S1S2 stimulation protocol, consisting of 8 successive basic stimulus (S1) (cycle length (CL): 250 ms) along with a stimulus (S2), the CL of which was progressively decreased from 100 ms to 1 ms. The ERP was defined as the longest S2 interval which was unable to catch the myocardium.

2.4. Action potential duration measurement

The atrial action potential duration (APD) measurement was conducted using an S1S1 stimulation procedure at pacing cycle lengths (PCLs) of 250 ms, 200 ms, 150 ms and 100 ms with 10 stimuli. The APD was measured at 90% repolarization (APD_{90}).

2.5. Arrhythmia induction

Atrial arrhythmia was induced using a burst pacing of 50 Hz for 2 s repeated up to six times, with AF defined as rapid irregular atrial rhythm occurring and maintaining for at least 2 s [18].

2.6. Heart rate variability analysis

Heart rate variability (HRV) was detected to assess the autonomic function (n = 7 in each group). Data was recorded by electrocardiogram using a PowerLab system and was analyzed using LabChart 8.0 software (4/35, AD Instruments, Australia). The RR variability was measured on segments of 250–300 cycles [19]. The time-domain variables included: the mean heart rate (HR), the mean of all normal RR-intervals (mean RR); the standard deviation of normal RR intervals (SDNN) and the square root of the mean squared differences of successive RR intervals (RMSSD). The frequency-domain variables included: the low frequency (LF, 0.25–0.75 Hz) and the high frequency (HF, 0.75–2.50 Hz) [19]. The LF/HF ratio was also calculated.

2.7. Histological examination

The left atrium was dissected for histological examination and the LAA for western blot analysis after HRV assessment (n = 7 in each group). The dissected left atrium was fixed in 4% paraformaldehyde and embedded in paraffin. Serial 5-um atrium sections were stained using the Masson trichrome method. Fibrosis within sections was measured using Image-Pro-Plus 6.0 software (Media Cybernetics, Inc., Rockville, MD).

2.8. Western blot analysis

Proteins were extracted from the LAA and western blot assays were performed according to our previous work [20] (n = 7 in each group). Antibodies included: Cx40 (1:1000; Abcam), Cav1.2 (1:500; Abcam), S1R (1:1500; Abcam), eNOS (1:2000; Abcam), p-eNOS (1:500; Abcam), and p-AKT (1:1000; CST). GAPDH (1:10,000; Abcam) served as a housekeeping reference protein.

2.9. Statistical analysis

Continuous variables and proportions were presented as mean ± standard deviation and percentages, respectively. Student's *t*-test, Pearson's chi-squared test, and one-way analysis of variance (ANOVA) followed by the Tukey post hoc test were used when appropriate. *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. The S1R inhibition induced atrial electrical remodeling

Figs. 1A and 2A showed the representative sample of the atrial electrogram and APD in the three groups, respectively. Compared with the CTL group, the mean ERP was markedly reduced in the BD group (36.80 ± 3.16 vs. 19.4 ± 2.50 ms, $P < 0.01$), but no significant difference was found between the CTL group and the BD + F group (Fig. 1B). Furthermore, the APD_{90} was significantly decreased in the four PCLs in the BD group compared with the CTL group; however, fluvoxamine treatment restored the decreased APD_{90} in the BD + F group (Fig. 2B). Moreover, AF inducibility was found in the S1S2 stimulation protocol and burst pacing protocol both in the BD and BD + F group, but not in the CTL group (Figs. 1A and 3A). In the burst pacing protocol, the AF incidence was 80% in the BD group but 30% in the BD + F group (Fig. 3B). The average duration of AF was dramatically longer in the BD group than that in the BD + F group (74.30 ± 28.07 vs. 11.3 ± 4.45 s, $P < 0.01$; Fig. 3C).

