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Study on functional abnormality of Na^+-driven ion exchangers in degenerative disease of skeletal and heart muscles

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Summary

Deficiency of delta-sarcoglycan, a component of the dystrophin-glycoprotein complex, causes muscular dystrophy in BIO14.6 hamsters (BIO). Abnormal ion homeostasis has been suggested to be a prerequisite for muscle dysgenesis. In this study, we tried to identify ion transport pathways responsible for the Ca^{2+} and Na^+ abnormality in myopathy using myotubes from normal and BIO. We found that the sarcolemmal Na^+/H^+ exchanger (NHE) was significantly activated in BIO myotubes, as evidenced by an alkaline shift of the intracellular pH (pH_i) dependence of NHE activity, enhanced $^{22}Na^+$ influx, and elevated pH_i and cytosolic Na^+ concentration ($[Na^+_i]$). In BIO myotubes, NHE was found to serve as the major Na^+ influx pathway because the specific inhibitor cariporide markedly (65%) inhibited it. Interestingly, NHE inhibitor significantly reduced the intracellular Ca^{2+} rise and the stretch-induced creatine phosphokinase release in BIO myotubes and ameliorated the myopathic damage *in vivo*, indicating that inhibition of NHE protects the muscle cell injury. Elevation in $[Na^+]_i$ may contribute to abnormal Ca^{2+} homeostasis by influencing the Na^+/Ca^{2+} exchange activity. These data suggest that Na^+-dependent ion exchangers may play an important role in muscle degeneration.