INSULIN REGULATES HUMAN ERYTHROCYTE Na\(^+\)/Mg\(^{2+}\) EXCHANGE

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Alterations in cellular magnesium levels have been shown to be associated with insulin resistance. In order to characterize cellular magnesium regulation, we tested the hypothesis that insulin regulates intracellular magnesium levels via activation of Na\(^+\)/Mg\(^{2+}\) exchange. We studied the effect of insulin on Na/Mg exchange in freshly isolated human erythrocytes from normal subjects after an overnight fast. We measured Na/Mg exchange activity as net total magnesium efflux driven by an inward Na gradient in Mg-clamped red cells in the presence or absence of insulin. All subjects studied show a Na/Mg activity that was 0.5 ± 0.07 mmol/L cell x h (mean ± SE, n=21) in Mg loaded cells (13.5 ± 0.39 mM). When 400 µU/mL of insulin were added to the flux media, Na/Mg activity increased to 0.72 ± 0.06 mmol/L cell x h (P<0.007, n=21). A dose response curve for insulin on Na/Mg activity showed an EC50 for insulin of 70.5 ± 8.6 µU/mL. Na/Mg exchange activity was also increased after incubation with an insulin receptor tyrosine kinase activator, IRTK. We also measured the Na/Mg exchange activity as a function of extracellular sodium and found that insulin decreased the Km for extracellular Na from 72.5 ± 2 to 54.8 ± 3.8 mM (n=6). However, the Km for intracellular Mg was not affected by pre-incubation with insulin. Insulin-stimulated Na/Mg activity was partially inhibited by PI3 kinase inhibitor, wortmannin, (from 0.99 ± 0.2 to 0.69 ± 0.1 mmol/L cell x h, n= 10, p<0.05) and 100nM of okadaic acid (from 0.99 ± 0.2 to 0.59 ± 0.1 mmol/L cell x h, n= 8, p<0.05). In summary, insulin stimulates the red cell Na/Mg exchanger via a pathway that includes activation of the insulin receptor, PI 3-kinase activation as well as protein phosphatases which might cause an increase in the affinity for the external sodium regulatory site of the exchanger. Therefore, we speculate that insulin’s effect on Na/Mg exchange may in part explain the low cellular magnesium levels observed in vivo under hyperinsulinemic conditions.

Key Words: Sodium Transport, Hyperinsulinemia, Insulin receptor