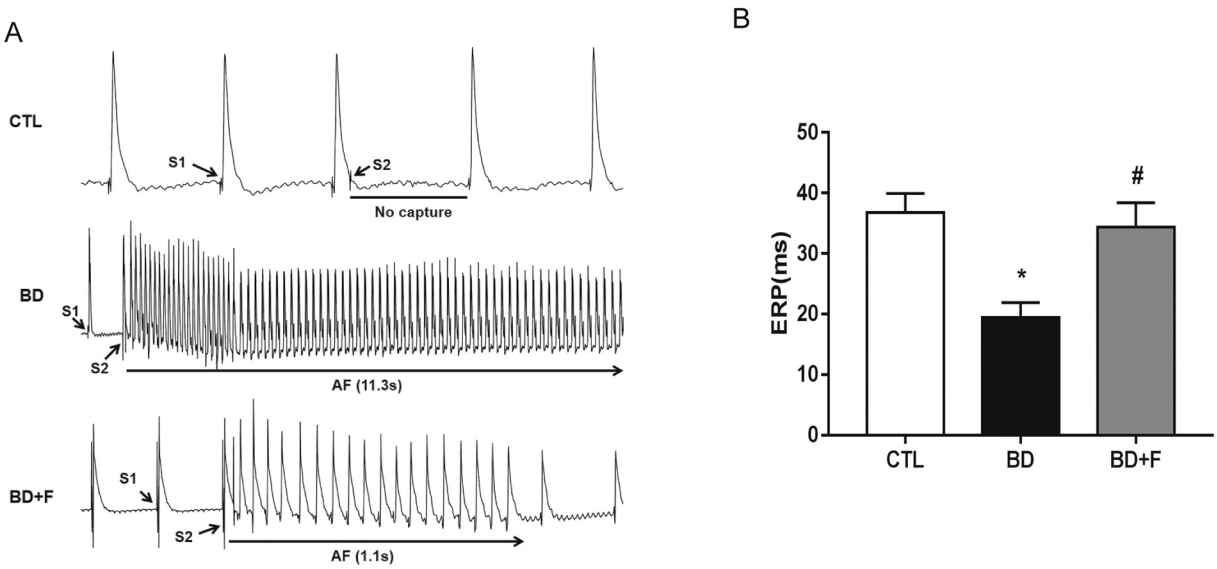

Fig. 1. Effect of the S1R inhibition on atrial ERP. n = 10 in each group. (A) Representative recordings of atrial electrogram in the three groups. (B) Atrial ERP in the three groups, respectively. *P < 0.01 vs. CTL; #P < 0.01 vs. BD. ERP, effective refractory period; S1R, sigma-1 receptor.

3.2. The S1R inhibition reduced heart rate variability

After four weeks of treatment, a remarkable increase in the mean HR was found in the BD group compared with the CTL group (406.07 ± 22.72 vs. 368.33 ± 13.93 bpm, P < 0.01), which was restored by fluvoxamine in the BD + F group (Fig. 4A). Additionally, compared with the CTL group, the BD group displayed a significant reduction in the mean RR, SDNN, RMSSD and HF, but a dramatic increase in the LH, and LH/HF ratio (Fig. 4B–G). Fluvoxamine administration significantly increased the mean RR, SDNN and RMSSD and decreased HR, LH, and LH/HF ratio.

3.3. The S1R inhibition induced atrial fibrosis and reduced Cx40 expression

The representative image of Masson staining is shown in Fig. 5A, indicating a significant increase of atrial fibrosis in the BD group compared with the CTL group. However, fluvoxamine administration markedly decreased atrial fibrosis in the BD + F group compared with the BD group (Fig. 5A, B). In addition, western blotting demonstrated that Cx40 expression was dramatically lower in the BD group than that in the CTL group (0.04 ± 0.01 vs. 0.60 ± 0.010, P < 0.01), which was significantly increased in the BD + F group (Fig. 5C, D).

3.4. The S1R inhibition downregulated ICa-L and S1R

As shown in Fig. 6A, B, Cav.1.2 expression was markedly reduced in the BD group compared with the CTL group (0.25 ± 0.03 vs. 0.37 ± 0.05, P < 0.05), while there was no significant difference between the BD + F group and the CTL group. In addition, the expression of the S1R in the BD group was significantly lower than that in the CTL group, and the reduced S1R was dramatically increased in the BD + F group (all P < 0.01; Fig. 6A, C), indicating that the S1R antagonist BD1047 downregulated the S1R, which was upregulated by fluvoxamine.

