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Inhibition of mitochondrial translocator protein prevents atrial fibrillation

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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

Mitochondria
Ca^{2+} overload

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.

1. Introduction

Atrial fibrillation is characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. It is the most common sustained cardiac rhythm disturbance in clinical practice, affecting 1.5–2.0% of the population in the developed world. According to population-based studies in the US, the number of adults with atrial fibrillation will swell by 2.5–3.0-fold by 2050. Atrial fibrillation confers a substantial mortality, morbidity and health care cost from stroke, thromboembolism, heart failure, and impaired quality of life. It is associated with a 6-fold increased risk for ischemic stroke. Observational studies suggest that one in four to five strokes is due to atrial fibrillation. Globally, the annual cost per patient is close to U.S. $3600. Based on the prevalence of atrial fibrillation, the total societal burden is approximately U.S. $15.7 billion in the European Union (Khairy and Nattel, 2002; Iqbal et al., 2005; Veenhuyzen et al., 2004).

Despite advances in non-pharmacological therapies for atrial fibrillation, conventional anti-arrhythmic drugs continue to be the cornerstone of atrial fibrillation treatment. Ongoing drug development has focused on atria-specific ion channels as well as mechanism-based targets. Novel drugs targeting inflammation, oxidative injury, atrial myocyte metabolism and extracellular matrix remodeling, have also shown therapeutical potentials (Veenhuyzen et al., 2004). However, all the existing anti-arrhythmic therapy remains to be hampered by the lack of strong efficacy and unacceptable potential side effects, such as fatal ventricular proarrhythmia and negative inotropy. Thus, identification of prime targets for efficient therapeutic intervention is a new challenge that we are facing.

Mitochondrial dysfunction has been increasingly recognized as important mechanisms for cardiac diseases including arrhythmias (Rosenberg, 2004). Many ion channels or transporter on the mitochondrial membrane contributes to the maintenance of normal mitochondrial functions. Among all these ion channels or transporter, mitochondrial translocator protein (TSPO) spans the inner and outer membranes. This protein was, for many years, known as the mitochondria benzodiazepine receptor. Regarding the structure and molecular function of this protein, the new nomenclature is proposed (Papadopoulos et al., 2006). It is involved in the regulation of the mitochondrial respiratory chain, metabolic/oxidative stress and inner

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