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ORIGINAL ARTICLE

Short- and long-term inhibition of cardiac inward-rectifier potassium channel current by an antiarrhythmic drug bepridil

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Abstract Bepridil is an effective antiarrhythmic drug on supraventricular and ventricular arrhythmias, and inhibitor of calmodulin. Recent investigations have been elucidating that bepridil exerts antiarrhythmic effects through its acute and chronic application for patients. The aim of this study was to identify the efficacy and the potential mechanism of bepridil on the inward-rectifier potassium channel in neonatal rat cardiomyocytes in acute- and long-term conditions. Bepridil inhibited inward-rectifier potassium current (I_{K1}) as a short-term effect with IC_{50} of 17 μM. Bepridil also reduced I_{K1} of neonatal cardiomyocytes when applied for 24 h in the culture medium with IC_{50} of 2.7 μM. Both a calmodulin inhibitor (W-7) and an inhibitor of calmodulin-kinase II (KN93) reduced I_{K1} when applied for 24 h as a long-term effect in the same fashion, suggesting that the long-term application of bepridil inhibits I_{K1} more potently than that of the short-term application through the inhibition of calmodulin kinase II pathway in cardiomyocytes.

Keywords Bepridil · Inward-rectifier K^+ channel · Calmodulin · W-7 · KN93

Introduction

Bepridil is an effective drug for a wide range of supraventricular and ventricular tachyarrhythmias. Although bepridil has originally been recognized as a class IV antiarrhythmic agent, an improved understanding of the pharmacological effects of this drug has reinforced the characteristics; bepridil is referred to as a multichannel blocker nowadays. In view point of pharmacodynamics, bepridil is a highly lipophilic drug (log $P = 5.49$, pKa = 9.16 at 37 °C) of which protein binding is approximately 99 % [1], and therapeutic plasma concentration may range from 0.5 to 5.0 μM [2]. In electropharmacological investigations, reported short-term effects of bepridil have included the blocking of various types of ion channels and transporters, such as inward-rectifier potassium current (I_{K1}) [3], transient outward potassium current (I_{to}) [3], rapid component of delayed rectifier potassium current (I_{Kr}), slow component of delayed rectifier potassium current (I_{Ks}), ultra-rapid component of delayed rectifier potassium current (I_{Kur}) [4, 5], muscarinic acetylcholine-activated K^+ current ($I_{K,ACh}$), Na^+-activated K^+ current ($I_{K,Na}$), sarcolemmal ATP-sensitive K^+ current ($I_{K,ATP}$) [6–8], voltage-gated sodium channel current (I_{Na}), L-type calcium channel current ($I_{Ca,L}$), T-type calcium channel current ($I_{Ca,T}$) [2] and Na^+–Ca^{2+} exchanger current [9–11]. More recently, long-term effects of bepridil on ionic currents have been recognized [12, 13]. Also several clinical researches have demonstrated that bepridil could be effective for treatment of persistent atrial fibrillation (AFib) and for the maintenance of normal sinus rhythm [14]. Remarkably, bepridil terminated AFib in 2 weeks after starting the administration in this clinical study, which suggests that bepridil has a long-term effect to reverse atrial electrical remodeling. Also several in vivo animal studies demonstrated that a long-term administration of bepridil prevented the shortening of the effective refractory period in the atrium when high-frequent electrical pacing was applied [15, 16]. These results also suggest that bepridil has a long-term antiarrhythmic effect besides its inhibitory action on various ionic channels, although the underlying

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