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Mechanism of Action of the Antiarrhythmic Agent AZD7009

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson salen, Akademikum, Medicinaregatan 3

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av
Frida Persson

Fakultetsopponent:
Professor Emeritus Edward Carmeliet
University Leuven, Belgium

Avhandlingen baseras på följande delarbeten:

I. Persson F., Carlsson L., Duker G., Jacobson I. Blocking characteristics of hERG, hNav1.5 and hKvLQT1/hminK after administration of the novel antiarrhythmic compound AZD7009.
J Cardiovasc Electrophysiol 2005; 16:329-341.

II. Persson F., Carlsson L., Duker G., Jacobson I. Blocking characteristics of hKv1.5 and hKv4.3/hKChIP2.2 after administration of the novel antiarrhythmic compound AZD7009.
J Cardiovasc Pharmacol 2005; 46:7-17.

III. Persson F., Andersson B., Duker G., Jacobson I., Carlsson L. Functional effects of the late sodium current inhibition by AZD7009 and lidocaine in rabbit isolated atrial and ventricular tissue and Purkinje fibre.
Eur J Pharmacol, in press.

IV. Persson F., Duker G., Hermansson N-O., Jacobson I., Carlsson L. Effects of AZD7009 on Kir3.1/Kir3.4 inward rectifier potassium current expressed in CHO cells.
Manuscript.

V. Persson F., Duker, G., Jacobson I., Carlsson L. Effects of AZD7009 on L-type calcium current in acutely isolated rabbit cardiomyocytes and H9c2 cells.
Manuscript.

Mechanism of Action of the Antiarrhythmic Agent AZD7009

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Abstract

Atrial fibrillation (AF) is the most common tachyarrhythmia in the adult population and is a major cause of morbidity and mortality. AF can be terminated and sinus rhythm restored by prolonging the action potential duration (APD) and the refractory period. Unfortunately, antiarrhythmic agents that prolong the APD and increase the refractory period via selective inhibition of the rapid delayed rectifier potassium current (IK_r), i.e. class III antiarrhythmic drugs, are associated with an increased risk of the ventricular tachycardia Torsades de Pointes. AZD7009 is an antiarrhythmic agent with predominant actions on atrial electrophysiology that shows high antiarrhythmic efficacy and low proarrhythmic potential in animals and man. The aim of the current studies was to characterize the effect of AZD7009 on cardiac ion currents and APD in order to provide a mechanistic explanation for its predominant atrial effects and low proarrhythmic potential.

The human cardiac ion channels hERG (IK_r), Kv1.5 (IK_{ur}), Kv4.3/KChIP2.2 (I_{to}), KvLQT1/minK (IK_s), Kir3.1/Kir3.4 (IK_{ACh}) and Nav1.5 (INa) were expressed in mammalian cells. Whole-cell currents were inhibited by AZD7009 with the following IC_{50} values: hERG 0.6 μM, Nav1.5 8 μM, Kv4.3/KChIP2.2 24 μM, Kv1.5 27 μM, Kir3.1/Kir3.4 166 μM and KvLQT1/minK 193 μM. Whole-cell sodium and calcium currents were recorded in isolated rabbit atrial and ventricular myocytes using amphotericin B perforated patch. The late sodium current in rabbit atrial and ventricular myocytes was inhibited by AZD7009 in a concentration dependent way, with approximately 50% inhibition at 10 μM AZD7009. The L-type Ca^{2+} current (ICa_L) in rabbit ventricular myocytes was inhibited with an IC_{50} of 90 μM. Transmembrane action potentials were recorded in tissue pieces from rabbit atrium, ventricle and Purkinje fibre in control, during exposure to the selective IK_r blocker E-4031 and to E-4031 in combination with AZD7009. In Purkinje fibres, but not in ventricular tissue, AZD7009 attenuated the E-4031-induced APD prolongation. In contrast, in atrial cells, AZD7009 further prolonged the APD. In addition, AZD7009 was able to suppress early afterdepolarisations (EADs) induced by E-4031 in Purkinje fibre preparations.

In conclusion, AZD7009 delays repolarisation and increases refractoriness in atrial tissue through synergistic inhibition of IK_r, I_{to}, IK_{ur} and INa, a mixed ion channel blockade that may underlie its high antiarrhythmic efficacy. Inhibition of the late sodium current, counteracting excessive APD prolongation and EADs in susceptible cells (midmyocardial and Purkinje cells), may explain the low proarrhythmic potential of AZD7009.

Key words: atrial fibrillation, antiarrhythmic drug, cardiac action potential, early after-depolarisation, IK_r, IK_{ur}, I_{to}, IK_s, IK_{ACh}, INa, ICa_L,

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