

# Hypomagnesemic down-regulation of L-type $\text{Ca}^{2+}$ channel in cardiomyocyte as an arrhythmogenic substrate in rats

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## Abstract

The present study was designed to investigate the effect of magnesium (Mg) depletion on the expression of voltage-gated calcium ( $\text{Ca}^{2+}$ ) channels and  $\text{Ca}^{2+}$  currents in the heart and thereby on hypomagnesemic arrhythmogenesis in adult male rats. Male Wistar rats were fed an Mg-free diet or a normal diet for up to 16 weeks. Serum Mg concentrations were significantly reduced at week 4 or later with an Mg-free diet, which experimentally represents hypomagnesemia. Myocardial Mg contents were also reduced at week 16 accompanied by myocardial hypertrophy. Telemetric ECG recordings revealed a long-term changes of ECG parameters in hypomagnesemic rats; RR shortening, QT prolongation and appreciable PR prolongation. At the same time, hypomagnesemic rats demonstrate various bradycardiac arrhythmias including ventricular premature beats, atrioventricular blocks and sinus arrest, which were never recoded in rats fed by a normal diet. Electrophysiological studies elucidated that the L-type  $\text{Ca}^{2+}$  channel current was decreased in Mg-deficient cardiomyocytes, and these findings were consistent with down-regulation of  $\text{Ca}_v1.2$ -mRNA but not in levels of  $\text{Ca}_v1.3$ ,  $\text{Ca}_v3.1$  or  $\text{Ca}_v3.2$ . These findings provide novel insights into hypomagnesemic electrophysiological disorders in the heart, and should be considered when assessing the design of effective antiarrhythmic treatments in patients with hypomagnesemia.

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## 1. Introduction

Magnesium (Mg) is an important cation and has many significant physiological and pharmacological effects on different organ systems. The physiological role of Mg or magnesium ion ( $\text{Mg}^{2+}$ ) is partly due to its calcium channel blocking properties at smooth muscle, skeletal muscle, and cardiac muscle including the conduction system [1]. Accordingly, Mg or  $\text{Mg}^{2+}$  is recognized as a naturally occurring calcium ( $\text{Ca}^{2+}$ ) channel antagonist or an endogenous  $\text{Ca}^{2+}$  antagonist which reduces movement of extracellular  $\text{Ca}^{2+}$  into the myocardial cells by a competitive process localized at

the sarcolemmal membranes [2–4]. In this context, Mg is beneficial in acute myocardial infarction, protection during open heart surgery and treatment and prevention of heart rhythm disturbances [5]. On the other hand, Mg has an established role in the management of preeclampsia and eclampsia. Mg prevents or controls convulsions by blocking neuromuscular transmission and decreasing the release of acetylcholine at the motor nerve terminals [1]. The use of  $\text{MgSO}_4$  in treating tetanus and acute asthma is also established [1]. These findings indicate that Mg is an essential element and drug with multidisciplinary applications mostly depending on its effects attributed to  $\text{Ca}^{2+}$  channel blocking properties [2–4]. Based on these understandings, it is conventionally accepted that long-term excess or loss of Mg is frequently responsible for an increase or decrease of endogenous  $\text{Ca}^{2+}$  antagonist as a consequences of chronic electrolyte imbalance.

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