**Effects of β-adrenoceptor stimulation in human atrial repolarizing currents**

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**INTRODUCTION**

Atrial fibrillation (AF) is the most prevalent arrhythmia and the main risk factor associated with myocardial-related cerebrovascular events (1). Nowadays, pharmacological treatment of AF is clearly suboptimal (2), mainly due to rapid failure (4 to 6 months after the onset) in the electrical properties of the atria (electrical remodeling) induced by the arrhythmia itself (3). **It has been proposed that β-adrenoceptor stimulation has profound influence in the genesis and maintenance of AF. Indeed, CAF has been associated with an increased atrial sympathetic innervation (8), suggesting that autonomic remodeling may be part of atrial substrate for AF.** Stimulation of β-adrenoceptors is able to induce a decrease in the atrial refractory period (9) and in the atrial effective refractory period (10). Furthermore, β-adrenoceptor stimulation induces an increase in the atrial automaticity (11). It has been shown that the increase in the late-Ca2+ current induced by β-adrenoceptor stimulation is potentiated by CAF (12).** Moreover, the atrial automaticity increases with the rise of intracellular levels of calcium (11), which is augmented in human atrial myocytes from CAF patients (13).**

**MATERIAL & METHODS**

- Human atrial myocytes were enzymatically isolated from RAA and LAA samples obtained from SR and CAF patients that underwent cardiac surgery at the Hospital Gregorio Marañón in Madrid (8-12). The study was approved by the local ethics committee of the hospital and informed consent was obtained from each volunteer.

  • Action potentials were recorded from RAA myocytes under the current clamp configuration (14). The external solution contained NaCl 137, KCl 5, MgCl2, CaCl2 2, glucose 10, and HEPES 10 (pH 7.4, with NaOH), whereas internal solution contained K-aspartate 100, NaCl 140, MgCl2 10, CaCl2 10, and HEPES 10 (pH 7.4, with NaOH).

  • The CAF-induced potentiation of the β-adrenergic effect on Ito1 is critical to account for the different effects produced by the CAF and the SR on K+ currents elicited in two RAA cells obtained from an SR (A) and a CAF (B) patient.** Percentage of isoproterenol-induced Ito1 inhibition at +30 mV induced in LAA and RAA myocytes from SR and CAF patients.** Each bar represents the mean ± SEM of n = 8.** A and B, Detection of the increase in K+ currents during plateau.** Action potentials were recorded using the whole-cell configuration of the patch clamp technique (14). The extracellular solution contained NaCl 137, KCl 5, MgCl2, CaCl2 2, glucose 10, and HEPES 10 (pH 7.4, with NaOH), whereas the internal solution contained K-aspartate 100, NaCl 140, MgCl2 10, CaCl2 10, and HEPES 10 (pH 7.4, with NaOH).

  • The CAF-induced potentiation of the β-adrenergic effect on Ito1 is critical to account for the different effects produced by the CAF and the SR on K+ currents elicited in two RAA cells obtained from an SR (A) and a CAF (B) patient.** Percentage of isoproterenol-induced Ito1 inhibition at +30 mV induced in LAA and RAA myocytes from SR and CAF patients.** Each bar represents the mean ± SEM of n = 8.** A and B, Detection of the increase in K+ currents during plateau.** Action potentials were recorded using the whole-cell configuration of the patch clamp technique (14). The extracellular solution contained NaCl 137, KCl 5, MgCl2, CaCl2 2, glucose 10, and HEPES 10 (pH 7.4, with NaOH), whereas the internal solution contained K-aspartate 100, NaCl 140, MgCl2 10, CaCl2 10, and HEPES 10 (pH 7.4, with NaOH).

**CONCLUSIONS**

- CAF potentiates the inhibition of the Ito1, and the increase of the Ito1 produced by β-AR stimulation, this effect being greater in LAA than in RAA myocytes.

- CAF potentiates the β-adrenergic-induced decrease of the Ito1, and the CAF-induced Ito1 inhibition at -100 mV in LAA and RAA myocytes from SR and CAF patients.** C and D, Percentage of Ito1 inhibition (C) and Ito1 change at +30 mV induced by isoproterenol on LAA and RAA myocytes from SR and CAF patients.** Each bar represents the mean ± SEM of n = 8.

**REFERENCES**


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4. ARAF (2 μM) and dopamine (1 μM) were added to the internal solution and the intracellular solution contained (mM): NaCl 137, KCl 5, MgCl2 10, CaCl2 2, glucose 10, and HEPES 10 (pH 7.4, with NaOH). To record Ito1 and Ito2, the external solution consisted of (mM): NaCl 140, MgCl2 10, CaCl2 10, and HEPES 10 (pH 7.4, with NaOH).

5. Action potentials were recorded using the whole-cell configuration of the patch clamp technique (14). The extracellular solution contained NaCl 137, KCl 5, MgCl2, CaCl2 2, glucose 10, and HEPES 10 (pH 7.4, with NaOH), whereas the internal solution contained K-aspartate 100, NaCl 140, MgCl2 10, CaCl2 10, and HEPES 10 (pH 7.4, with NaOH).

6. Bar graphs showing the percentage of cells that exhibited Ito1 inhibition and Ito1 change at +30 mV induced in LAA and RAA myocytes from SR and CAF patients.** Each bar represents the mean ± SEM of n = 8.

7. While the shapes of the holding currents were similar, CAF caused a marked increase in the late-Ca2+ current in the absence and presence of β-AR stimulation of a frequency of 1 Hz.**

8. The CAF-induced potentiation of the β-adrenergic effects on human atrial ion currents can be attributed to an increase in the Ito1 expression. Moreover, the mRNA expression of the β1-AR is higher in LAA than in RAA myocytes.

9. The increase in Ito1 expression as well as the ion channel derangements produced by CAF could account for the different effects produced by the CAF and the SR on K+ currents elicited in two RAA cells obtained from an SR (A) and a CAF (B) patient.** Percentage of isoproterenol-induced Ito1 inhibition at +30 mV induced in LAA and RAA myocytes from SR and CAF patients.** Each bar represents the mean ± SEM of n = 8.

10. The CAF-induced potentiation of the β-adrenergic effects on human atrial ion currents can be attributed to an increase in the Ito1 expression. Moreover, the mRNA expression of the β1-AR is higher in LAA than in RAA myocytes.

11. In conclusion, the CAF-induced potentiation of the β-adrenergic effects on human atrial ion currents can be attributed to an increase in the Ito1 expression. Moreover, the mRNA expression of the β1-AR is higher in LAA than in RAA myocytes.**

12. The increase in Ito1 expression as well as the ion channel derangements produced by CAF could account for the different effects produced by the CAF and the SR on K+ currents elicited in two RAA cells obtained from an SR (A) and a CAF (B) patient.** Percentage of isoproterenol-induced Ito1 inhibition at +30 mV induced in LAA and RAA myocytes from SR and CAF patients.** Each bar represents the mean ± SEM of n = 8.

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