Roles of the sodium-magnesium exchange transport in physiological and pathophysiological changes of intracellular free Mg concentration

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Summary

We investigated regulation of intracellular Mg^{2+} concentration ($[Mg^{2+}]_i$) in cardiac muscle. $[Mg^{2+}]_i$ measured by ^{31}P-MRS in the Langendorff-perfused rat hearts was decreased by β-adrenergic stimulation or application of forskolin. Muscarinic stimulation by carbachol did not change $[Mg^{2+}]_i$ by itself, but antagonized the $[Mg^{2+}]_i$ change induced by β-adrenergic stimulation. Insulin increased $[Mg^{2+}]_i$ and suppressed the decrease in $[Mg^{2+}]_i$ caused by β-adrenergic stimulation. Since these effects of insulin were inhibited by LY333531, a protein kinase C inhibitor, insulin modulates $[Mg^{2+}]_i$ presumably via activation of protein kinase C. We have further characterized the Mg^{2+} transporter that is responsible for the modulation of $[Mg^{2+}]_i$ by measurements of $[Mg^{2+}]_i$ with a fluorescent indicator furaptra in ventricular myocytes enzymatically isolated from rat hearts. After $[Mg^{2+}]_i$ was raised by ionomycin and high extracellular Mg^{2+} concentration ($[Mg^{2+}]_o$), washout of ionomycin and lowering $[Mg^{2+}]_o$ caused rapid decline of $[Mg^{2+}]_i$ in the presence of Na^+. This Mg^{2+} efflux was completely inhibited by withdrawal of extracellular Na^+ (half activated by 90 mM Na^+), and was largely attenuated by imipramine, an inhibitor of the Na^+-Mg^{2+} exchange. The results suggest that Na^+-Mg^{2+} exchange is an important mechanism to extrude Mg^{2+} in cardiac myocytes. To identify the transporter molecule, we established a mutant strain of mouse renal tubular (MCT) cells that can grow in the culture media with very high Mg^{2+} concentrations (>100 mM). An average $[Mg^{2+}]_i$ (measured with furaptra) in the Mg^{2+}-tolerant cells was kept lower than that in wild cells either at 51 mM or 1 mM $[Mg^{2+}]_o$. When $[Mg^{2+}]_o$ was lowered from 51 mM to 1 mM, decrease in $[Mg^{2+}]_i$ was significantly faster in the Mg^{2+}-tolerant cells than in wild cells. These differences between the Mg^{2+}-tolerant cells and wild cells were abolished in the absence of extracellular Na^+. These results suggest that expression of Na^+-Mg^{2+} exchanger was enhanced in the Mg^{2+}-tolerant cells to prevent $[Mg^{2+}]_i$ increase to higher levels.