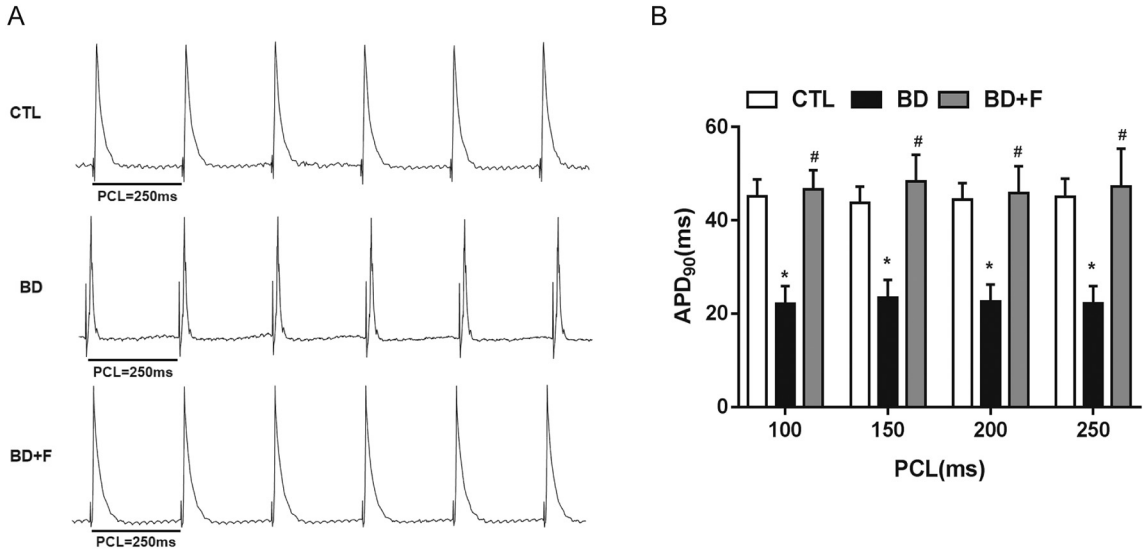

Fig. 2. Effect of the S1R inhibition on atrial APD. n = 10 in each group. (A) Representative recordings of APD at PCL of 250 ms. (B) Atrial APD90 at PCL of 100, 150, 200 and 250 ms in the three groups, respectively. *P < 0.01 vs. CTL; #P < 0.01 vs. BD. PCL, pacing cycle length; APD_{90}, action potential duration at 90% repolarization; S1R, sigma-1 receptor.

