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Bisoprolol reversed small conductance calcium-activated potassium channel (SK) remodeling in a volume-overload rat model

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Abstract A recent study indicated that apamin-sensitive current (I_{KAS}, mediated by apamin-sensitive small conductance calcium-activated potassium channels subunits) density significantly increased in heart failure and led to recurrent spontaneous ventricular fibrillation. While the underlying molecular correlation with SK channels is still undetermined, we hypothesized that they are remodeled in HF and that bisoprolol could reverse the remodeling. Volume-overload models were created on male Sprague-Dawley rats by producing an abdominal arteriovenous fistula. Confocal microscopy, quantitative real-time PCR, and western blot were performed to investigate the expression of SK channels and observe the influence of β-blocker bisoprolol on the expression of SK channels I_{KAS}, and the effect of bisoprolol on I_{KAS} and the sensitivity of I_{KAS} to $[Ca^{2+}]i$ at single isolated cells were also explored using whole-cell patch clamp techniques. SK channels were remodeled in HF rats, displaying the significant increase of SK1 and SK3 channel expression. After the treatment of HF rats with bisoprolol, the expression of SK1 and SK3 channels was significantly downregulated, and bisoprolol effectively downregulated I_{KAS} density as well as the sensitivity of I_{KAS} to $[Ca^{2+}]i$. Our data indicated that the expression of SK1 and SK3 increased in HF. Bisoprolol effectively attenuated the change and downregulated I_{KAS} density as well as the sensitivity of I_{KAS} to $[Ca^{2+}]i$.

Keywords Bisoprolol · SK channels · Remodeling

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Introduction

Heart failure (HF) severely impairs human health with a high prevalence rate and mortality rate [1]. In HF, malignant arrhythmias occur frequently, even sudden death. An important mechanism of arrhythmia genesis is electric remodeling, resulting from abnormal activity of the ion channels on the myocardial membrane, the molecular basis of which is that ion channel expression and function significantly changed in HF [2, 3].

A recent study concluded that apamin-sensitive (defined as I_{KAS}) currents of small conductance calcium-activated potassium (SK) channels led to recurrent spontaneous ventricular fibrillation (SVF) [4]. It is likely that SK channels are remodel in HF, though the underlying molecular correlation is undetermined. The activation of SK channels is considered to be dependent on the concentration of intracellular-free Ca^{2+} and it plays an important role in cardiac electrical activity since they directly integrate $[Ca^{2+}]i$ with membrane potential. Multiple laboratories showed that SK channels are expressed abundantly in human, murine, rat, rabbit, and canine cardiac tissue. SK channels differ in the sensitivity to apamin, on the basis of which they are categorized into three major