PGC-1α and PGC-1β regulate creatine uptake via ERRα/CrT

E.L. Brown,[1] A. Kralli,[2] Y. Cho,[2] R.J. Snow[1] and A.P. Russell,[1] [1]Centre for Physical Activity and Nutrition research, School of Exercise and Nutrition Sciences, Deakin University, Burwood, VIC 3125, Australia and [2]Department of Chemical Physiology, The Scripps Research Institute, La Jolla, CA, USA.

Creatine plays an important role in maintaining cellular energy homeostasis by resynthesising ATP when in its phosphorylated form, phosphocreatine. Creatine uptake into the cell is controlled via the Na^+/Cl^- dependent Creatine transporter (CrT). Currently, the molecular mechanisms regulating CrT expression are unknown. Peroxisome proliferator-activated receptor γ, coactivator-1α (PGC-1α) and coactivator-1β (PGC-1β) are transcriptional coactivators that regulate the expression of many genes involved in skeletal muscle energy metabolism, including the uptake and oxidation of glucose and fatty acids (Espinoza *et al.*, 2010; Kelly *et al.*, 2009; Michael *et al.*, 2001). Whether PGC-1α or PGC-1β can regulate CrT expression and creatine uptake has not been investigated.

This study investigated the role of PGC-1α and PGC-1β in creatine uptake in L6 myotubes. Adenoviral overexpression of PGC-1α and PGC-1β increased creatine uptake by 1.8 fold and 1.6 fold respectively, compared to the GFP control. This was associated with a 2.1 fold and 1.7 fold increase in CrT mRNA levels. siRNA knockdown of the CrT in L6 myotubes significantly reduced basal levels of creatine uptake, as well as blocking the PGC-1α and PGC-1β up-regulation of creatine uptake. As many of the effects of PGC-1α and PGC-1β in skeletal muscle are mediated via their coactivation of estrogen-related receptor α (ERRα), it was of interest to determine whether ERRα was involved in this response. siRNA knockdown of ERRα prevented the PGC-1α and PGC-1β-induced increase in CrT mRNA and creatine uptake, but did not alter creatine uptake under basal conditions. Further supporting the role of ERRα in creatine uptake, expression of a constitutively active ERRα increased CrT mRNA and creatine uptake by 7 fold and 2 fold, respectively. Finally, ChIP experiments revealed that PGC-1α and ERRα directly bind to the CrT promoter to induce its expression.

These novel findings provide insight into how the CrT and creatine uptake are regulated in skeletal muscle, which may assist in the treatment of patients suffering from myopathies associated with decreased CrT and intracellular creatine levels.

Espinoza DO, Boros LG, Crunkhorn S, Gami H & Patti ME. (2010) *FASEB Journal* **24**, 1003-14.
Kelly TJ, Lerin C, Haas W, Gygi SP & Puigserver P. (2009) *Journal of Biological Chemistry* **284**, 19945-52.
Michael LF, Wu Z, Cheatham RB, Puigserver P, Adelmant G, Lehman JJ, Kelly DP & Spiegelman BM. (2001) *Proceedings of the National Academy of Sciences USA.* **98**, 3820-25.