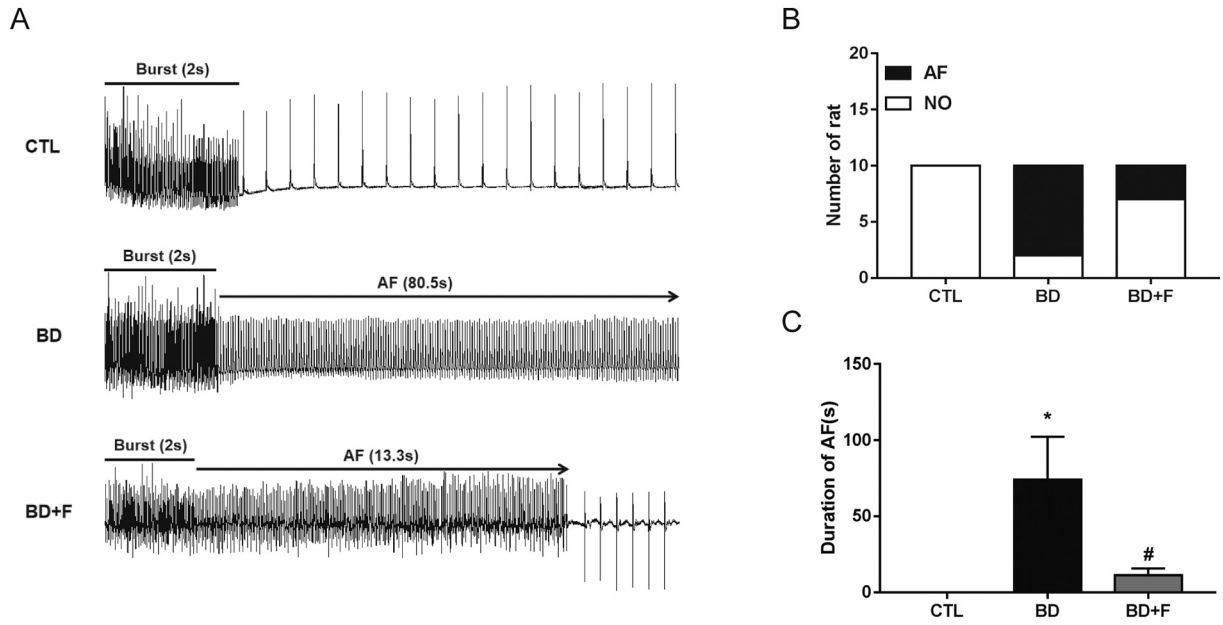

Fig. 3. Effect of the S1R inhibition on AF vulnerability. n = 10 in each group. (A) Representative recordings of burst pacing in the three groups. (B) Inducibility of AF in the three groups, respectively. (C) The duration of AF in the three groups. *$P < 0.01$ vs. CTL; #$P < 0.01$ vs. BD. AF, atrial fibrillation; S1R, sigma-1 receptor.

3.5. The S1R inhibition and the eNOS/AKT signaling pathway

Although no significant difference was found in the eNOS expression (Fig. 7A, B), Fig. 7A, C, and D displayed a significant reduction in the expression of p-eNOS and p-AKT in the BD group compared with the CTL group. However, fluvoxamine treatment significantly increased p-eNOS and p-AKT expression, indicating that fluvoxamine treatment attenuated BD1047-induced eNOS and AKT inhibition.

4. Discussion

Current opinions suggest that reentry and ectopic activity are the main mechanisms of AF [2,21]. Multiple factors, including risk factors and co-morbidities, can provide abnormal substrates by affecting atrial remodeling, leading to the maintenance of AF. Spontaneous focal ectopic discharge can serve as the trigger of reentry to initiate AF, which is caused by afterdepolarizations [22]. Reentry maintenance is relatively correlated with the product of the refractory period (RP) and conduction velocity [21]. Commonly, the small product is often associated with the increased risk of AF maintenance. RP is believed to depend on APD, which is abbreviated mostly by the reduced ICa-L, as well as the increased outward K^+ current [23].

To investigate whether S1R inhibition alters the atrial electrophysiology, we assessed the atrial electrophysiological parameters. Despite the absence of the transmural dispersion of atrial ERP and APD, the ERP and APD in the left atria were conducted. Our results showed that, compared with the CTL group, S1R inhibition contributed to significant reduction in both atrial ERP and APD_{90}, which then increased the inducibility and duration of AF. Importantly, we found that fluvoxamine treatment significantly prolonged the shortened ERP and

