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Molecular Physiological Investivation of Arrhythmogenecity in Cardiomyocytes Induced by Mg^{2+}-Deficiency Diet

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Summary

Numerous studies have shown the beneficial application of magnesium in the treatment of arrhythmias. However, molecular and cellular mechanisms underlying the arrhythmogenecity in magnesium deficiency have not fully clarified in human and animal models. There are quite few numbers of studies have been carried out in an attempt to define the role of both intracellular and extracellular magnesium in the physiopathology and treatment of arrhythmias. Hypomagnesaemia has been suggested as a cause for arrhythmias of both supraventricular and ventricular origin, but any relationship between hypomagnesaemia and the development of arrhythmias is extremely complex since patients with normal plasma levels of magnesium may in fact have a reduced body content of the ion which, as we know is located primarily inside the cells.

In this context, based on the fact that magnesium is an important cofactor of many cellular signal transductions, we hypothesized that cardiac arrhythmias in magnesium deficiency were caused not only by the luck of serum magnesium but also by the malfunction of the cellular ion channels associated with intracellular signal derangement. To do this, we have employed an animal model by use of rats (8 weeks old male Wistar rat) with magnesium deficient diet in comparison with normal diet (magnesium contents of 0.26 g/100g). By feeding magnesium deficient diet, serum magnesium concentration was reduced from 0.23 ± 0.1 mg/dl in the control condition to 1.1 ± 0.1 mg/dl at week 2 and 0.8 ± 0.1 mg/dl at week 6. At the same time, intracellular magnesium concentration, as assessed by red blood cell contents, was reduce from 6.9 ± 0.2 mg/dl in the control condition to 5.5 ± 0.3 mg/dl at week 2 and 4.8 ± 0.3 mg/dl at week 6. Telemetric ECG recordings revealed that RR intervals were shortened from 192 ± 6 ms to 150 ± 11 ms, QT intervals were prolonged from 57 ± 1 ms to 72 ± 1 ms, and QT/RR ratios were increased from 0.30 ± 0.01 ms to 0.49 ± 0.03 ms at week 6 in rats treated by magnesium deficient diet. ECG recordings demonstrated quite a few numbers of ventricular and supraventricular premature beats in magnesium deficient rats. Electrophysiological study indicates that action potential duration (APD_{90}) recorded from left ventricular myocytes in magnesium deficient rats was markedly increased from 101 ± 3 ms to 314 ± 12 ms at week 6. Patch clamp analysis shows that inward-rectifier K^+ channel currents (I_{K1}) were significantly repressed by 10 - 25% in magnesium deficient rats at the fixed intracellular magnesium concentration of 0.1 mM, 2 mM and 5 mM. Among a pair of K^+ channel isoforms that are responsible for rat cardiac I_{K1}, Kir2.1 mRNA but not Kir2.2 mRNA was roughly halved in ventricular myocytes in magnesium deficient rats. In order to confirm the action of intracellular magnesium as a cofactor of Kir2.1 transcription, we employed a cell culture system in combination with a magnesium ionophore, ionophore II. Administration of a magnesium ionophore increased intracellular concentration of magnesium as well as Kir2.1 expression in cardiomyocytes.

In conclusion, we have successfully demonstrated that intracellular magnesium acts as a co factor to modulate Kir2.1 expression, resulting in a down-regulation of I_{K1} and prolongation of QT intervals in ECG in magnesium deficiency.