Gene expression profiling of skeletal muscle in exercise-trained and sedentary rats with inborn high and low VO$_{2\text{max}}$

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Bye A, Høydal MA, Catalucci D, Langaa M, Kemi OJ, Beisvag V, Koch LG, Britton SL, Ellingsen O, Wisløff U. Gene expression profiling of skeletal muscle in exercise-trained and sedentary rats with inborn high and low VO$_{2\text{max}}$. Physiol Genomics 35: 213–221, 2008. First published September 9, 2008; doi:10.1152/physiolgenomics.90282.2008.—The relationship between inborn maximal oxygen uptake (VO$_{2\text{max}}$) and skeletal muscle gene expression is unknown. Since low VO$_{2\text{max}}$ is a strong predictor of cardiovascular mortality, genes related to low VO$_{2\text{max}}$ might also be involved in cardiovascular disease. To establish the relationship between inborn VO$_{2\text{max}}$ and gene expression, we performed microarray analysis of the soleus muscle of rats artificially selected for high- and low running capacity (HCR and LCR, respectively). In LCR, a low VO$_{2\text{max}}$ was accompanied by aggregation of cardiovascular risk factors similar to the metabolic syndrome. Although sedentary HCR were able to maintain a 120% higher running speed at VO$_{2\text{max}}$ than sedentary LCR, only three transcripts were differentially expressed (FDR ≤ 0.05) between the groups. Sedentary LCR expressed high levels of a transcript with strong homology to human leucyl-transfer RNA synthetase, of whose overexpression has been associated with a mutation linked to mitochondrial dysfunction. Moreover, we studied exercise-induced alterations in soleus gene expression, since accumulating evidence indicates that long-term endurance training has beneficial effects on the metabolic syndrome. In terms of gene expression, the response to exercise training was more pronounced in HCR than LCR. HCR upregulated several genes associated with lipid metabolism and fatty acid elongation, whereas LCR upregulated only one transcript after exercise training. The results indicate only minor differences in soleus muscle gene expression between sedentary HCR and LCR. However, the inborn level of fitness seems to influence the transcriptional adaption to exercise, as more genes were upregulated after exercise training in HCR than LCR.

microarray analysis; gene ontology; metabolic syndrome; MELAS; soleus muscle

LOW MAXIMAL OXYGEN UPTAKE (VO$_{2\text{max}}$) has a strong link to cardiovascular disease (CVD) in both men and women (22, 30). Hence, the ability to utilize and deliver oxygen (O$_2$) during exercise seems to represent a point of divergence for future health (15). Identifying mechanisms underlying low VO$_{2\text{max}}$ may also identify causes of susceptibility to CVD, and suggest molecular targets for prevention and treatment.

In the last several decades, physical inactivity accompanying modern lifestyle has impaired skeletal muscle contractile and metabolic functions, contributing to the current epidemic of the metabolic syndrome. The metabolic syndrome is defined as a cluster of cardiovascular risk factors including hypertension, dyslipidemia, impaired glycemic control, and abdominal obesity (26), and serves as a more powerful predictor of premature CVD death than each separate factor alone (12).

Exercise training has beneficial effects on the metabolic syndrome through adaptations in skeletal muscle. Skeletal muscle tissue represents about half of the body mass and plays a fundamental role in whole body metabolism. Exercise-induced adaptations include e.g., increased expression of mitochondrial enzymes regulating fatty acid ß-oxidation (FAO) and increased skeletal muscle oxidative phosphorylation capacity (17, 27). The exact mechanisms by which these metabolic changes are connected to improved health, however, have not been resolved.

To study extremities in inborn VO$_{2\text{max}}$ and genetic contribution to the development of CVD, rats were artificially selected for running capacity over several generations to generate strains with genetically determined high or low VO$_{2\text{max}}$ (24). In this rat model, genes responsible for aerobic fitness are concentrated, while environmental components are minimized by maintaining a standardized environment. This makes these strains of substantial value for determining the genes causative of variation in VO$_{2\text{max}}$. Moreover, as almost all human genes known to be associated with disease have orthologs in the rat genome, the rat is a highly applicable model system for questions regarding gene expression in humans (10).