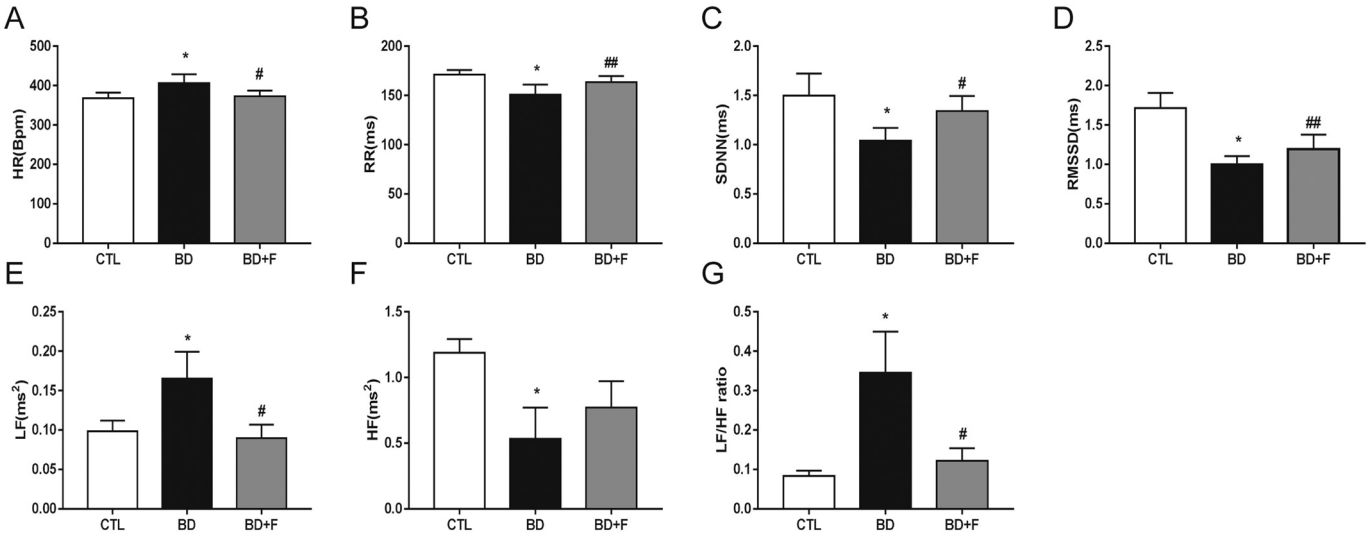

Fig. 4. Effect of the S1R inhibition on HRV. n = 7 in each group. (A–G) Statistical analysis of the mean HR, mean RR, SDNN, RMSSD, LF, HF and LF/HF ratio of the three groups, respectively. *$P < 0.01$ vs. CTL; #$P < 0.01$ vs. BD; ##$P < 0.05$ vs. BD. HRV, heart rate variability; HR, heart rate; mean RR, the mean of all normal RR-intervals; SDNN, the standard deviation of normal-to-normal intervals; RMSSD, the square root of the mean squared differences of successive RR intervals; LF, low-frequency; HF, high-frequency; Hz, herz; S1R, sigma-1 receptor.

