A genetic disease in humans demonstrates the importance of hypoxia-inducible factor in skeletal muscle metabolism

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Abstract

The transcription factor, hypoxia-inducible factor (HIF), regulates the expression of a number of metabolic genes. In the recessive condition of Chuvash Polycythemia (CP), the normal degradation of HIF in euoxia is slowed by functional mutation within the von Hippel–Lindau (VHL) gene. Thus the disease of CP provides an opportunity to understand the role of the HIF–VHL pathway in metabolic regulation at a systemic level. We recruited 5 CP patients and 5 controls, matched for gender, and similar for age, height and weight (CP vs control: 28±8 vs 32±12 yrs; 1.67±0.1 vs 1.74±0.1 m; 61±6 vs 72±6 kg; mean±s.d.). We measured work rate and lactate during an exercise capacity test on a cycle ergometer, and skeletal muscle magnetic resonance spectroscopy at rest and during light exercise (3, 4 & 5 Watt). Compared with controls, CP patients showed a limited exercise capacity (CP vs control: 2.4±0.9 vs 3.4±0.8 W/kg; p < 0.05), early lactate accumulation, greater phosphocreatine (PCr) deplolition (Fig. 1) and a greater fall in pH during exercise. We conclude that the VHL–HIF pathway significantly affects metabolic regulation at a systemic level.

Figure 1

![Figure 1]