In the present study, generation 16 of the strains of high capacity runners (HCR) and low capacity runners (LCR) had an inborn 30% difference in VO$_{2\text{max}}$ (20). Interestingly, throughout the generations LCR accumulated risk factors of CVD, such as hypertension, endothelial dysfunction, insulin resistance, impaired glucose tolerance, visceral adiposity, hyperglycemia, hypertriglyceridemia, and elevated plasma free fatty acids; commonly diagnosed as the metabolic syndrome (20, 43). This makes this model of substantial value for studying the genetic background for the development of metabolic dysfunction. Gene expression profiling of the left ven-

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tricle from HCR and LCR revealed several differences that partly account for the divergence between the strains and the development of the metabolic syndrome in LCR (4), but the gene expression profiles of sedentary and exercise-trained rats from this model has not yet been determined in skeletal muscle. For that reason, we tested the hypothesis that selection for different inborn levels of VO$_{2\text{max}}$ results in differential gene expression patterns in the soleus muscle, and examined whether different levels of inborn VO$_{2\text{max}}$ affects transcriptional adaptation to exercise training.

**MATERIALS AND METHODS**

**Animals.** We used rats artificial selected for high and low VO$_{2\text{max}}$, starting from the N: NIH stock obtained from the National Institutes of Health (USA). The model is described elsewhere (24, 43). Briefly, the rats in each generation were tested for exercise capacity by treadmill running at 11 wk of age. The individuals with the highest and lowest running capacity were selected and each group served as the mating population for the next generation. Female rats from generation 16 were used in this study. The study includes four groups; exercise-trained LCR (LCR-T) (n = 4), sedentary LCR (LCR-S) (n = 4), exercise-trained HCR (HCR-T) (n = 4) and sedentary HCR (HCR-S) (n = 4). Experimental protocols were approved by the respective Institutional Animal Research Ethics Councils.

**Exercise training.** We trained the rats by an aerobic interval training program previously described (20, 41). Briefly, after 10 min of warm-up, rats ran uphill (25°) on a treadmill for 1.5 h, alternating between 8 min at an exercise intensity corresponding to 85–90% of VO$_{2\text{max}}$ and 2 min active recovery at 50–60%. Exercise was performed 5 days per week over 8 wk; controls were age-matched rats that remained sedentary. We measured VO$_{2\text{max}}$ every week to adjust speed to maintain the intended relative intensity throughout the experimental period. The VO$_{2\text{max}}$ test protocol consisted of 20 min warm-up at 50–60% of VO$_{2\text{max}}$, whereupon treadmill velocity was increased by 0.03 m/s every 2 min until VO$_2$ plateaued despite increased workload. The animals in the sedentary groups were treated similarly to the exercise groups, except they were not exposed to increased workload. The animals in the sedentary groups were treated.

**Tissue collection.** At ~7 mo of age, and 48 h after the last exercise session, all the animals were killed. One of the soleus muscles was formalin fixated for immunohistochemistry and morphological studies, whereas the other was snap-frozen in liquid nitrogen and stored at −80°C for later genetic screening and protein analysis.

**Total RNA isolation.** Tissue samples (20 mg) were homogenized in 100 μl TRIzol (Life Technologies, Gaithersburg, MD) using a Mixer Mill MM301 (Geneq, Montreal, Canada) at 20–25 Hz. RNA was further isolated and cleaned using RNeasy Mini kit (Qiagen, Germantown, MD) according to the manufacturer’s instructions. RNA integrity, purity and quantity were assessed by Bioanalyzer (Agilent Technologies, Santa Clara, CA) and Nanodrop (NanoDrop Technologies, Baltimore, MD). There were no significant differences in total RNA quantity obtained from the samples from the different groups.

**Processing of Affymetrix data.** High quality RNA classified with a RNA integrity number value >7 and 260/280 ratio >1.8 was used for the microarray experiments. We used 5 μg total RNA from each sample for cDNA synthesis and further analysis. Labeled cRNA was prepared and hybridized to the RAE 230 2.0 chip from Affymetrix GeneChip (Affymetrix, Santa Clara, CA) comprising 31,042 probe sets.

**Statistical analysis for finding differentially expressed genes.** The summary measure for each probe set was background-corrected, quantile-normalized and log-transformed by use of the robust multi-array average (RMA) method (21). For each gene (probe set), a linear regression model, including parameters representing the effect of running capacity, is specified. Tests for significant differential expression between the groups were performed using moderated t-tests (37). To account for multiple testing, we calculated adjusted p-values controlling the false discovery rate (FDR), with the use of the Benjamini-Hochberg step-up procedure (3). All statistical analyses on the gene expression data were performed using the R language (R Development Core Team, 2004) and packages affy, affyPLM, and limma from the Bioconductor project (9).

**Database submission.** The microarray data were prepared according to the “minimum information about microarray experiment” (MIAME) recommendations, and deposited in the Gene Expression Omnibus database (http://www.ncbi.nlm.nih.gov/geo/) with accession number GSE10527.

