Magnesium Deficiency Causes Transcriptional Downregulation of Kir2.1 and Kv4.2 Channels in Cardiomyocytes Resulting in QT Interval Prolongation

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Background: Mechanisms for QT interval prolongation and cardiac arrhythmogenesis in hypomagnesemia are poorly understood. This study investigated the potential molecular mechanism for QT prolongation caused by magnesium (Mg) deficiency in rats by using the patch clamp technique and molecular biology.

Methods and Results: Male Wistar rats were fed an Mg-free diet or a normal diet for up to 12 weeks. There was QT prolongation in the ECG of Mg-deficient rats, and cardiomyocytes from these rats showed prolongation of action potential duration. Electrophysiological studies showed that inward-rectifying K+ current (I\textsubscript{K1}) and transient outward K+ current (I\textsubscript{to}) were decreased in Mg-deficient cardiomyocytes, and these findings were consistent with the downregulation of mRNA, as well as protein levels of Kir2.1 and Kv4.2. In Mg-deficient cardiomyocytes, transcription factors, GATA4 and NFAT, were upregulated, whereas CREB was downregulated. In contrast to Mg deficiency, cellular Mg\textsuperscript{2+} overload in cultured cardiomyocytes resulted in the upregulation of Kir2.1 and Kv4.2, which was accompanied by the downregulation of GATA4 and NFATc4, and the upregulation of CREB. Activation of NFAT and inhibition of CREB reduced Kv4.2-I\textsubscript{to}, whereas Kir2.1+I\textsubscript{K1} was reduced by CREB inhibition but not by NFAT activation.

Conclusions: Intracellular Mg deficiency downregulates I\textsubscript{K1} and I\textsubscript{to} in cardiomyocytes, and this is mediated by the transcription factors, NFAT and CREB. These results provide a novel mechanism for the long-term QT interval prolongation in hypomagnesemia.

Key Words: Electrical remodeling; Hypomagnesemia; I\textsubscript{K1}; I\textsubscript{to}

Magnesium (Mg) is the second most abundant intracellular cation next to potassium (K) and the fourth most abundant cation in the body, playing an important role in many cellular functions.\(^1\) It is an essential element that regulates membrane stability and has neuromuscular, cardiovascular, immune and hormonal functions.\(^2\) Mg or magnesium ion (Mg\textsuperscript{2+}) deficiency leads to a wide variety of metabolic abnormalities and clinical consequences.\(^3\) Mg deficiency has also been identified as a risk factor for cardiovascular diseases such as coronary artery disease.\(^4\) Epidemiological observations suggest that patients dying suddenly from ischemic heart disease have lower concentrations of myocardial tissue Mg and K than patients dying from other causes.\(^5\) Hypomagnesemia has also been shown to contribute to the onset and maintenance of various arrhythmias. Supraventricular arrhythmias in hypomagnesemia commonly include tachycardia and atrial premature contractions. Ventricular arrhythmias observed in patients with hypomagnesemia are usually associated with prolonged QT intervals.\(^6\) On the cellular level, hypomagnesemia is often associated with prolonged action potential duration (APD).\(^7\)

Intracellular Mg\textsuperscript{2+} certainly has a role in the regulation of the inward rectifier potassium channel current (I\textsubscript{K1}), and an increase in intracellular Mg concentration can block I\textsubscript{K1}.\(^8\) The block of I\textsubscript{K1} by increased intracellular Mg\textsuperscript{2+} appears to prolong APD and QT interval. Based on this mechanism, a reduction of intracellular Mg\textsuperscript{2+} would be expected to cause QT shortening; however, hypomagnesemia is often accompanied by QT prolongation, and hypermagnesemia is often associated with QT shortening. Accordingly, the direct action of intracellular Mg\textsuperscript{2+} on I\textsubscript{K1} may not be correlated with changes in QT intervals on the surface electrocardiogram (ECG). Conventional understanding of QT changes with changes in extracellular Mg\textsuperscript{2+} is based on the notion that Mg\textsuperscript{2+} is a natural intrinsic blocker of the Ca\textsuperscript{2+} channel. Increased extracellular Mg blocks the inward Ca\textsuperscript{2+} current and shortens the QT interval, whereas decreased extracellular Mg\textsuperscript{2+} may increase the inward Ca\textsuperscript{2+} current and prolong the QT interval. Clinical findings that

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