Depletion of muscle taurine levels is tolerated by the heart but results in severe impairment of skeletal muscle

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Introduction

Taurine is the most abundant free amino acid in mammalian heart and skeletal muscle with intracellular concentrations of 20-70 mmol/kg. Multiple actions of taurine on ion channels and transport systems have been suggested to contribute to its tissue-protective effects in many models of oxidant-induced injury (1). Pharmacologically-induced taurine deficiency has been shown to result in dilative cardiomyopathy in cat, fox, and rat (2-4). In clinical studies, a correlation between low plasma taurine concentrations and echocardiographic findings representative of dilated cardiomyopathy were reported (5). Therefore a direct link between decreased myocardial taurine levels and decreased cardiac function was proposed. In order to further explore the role of taurine in muscle physiology, cardiac and skeletal muscle function and morphology were examined in detail in the recently generated taurine-deficient mouse model (*taut*-/-) with a disrupted gene coding for the taurine transporter (6).

Methods

MR investigations were performed at a Bruker DRX 9.4 Tesla Wide Bore NMR Spectrometer equipped with an actively shielded 40-mm gradient set (1 T/m maximum gradient strength). Cardiac function of mice was evaluated *in vivo* by acquisition of high resolution images using an ECG- and respiratory-triggered FLASH cine sequence. For isolated heart studies a 10-mm $^{31}P/^{1}H$ dual probe was used. Contractile function was evaluated *via* a balloon inserted into the left ventricle and cardiac enegetics was monitored by ^{31}P NMR spectroscopy. Hearts were challenged in separate series by dobutamine infusion (200 nM) and a 12-min period of a global no-flow ischemia followed by one hour of reperfusion, respectively. ^{1}H NMR spectra of lyophilized tissue extracts were recorded from a 5-mm $^{1}H/^{13}C$ dual probe and chemical shifts were referenced to TSP at 0 ppm. Additionally, echocardiographic, ergometric, microscopic as well as electromyographic analysis were carried out.

Results and Discussion

Disruption of the taurine transporter resulted in almost complete depletion of heart and skeletal muscle taurine levels (Fig. 1). Surprisingly, cardiac function of *taut*-/- mice as assessed by MRI, echocardiography, and isolated heart studies showed a largely normal phenotype under both control and stress conditions (dobutamine challenge as well as ischemia/reperfusion). Furthermore, only minor differences were observed by light and electron microscopy between *taut*-/- and wild-type (WT) hearts. However, analysis of *taut*-/- skeletal muscle revealed severe structural defects and electromyographic abnormalities. ^{1}H NMR spectroscopy of tissue extracts showed that in the heart of *taut*-/- mice the lack of taurine was fully compensated by the upregulation of various organic solutes, predominantly glutamine, alanine, actetate, and glycine (*cf.* Fig. 1, top). In contrast, in skeletal muscle the osmotic balance could not be maintained in the absence of taurine resulting in a deficit of more than 10 mM in total organic osmolyte concentration (Σ = 28.1±4.1 mM (WT) vs. 17.7±3.0 mM (*taut*-/-), n=6, $P<0.05$). Treadmill experiments showed that total exercise capacity of *taut*-/- mice was reduced by 81±9 % compared to wild-type (WT) controls (n=6, $P<0.01$). The decreased performance of *taut*-/- mice correlated with increased lactate levels in serum during exercise (4.4±0.9 mM (*taut*-/-) vs. 2.8±1.0 mM (WT), n=4, $P<0.05$). In summary, the results of this study show that depletion of cardiac taurine pools can be osmotically compensated by upregulation of a variety of other osmolytes which leaves cardiac function uncompromised. In contrast, disturbance of the osmotic balance in skeletal muscle results in severe impairment of total exercise capacity.

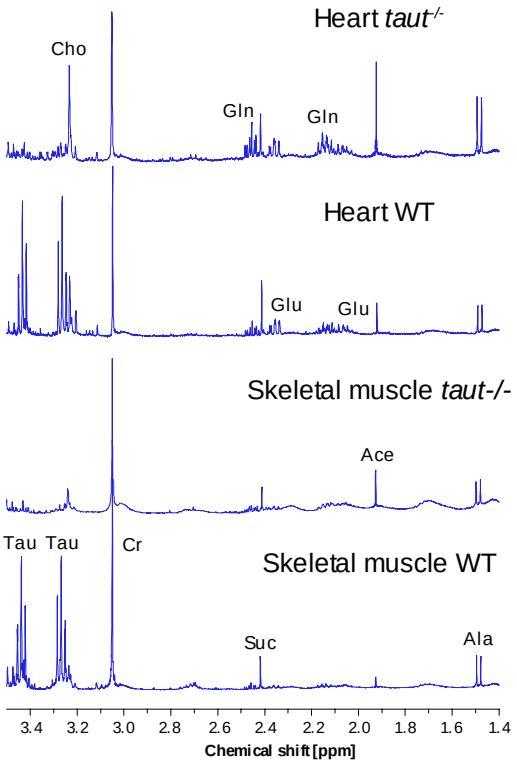

Figure 1: Sections of ^{1}H NMR spectra obtained from perchloric acid extracts of *taut*-/- and wild-type (WT) hearts and skeletal muscles, respectively. Abbreviations: Ace, acetate; Ala, Alanine; Cho, cholines; Cr, creatine; Gln, glutamine; Glu, glutamate; Suc, succinate; Tau, taurine.

References

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