**Functional clustering according to gene ontology (GO) annotations.** To obtain information about gene/protein function, we used GeneTools (eGOn) (www.genetools.net) described previously (1). Lists of differentially expressed genes (FDR ≤ 0.05) were submitted to eGOn, which automatically associates gene ontology terms from Entrez Gene to the submitted gene reporters. The annotations used were derived from UniGenebuild 157 (November 2006) at the time of the analysis. In addition, we used the NetAffx Analysis Center to correlate the microarray results with gene and annotation information (www.affymetrix.com).

In eGOn, Fisher’s exact test assessed the relative numbers of GO annotations linked to differentially expressed genes, compared with the relative numbers of the same GO annotations linked to all the genes on the microarray. In a master-target situation the GO categories of the differentially expressed genes (target list) are compared with the distribution of GO categories for all gene reporters represented as physical probes on the microarray (master list). The purpose is to find whether, in any of the GO categories, the genes of interest are over- or underrepresented compared with the genes represented on the microarray. In addition, the differentially expressed genes were analyzed by the Ingenuity Pathway Analysis Application Tool (www.ingenuity.com) for pathway analysis.

**Western analysis.** Soleus protein levels of insulin-like growth factor 1 (IGF1) and leucyl-transfer RNA synthetase 2 (LARS2) were measured to confirm the gene expression data. Homogenized samples (n = 4 per group) were loaded onto a 4–12% or 10–20% NuPAGE Bis-Tris Gel (Invitrogen, Carlsbad, CA), separated by electrophoresis, and transferred to a PVDF membrane (Millipore, Bedford, MA). The membranes were incubated with LARS2 (Abcam, Cambridge, UK) and IGF1 (Abcam) primary antibodies. Horseradish peroxidase-conjugate secondary antibodies and enhanced chemiluminescence (ECL) (Thermo Fisher Scientific Inc, Rockford, IL) were used for protein detection with GBOX/Chemi-HR16E (Synoptics, Cambridge, UK). All protein levels were normalized to total tubulin (Novus Biologicals, Littleton, CO) and quantified using ImageJ software (NIH Image, Bethesda, MD).

**Fiber typing.** Formalin-fixed, paraffin-embedded soleus muscle sections (4 μm) were prepared by a standard immunohistochemistry

### Table 1. VO$_{2\text{max}}$ of LCR and HCR, separated in groups of sedentary controls and exercise-trained, as previously reported by Høydal et al. (20)

<table>
<thead>
<tr>
<th></th>
<th>LCR-S</th>
<th>HCR-S</th>
<th>LCR-T</th>
<th>HCR-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_{2\text{max}}$, ml·kg$^{-0.75}$·min$^{-1}$</td>
<td>39.1 ± 2.3</td>
<td>50.6 ± 4.2</td>
<td>38.8 ± 2.2</td>
<td>50.9 ± 3.9</td>
</tr>
<tr>
<td>P-Values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO$_{2\text{max}}$, ml·kg$^{-0.75}$·min$^{-1}$ End-point values</td>
<td>38.0 ± 2.3</td>
<td>49.6 ± 3.4</td>
<td>57.0 ± 4.6</td>
<td>70.4 ± 4.1</td>
</tr>
</tbody>
</table>

*LCR-S and HCR-S differed significantly (P < 0.01), †LCR-T had significantly improved function compared with LCR-S (P < 0.01), ‡HCR-T had improved function compared with HCR-S (P < 0.01). VO$_{2\text{max}}$, maximal oxygen uptake; LCR-S, sedentary low capacity runners; HCR-S, sedentary high capacity runners; LCR-T, exercise-trained low capacity runners; HCR-T, exercise-trained high capacity runners.
LCR-S had 17% higher O2 cost of running compared with LCR (Fig. 1). Consistent with a low tolerance for exercise, training significantly increased running speed in both HCR and exercise-trained animals compared (Fig. 1). The exercise ners; HCR-T, exercise-trained high capacity runners.

HCR-S at generation 11 reported that the adaptation to exercise in the soleus muscle of obesity, hypertensive, and had vascular and cardiac dysfunction they were insulin-resistant, hyperglycemic, hyperlipidemic, reported that LCR were born with a predisposition for CVD, as baseline levels between groups we applied the Mann-Whitney test in SPSS v. 14.0. Data are presented as means ± SD, and only P < 0.05 was considered statistically significant.

