European Journal of Pharmacology

Volume 632, Issues 1–3, 25 April 2010, Pages 60–64

Cardiovascular Pharmacology

Inhibition of mitochondrial translocator protein prevents atrial fibrillation

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http://dx.doi.org/10.1016/j.ejphar.2010.01.014, How to Cite or Link Using DOI

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Abstract

Atrial fibrillation is the most common arrhythmia encountered in clinical practice. It can cause severe complications such as congestive heart failure and stroke. However, identification of prime targets for efficient therapeutic intervention remains a challenge. *In vitro* rabbit heart models of ischemia-, stretch-, and cholinergic agitation-induced atrial fibrillation were developed, and pharmacological interventions of mitochondrial translocator protein (TSPO) were adopted to explore the role of the mitochondrial protein in the aforementioned atrial fibrillations. Fura-2 AM and Mg^{2+}-Fura-2 AM were used to monitor the alterations of intracellular Ca^{2+} and ATP respectively under chemical ischemia or cholinergic agitation. The results showed that inhibition of TSPO significantly reduced the incidence of all three types of atrial fibrillation. In addition, TSPO inhibition ameliorated the cytoplasmic Ca^{2+} overload and energy compromise facing to chemical ischemia or cholinergic agitation in HL-1 cells, an atrial muscle cell line. Thus, TSPO may be an important molecule in the context of different kinds of atrial fibrillation, and a novel and common target for atrial fibrillation treatment.

Keywords

Atrial fibrillation; Mitochondria; Ca^{2+} overload

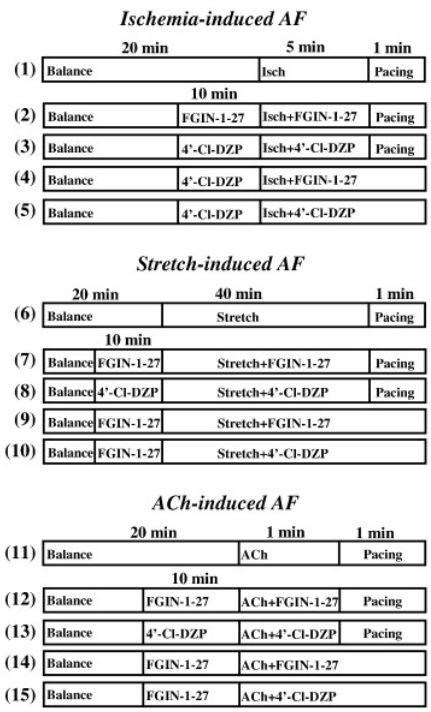

Fig. 1. Experimental protocols for atrial fibrillations. *In vitro* rabbit heart model of ischemia-, stretch-, and cholinergic agitation-induced atrial fibrillation was developed. Mitochondrial translocator protein (TSPO) agonist (FGIN-1-27) and antagonist (4'-Cl -DZP) were used to explore the role of TSPO in atrial fibrillation. ACh, acetylcholine.

Figure options

Fig. 2. Regulation of mitochondrial translocator protein (TSPO) on three types of atrial fibrillation. Inhibition of TSPO decreased the incidence of atrial fibrillation significantly. ACh, acetylcholine.

Figure options

Fig. 3. Modulation of mitochondrial translocator protein (TSPO) on ischemia- and cholinergic agitation-induced $[Ca^{2+}]_i$ overload in HL-1 cells. (A) Representative recording traces for $[Ca^{2+}]_i$ throughout balance and ischemic perfusion. (B) Statistical results of $[Ca^{2+}]_i$ changes during ischemia. (C) and (D) Effects of ACh on $[Ca^{2+}]_i$. (*$P < 0.05$ vs. corresponding control; **$P < 0.01$ vs. corresponding control). Bal, balance; Isch, ischemia; ACh, acetylcholine.

Figure options

Fig. 4. Modulation of mitochondrial translocator protein (TSPO) on ischemia- and cholinergic agitation-mediated $[ATP]_i$ changes in HL-1 cells. The changes of $[Mg^{2+}]_i$ indirectly indicated the changes of $[ATP]_i$, the Mg^{2+}-Fura-2 AM indicator was applied to monitor $[ATP]_i$ changes. (A) Representative recording traces for $[Mg^{2+}]_i$ throughout balance and ischemic perfusion. (B) Statistical results of $[Mg^{2+}]_i$ during ischemia. (C) and (D), Effects of ACh on $[Mg^{2+}]_i$. (*$P < 0.05$ vs. corresponding control; **$P < 0.01$ vs. corresponding control). Bal, balance; Isch, ischemia; ACh, acetylcholine.

Figure options

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