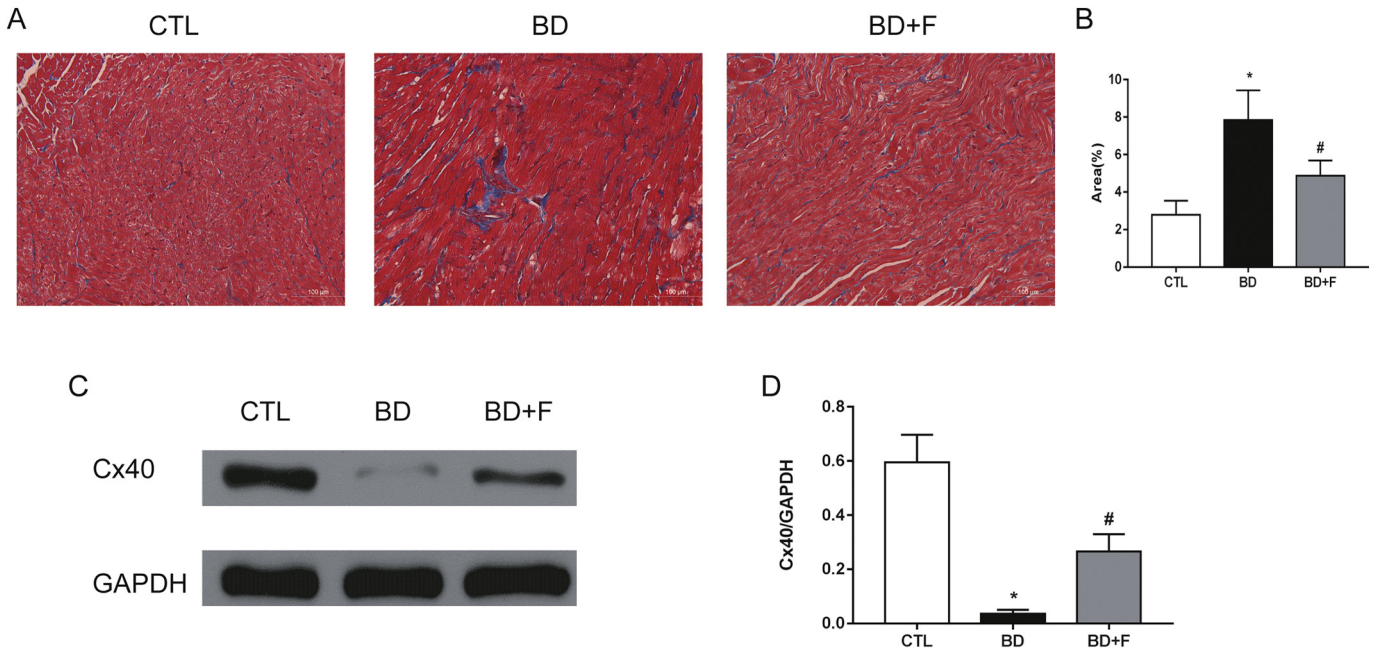

Fig. 5. Effect of the S1R inhibition on atrial myocardial fibrosis and Cx40 expression. n = 7 in each group. (A) Representative images of Masson staining of atria (original magnification: ×200). (B) Quantification of the fibrotic area in each group. (C) Immunoblotting of Cx40. (D) The expression ratio of Cx40. *$P < 0.01$ vs. CTL; #$P < 0.01$ vs. BD. S1R, sigma-1 receptor.

APD and decreased the AF inducibility and duration in the BD + F group, demonstrating that fluvoxamine could modulate the atrial electrical remodeling. The reduced ERP and abbreviated APD are believed to provide abnormal substrates for AF [24]. Although the ERP/APD showed no significant difference, patients with AF displayed decreased atrial ERP and APD compared with the control patients [25]. In addition, a recent study indicated that preventing the atrial ERP shortening contributed to the termination of AF in dogs [26], which proves that ERP plays an important role in atrial electrical remodeling.

Numerous studies have indicated that the cardiac autonomic nervous system (ANS), including sympathetic activity and parasympathetic activity, plays a crucial role both in the initiation and maintenance of AF [27–29]. Autonomic blockers restored the shortened ERP and attenuated atrial fibrillation susceptibility in a rapid atrial pacing model in dogs, demonstrating that ANS may be strongly involved in acute atrial electrical remodeling [30]. The HRV, applied to quantify the internal RR internals, is mainly used for monitoring the autonomic function, especially the cardiac parasympathetic activity [31].

Our results showed that S1R inhibition reduced the mean RR, SDNN, and RMSSD and increased the mean HR in the time-domain, along with the increased LF and LF/HF ratio and reduced HF in the frequency-domain. Fluvoxamine treatment restored most of the abovementioned HRV parameters. The HR is regulated by a variety of physiological factors that influence the ANS control, and the rapid HR increase is often associated with reduced parasympathetic activity [32,33]. The mean RR is the inverse of HR, which is a common measure of the ANS control, though not a variability parameter strictly. The increased mean RR is reported to imply a negative chronotropic effect, which may also be associated with an increased parasympathetic activity [34]. Other HRV parameters, including the time-domain and frequency-domain variables, are described in Table 1, which illustrates that in our present study, S1R inhibition reduced HRV, augmented sympathetic activity, and depressed parasympathetic activity, leading to a sympathovagal imbalance. Autonomic imbalance is highly associated with the trigger and maintenance of AF, which may result from its regulation in atrial electrical remodeling. Inhibition of cardiac ANS hyperactivity, especially the over-activated sympathetic activity, was found to suppress AF in several models [35,36]. Although the exact mechanism remains unclear, our findings indicated that fluvoxamine restored the reduced HRV and improved the sympathovagal imbalance, which may protect against the occurrence of AF.

Increased atrial fibrosis and reduced Cx40 expression were found in the BD group, which was attenuated by fluvoxamine treatment in the BD + F group. Atrial fibrosis, an important form of atrial structural remodeling, is often accompanied with a slow conduction velocity, providing a susceptible substrate for AF [37]. A recent study performed

