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

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Introduction: Atrial fibrillation (AF), the most common tachyarrhythmia, is often associated with cardiovascular comorbidities. 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. Therefore, it is necessary to find other safe and effective antiarrhythmic methods to intervene in AF. The sigma-1 receptor (S1R) is mainly localized on the membranes of endoplasmic reticulum, is recognized as a Ca2+-sensitive ligand-operated molecular chaperone. Numerous studies have indicated that the S1R plays an important role in neurological diseases. Emerging studies demonstrate that the S1R activation is beneficial in various conditions. The S1R activation could modulate the autonomic neurons activity, as well as the iron channels, including the L-type Ca2+ current (ICa-L) and the transient outward K+ current, which reveals the potential protective effects of the S1R on arrhythmia. Fluvoxamine, a selective serotonin reuptake inhibitor, mediated potent cardioprotection in several rodent models served as an S1R agonist. BD1047 is a selective S1R antagonist with a high affinity at the S1R. Our recent study indicated that chronic S1R stimulation with SA4503 facilitated autonomic nerve dysfunction and AF susceptibility in depressive rats. 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 affects AF vulnerability in rats and the potential mechanisms.

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.

Result: Our results showed that BD1047 significantly shortened atrial effective refractory period and action potential duration, increased AF inducibility and duration, augmented sympathetic activity, depressed parasympathetic activity, reduced heart rate variability, increased atrial fibrosis, and decreased the expression levels of S1R, Cx40, Cav1.2, p-eNOS, and p-AKT in the BD group compared with the CTL group. However, fluvoxamine administration mitigated most of alterations above.

Conclusion: Our findings indicate that S1R inhibition contributes 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.