Investigating the Role of PDH Inhibition on the Development of Hypertrophy in the Hyperthyroid Rat Heart

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Introduction: Thyroid hormones regulate many aspects of growth, development and energy metabolism, and are critical for normal cell function in multiple organs. Hyperthyroidism, caused by an elevated level of circulating thyroid hormones, leads to an increase in heart rate, contractility and cardiac output[1]. Cardiac hypertrophy is another effect of hyperthyroidism and, although the hypertrophy is initially beneficial, it can eventually lead to heart failure. Previous work has shown that hyperthyroidism is linked to an increase in fatty acid oxidation and a decrease in glucose oxidation, mediated by an inhibition of pyruvate dehydrogenase (PDH)[2]. The aim of this work was to determine whether alleviating PDH inhibition using dichloroacetate (DCA, a potent inhibitor of pyruvate dehydrogenase kinase), would affect the response of the heart to hyperthyroidism.

Methods: Hyperthyroidism was induced in male Wistar rats (~300 g, n = 12) with 7 daily injections of the thyroid hormone, triiodothyronine (T3; i.p.; 0.2 mg.kg.day). One group (n = 5) had their drinking water supplemented with DCA (0.75 g/L) after the first T3 injection. At day 0 (prior to first injection) and day 7, flux through PDH was assessed *in vivo* using hyperpolarized MRS[3]. Left ventricular (LV) mass and cardiac output were also assessed using cine MRI[4].

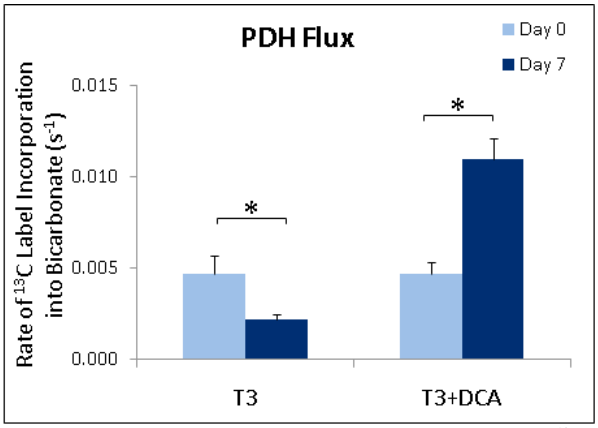
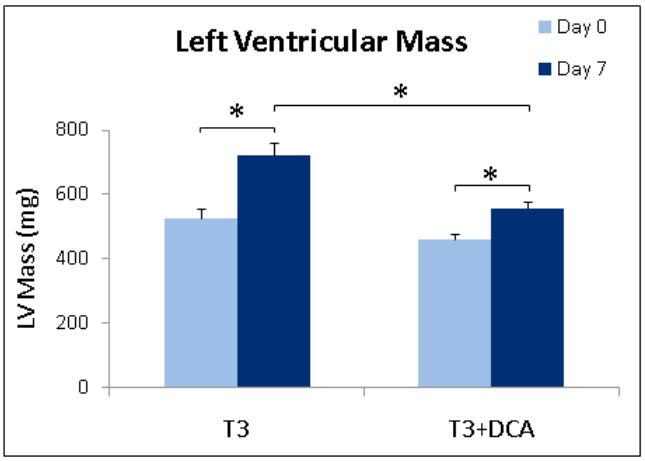


Figure 1: Alterations to PDH flux as assessed by the rate of ^{13}C label incorporation into $H^{13}CO_3^-$ from [1-^{13}C]pyruvate. *p<0.05

Results: Using hyperpolarized MRS, we found that 7 days of T3 administration reduced *in vivo* PDH flux by 52%. However, in the DCA treated animals (T3+DCA) PDH flux was increased by 134% at day 7 (Figure 1). Whilst all animals developed LV hypertrophy, cine MRI showed that DCA significantly reduced the level of hypertrophy observed (Figure 2). The increase in LV mass in the DCA treated animals (T3+DCA) was 96 mg compared to 199 mg in the untreated group (T3). The cardiac output was increased in all animals and the level of increase was unaffected by DCA treatment.



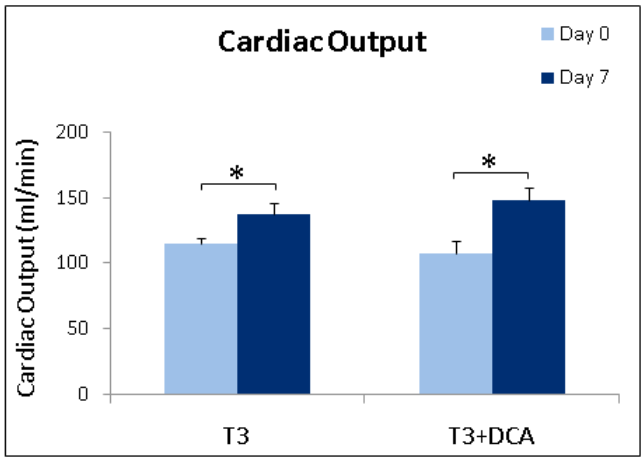


Figure 2: The level of hypertrophy induced by hyperthyroidism is reduced in DCA treated animals, despite no change in the level of increase in cardiac output, as assessed by CINE MRI. *p<0.05

Conclusions: Treatment with DCA significantly increased flux through PDH in the hyperthyroid heart, indicating a greater ability to produce energy through glucose oxidation. This increased metabolic flexibility led to a reduced level of hypertrophy in the hyperthyroid heart whilst still allowing the increase in cardiac output required to meet the high systemic metabolic demand induced by hyperthyroidism.

References: [1] Buccino et al, J. Clin. Invest. (1967) 46(10) 1669-1682 [2] Atherton *et al*, Proc. Intl. Soc. Mag. Reson. Med. 17 (2009) Abstract #52 [3] Atherton *et al,* NMR in Biomedicine (2010) 25 Aug – Epub ahead of print [4] Tyler *et al*, J. Cardiov. Mag. Reson. (2006) 8, 327-333

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