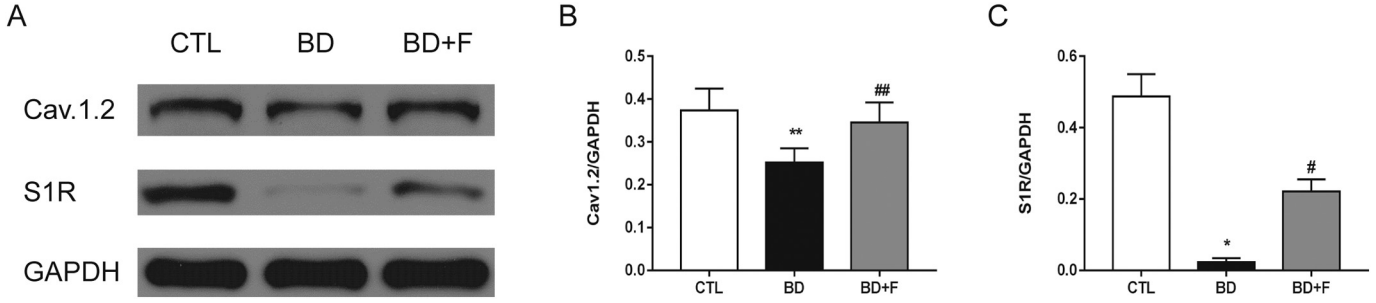

Fig. 6. Effect of the S1R inhibition on protein expression of Cav1.2 and S1R. n = 7 in each group. (A) Immunoblotting of Cav1.2 and S1R in each group, respectively. (B) The expression ratio of Cav1.2 and S1R in each group, respectively. **$P < 0.05$ vs. CTL; ##$P < 0.05$ vs. BD; *$P < 0.01$ vs. CTL; #$P < 0.01$ vs. BD. S1R, sigma-1 receptor.

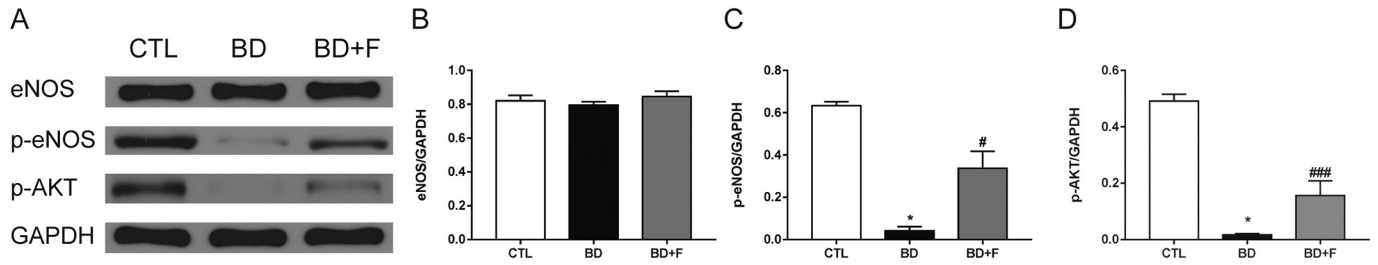

Fig. 7. Effect of the S1R inhibition on protein expression of eNOS, p-eNOS, and p-AKT. n = 7 in each group. (A) Immunoblotting of eNOS, p-eNOS, and p-AKT in each group, respectively. (B) The expression ratio of eNOS, p-eNOS, and p-AKT in each group, respectively. *$P < 0.01$ vs. CTL; #$P < 0.01$ vs. BD; ###$P = 0.01$ vs. BD. S1R, sigma-1 receptor.

in sheep indicated that AF susceptibility was attenuated by mitigating atrial structural remodeling, especially the atrial fibrosis, but not by preventing atrial electrical remodeling [38], which strongly confirmed that structural remodeling is an important regulatory target for AF. In addition, AF itself can adversely promote structural remodeling, causing positive feedback to accelerate the AF progression [39]. The gap junction is mainly composed of connexins, which connect the cardiomyocytes in a low-resistance manner. Cx40 is considered to be the most important connexin expressed in the atrium, and loss of Cx40 is closely related to a slow conduction, providing an abnormal substrate for the maintenance of AF [40]. In a recent clinical study, a significant reduction of the Cx40 level in the LAA was detected in AF patients, proving the importance of Cx40 in the progression of AF [41].

Our results also showed a significant reduction in the expression of Cav1.2 in the BD group compared with the CTL group, which could be increased by fluvoxamine in the BD + F group. The reduced ICa-L favored the decreased APD, thus playing an important part in atrial electrical remodeling [21,22]. A rapid mechanism is that the combination of Ca^{2+} with the ICa-L channel results in partial Ca^{2+}-dependent ICa-L inactivation, causing a rapid decrease in the current and APD [23]. Furthermore, a recent study demonstrated that ICa-L blockers effectively prolonged ERP, thus attenuating atrial electrical remodeling [42]. In addition, Ca^{2+} may also play a role in structural remodeling, and the potential mechanisms may be related to the enhanced activation and differentiation of fibroblasts [43].

