The involvement of Akt, mTOR, and S6K in the in vivo effect of IGF-1 on the regulation of rat cardiac Na^+/K^+-ATPase

Abstract

Background

We previously demonstrated that insulin-like growth factor-1 (IGF-1) regulates sodium/potassium adenosine triphosphatase (Na^+/K^+-ATPase) in vascular smooth muscle cells (VSMC) via phosphatidylinositol-3 kinase (PI3K). Taking into account that others' work show that IGF-1 activates the PI3K/protein kinase B (Akt) signaling pathway in many different cells, we here further questioned if the Akt/mammalian target of rapamycin (mTOR)/ribosomal protein p70 S6 kinase (S6K) pathway stimulates Na^+/K^+-ATPase, an essential protein for maintaining normal heart function.

Methods and results

There were 14 adult male Wistar rats, half of whom received bolus injections of IGF-1 (50 μg/kg) for 24 h. We evaluated cardiac Na^+/K^+-ATPase expression, activity, and serum IGF-1 levels. Additionally, we examined the phosphorylated forms of the following proteins: insulin receptor substrate (IRS), phosphoinositide-dependent kinase-1 (PDK-1), Akt, mTOR, S6K, and α subunit of Na^+/K^+-ATPase. Additionally, the mRNA expression of the Na^+/K^+-ATPase α_1 subunit was evaluated. Treatment with IGF-1 increases levels of serum IGF-1 and stimulates Na^+/K^+-ATPase activity, phosphorylation of α subunit of Na^+/K^+-ATPase on Ser^{23}, and protein expression of α_2 subunit. Furthermore, IGF-1 treatment increased phosphorylation of IRS-1 on Tyr^{1222}, Akt on Ser^{473}, PDK-1 on Ser^{241}, mTOR on Ser^{2481} and Ser^{2448}, and S6K on Thr^{421}/Ser^{424}. The concentration of IGF-1 in serum positively correlates with Na^+/K^+-ATPase activity and the phosphorylated form of mTOR (Ser^{2448}), while Na^+/K^+-ATPase activity positively correlates with the phosphorylated form of IRS-1 (Tyr^{1222}) and mTOR (Ser^{2448}).

Conclusion

These results indicate that the Akt/mTOR/S6K signalling pathway may be involved in the IGF-1 regulating cardiac Na^+/K^+-ATPase expression and activity.