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Cardiovascular diseases

Drug-induced long QT syndrome: molecular mechanisms for congenital and acquired QT prolongation

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Congenital and acquired long QT syndromes (LQTSs) are important causes of sudden cardiac death. Drug-induced LQTS, the most common cause, has particular importance to clinicians and pharmaceutical companies. In this review, we will discuss the molecular and genetic mechanisms of both congenital forms and acquired forms of LQTS. In particular, we will focus on the available *in vitro* techniques to test for QT prolongation and arrhythmogenesis.

Introduction

Prolongation of the QT interval on surface ECG can lead to torsade de pointes, a form of polymorphic ventricular tachycardia, which causes sudden cardiac death (Fig. 1). Prolonged QT intervals can be caused by a variety of inherited cardiac ion channel abnormalities, and thus, the term 'long QT syndrome' can be applied to a family of genetic defects. In the past few years, major progress has been made in defining these inherited sodium and potassium channel defects [1–3].

Acquired forms of long QT syndrome (ALQTS) are more common than the congenital forms. Patients with this condition have a normal ECG at baseline, but with exposure to specific precipitating factors, the QT interval prolongs. The most common precipitating factors are drugs, although electrolyte abnormalities and bradycardia can also be causes. The

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genetic basis for these 'acquired' forms is unclear, but a small number of patients have been found to have ion channel abnormalities akin to those seen in congenital LQTS [4–7].

The issue of drug-induced QT prolongation is of vital importance in drug development. QT prolongation is the primary cause of delayed drug approval by the Food and Drug Administration (FDA) and is the second most common cause for drugs being withdrawn from the market [8,9]. In this review, we will describe the genetic and molecular mechanisms of QT interval prolongation, and particularly, the mechanisms whereby drugs have been shown to prolong the QT interval.

Congenital long QT syndrome

The inherited form of LQTS was first described in the 1950s. However, it was not until the early 1990s that specific mutations that can cause the clinical syndrome were identified. At the cellular level, the basic anomaly in LQTS is prolongation of the cardiac action potential. Various ion currents mediate the different phases of the cardiac action potential (Fig. 2) [10]. Cardiac ion channels allow cations or anions to flow either into or out of myocytes. Inward cation currents cause depolarization of the cell membrane, while outward cation currents cause repolarization of the membrane. Defects in

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