The present study displayed a significant reduction of S1R expression in the BD group; however, fluvoxamine administration increased the reduced S1R expression. A recent study has shown that fluvoxamine treatment increased S1R expression in the thoracic aorta in a rat model of ovariectomy, whereas NE-100 (an antagonist of S1R) treatment did not [44]. Our recent study also showed that the S1R agonist SA4503 significantly upregulated S1R expression in depressive rats [18]. Interestingly, our results are consistent with the previous studies; however, the exact mechanism requires further investigation. Previous studies have shown the role of S1R in regulating the Ca^{2+} signaling pathway [4,5,17]. A direct association between ICa-L and S1R was also confirmed in retinal ganglion cells, proving the function of S1R in regulating Ca^{2+} homeostasis and signaling [45].

A previous study showed that AF was related to the decreased NOS expression, suggesting the association between normal atrial contraction and NOS expression [46]. Our latest study also indicated that chronic S1R stimulation by SA4503 was associated with eNOS/AKT activation, thereby protecting the cardiovascular system in depressive rats [18]. Furthermore, fluvoxamine was reported to upregulate S1R expression and increase the expression and activation of eNOS and AKT, thus contributing to the vascular protection in ovariectomized rats [44]. In our present study, although no significant difference was found in eNOS expression, fluvoxamine treatment resulted in significantly increased phosphorylation of eNOS and AKT, which was consistent with previous studies. Therefore, our results indicate that fluvoxamine-mediated antiarrhythmic effects resulted from the increased S1R expression, and subsequently benefits atrial arrhythmias, which may be associated with the activation of the eNOS/AKT signaling pathway.

5. Limitations

Our present study has several limitations. First, although sufficient attention has been paid to avoid unnecessary interference, ANS is still likely to be influenced in a state of anesthesia in rats. However, all three groups received the same anesthesia, which offset the differences among groups. Second, S1R may have other molecular mechanisms in regulating AF besides the eNOS/AKT pathway, which needs further investigation. Finally, our finding that S1R regulates AF is based on S1R agonists and antagonists, which needs to be further verified from the perspective of S1R knockout in our next studies.

6. Conclusions

The present study demonstrated in a rat model that S1R inhibition significantly promoted atrial electrical remodeling, autonomic remodeling (augmented sympathetic activity and suppressed parasympathetic activity) and atrial fibrosis, which resulted from the

Table 1
Summary of HRV variables in our present study.

Variables	Description	Autonomic reference
Time-domain variables		
Mean heart rate (bpm)	The mean heart beats per minute	–
Mean RR (ms)	The mean value of all normal RR-intervals	–
SDNN (ms)	The standard deviation of normal RR intervals, a measure of overall variability	Parasympathetic activity
RMSSD (ms)	The square root of the mean squared differences of successive RR intervals, a measure of beat-to-beat variability	Parasympathetic activity
Frequency-domain variables		
LF (ms^2)	Low frequency (0.25–0.75 Hz)	A combination of both sympathetic activity and parasympathetic activity
HF (ms^2)	High frequency (0.75–2.50 Hz)	Parasympathetic activity
LF/HF ratio	Ratio of LF to HF	Sympathetic activity

Abbreviation: HRV: heart rate variability.

decreased S1R expression and may be associated with the inhibition of the eNOS/AKT signaling pathway; however, the alterations were mitigated by fluvoxamine. Our findings indicate the function of the S1R inhibition in regulating AF susceptibility, suggesting a novel target for prevention and treatment of AF.

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Author contributions

The present study was performed by all authors. Tianxin Ye, Xin Liu and Bo Yang designed the study. Tianxin Ye, Xin Liu, Yuhong Fo, Yan Guo and Xiuhuan Chen carried out the experiment. Tianxin Ye and Xin Liu analyzed the data and wrote the paper. Bo Yang, Chuan Qu, Cui Zhang and Shaobo Shi revised the paper. All authors were responsible for the final content.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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