The nuclear receptor, Nor-1, in skeletal muscle effects expression of Z-disk/sarcomeric binding proteins, and intracellular recycling

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Nuclear receptors (NRs) are ligand/agonist dependent DNA binding proteins that translate metabolic, nutritional and physiological signals into gene regulation. The NR4A subgroup of nuclear hormone receptors includes three members Nur77/NR4A1, Nurr1/NR4A2 and Nor-1/NR4A3. The expression of the mRNAs encoding the NR4A subgroup are dramatically and transiently stimulated by adrenergic activation in skeletal muscle (Pearen *et al.*, 2006 & 2008). In skeletal muscle cells, Nor-1 expression is necessary for aerobic metabolism, knockdown of Nor-1 expression leads to lactate accumulation and a switch to anaerobic metabolism. Transgenic muscle specific over-expression of activated Nor-1/NR4A3 (Tg-Nor-1) resulted in the acquisition of a fatigue resistant phenotype, oxidative type II muscle fibers, and improved glucose tolerance. The Tg-Nor-1 mice display decreased adiposity, resistance to weight gain, and normoglycemia on a high fat diet, in contrast to wild type littermates. Expression profiling identified significant increases in genes involved in glucose utilization, oxidation and storage. In addition we observe increased PGC-1α1 protein/mRNA expression, and increased expression of the genes involved in the malate-aspartate shuttle which increases oxidative ATP production. This shuttle mediates the most efficient and optimal translocation of glycolytic redox potential across the mitochondrial inner membrane for the oxphos process. Furthermore, transgenic Nor-1 expression effected the expression of many critical Z-disc and sarcomeric binding proteins (αactinin-2 and 3, STARS, MyoZ2, etc) that regulate skeletal muscle metabolic capacity, Ca^{2+}/calcineurin signalling and fatigue resistance in humans (Pearen *et al.*, 2012 & 2013). Current experiments are focused on further exploring the links between exercise, adrenergic, Ca^{2+}/calcineurin, and Nor-1 dependent signaling in the regulation of fibre type, glucose tolerance, endurance and fat deposition. Furthermore, changes in exercise performance, and glucose handling are often associated with intracellular recycling, and autophagy. qPCR and western analysis have identified the differential expression of genes/proteins involved in the autophagy process. Further experiments suggest Nor-1 signalling controls the formation of the autophagolysosome, an important organelle in intracellular reutilization and the autophagy process during changing physiological demands.

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