RESULTS

Physiological data. Previous studies of this animal model protocol. Anti-fast skeletal myosin (Abcam) were used to detect the relative number of fast twitch fibers in the soleus muscle of all groups (n = 4 per group). Results were visualized by Envision + TM detection system (DakoCytomation, Glostrup, Denmark). The degree of positive-staining was determined by semi-quantitative microscopy.

Statistics for protein levels. To analyze differences in running speed between all groups and after the exercise intervention we applied one-way analysis of variance, with Scheffé’s post hoc test. To analyze statistical differences in fiber type distribution and in protein levels between groups we applied the Mann-Whitney test in SPSS v. 14.0. Data are presented as means ± SD, and only P < 0.05 was considered statistically significant.

Fig. 1. Running speed (m/s) at maximal oxygen uptake (VO2max) before and after the exercise period; LCR-S, sedentary low capacity runners; HCR-S, sedentary high capacity runners; LCR-T, exercise-trained low capacity runners; HCR-T, exercise-trained high capacity runners.

Fig. 2. Staining of myosin fast fibers in soleus muscle cross sections. An example of myosin fast staining (dark fields) of a sedentary HCR is included. LCR, low capacity runners; HCR, high capacity runners; NS, not significant.
HCR-S was also conserved at the protein level, as LCR-S expressed 65% more of the LARS2 protein than HCR-S (Fig. 4B).

**DISCUSSION**

Although there was a significant difference in physical performance between HCR-S and LCR-S, only three transcripts were differentially expressed in the soleus muscle between the groups. After exercise training, significant transcriptional changes occurred in both HCR and LCR. However, the changes were much more pronounced in HCR than LCR, indicating a substantial difference in the ability of transcriptional adaptation to exercise.

**Inborn differences in soleus muscle gene expression.** We have previously reported that LCR-S expressed low levels of several proteins required for mitochondrial biogenesis and function in the soleus muscle, compared with HCR-S (43). Yet, in the present study, only three genes were differentially expressed between HCR-S and LCR-S.

Table 3. GO categories overrepresented among the transcripts significantly upregulated after exercise in HCR

<table>
<thead>
<tr>
<th>GO Name</th>
<th>Master List</th>
<th>HCR-T &gt; HCR-S</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological process</td>
<td>8586</td>
<td>9</td>
<td>0.013</td>
</tr>
<tr>
<td>Carboxylic acid metabolism</td>
<td>498</td>
<td>3</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatty acid metabolism</td>
<td>203</td>
<td>2</td>
<td>0.018</td>
</tr>
<tr>
<td>Cellular component</td>
<td>8333</td>
<td>7</td>
<td>0.002</td>
</tr>
<tr>
<td>Peroxisome</td>
<td>85</td>
<td>2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Calculated in GeneTools (gGON) by a Master-Target test (based on Fisher’s exact test) (P < 0.05). GO, gene ontology.

One of the differentially expressed transcripts between HCR-S and LCR-S had homology with the human mitochondrial gene *Lars2*. This transcript was more abundant in LCR-S than HCR-S, and upregulation of the human homolog is regarded as a hallmark of the mitochondrial DNA A-to-G point mutation in the leucyl-transfer RNA [tRNA^Leu(UUR)] (29). The mutation generates structural and functional defects of the tRNA^Leu(UUR) that disrupts intramitochondrial protein synthesis (5). Humans suffering from this mutation are diagnosed with the disorder “Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes” (MELAS), which involves maternally inherited diabetes and mitochondrial dysfunction (23, 31). In humans, such a mutation causes impaired O2 extraction from blood, hyperglycemia, and exercise intolerance (28, 31, 34), which is in accordance with the previously reported characteristics of LCR-S (8, 11, 16, 20, 24, 43). This finding suggests that low aerobic fitness with a concomitant development of metabolic dysfunction (19, 39, 43) also may predispose for a development of a MELAS-like pathology, albeit at this stage, this observation is only preliminary and serves as a hypothesis for further studies.
The low number of genes differentially expressed between HCR-S and LCR-S in this study is in contrast to the earlier reported differences between HCR-S and LCR-S at protein level. We cannot rule out the possibility that the low number of differentially expressed genes between HCR-S and LCR-S are at least partly explained by the low number of animals included in each group.

Response to exercise training in HCR and LCR. Rats participating in the high-intensity interval program display most of the cardiorespiratory changes observed in humans, as increased VO$_{2\text{max}}$, physiological hypertrophy, improved endothelial function, and reduced resting heart rate (41, 42). Most of these changes occur within the first 4 wk of endurance training, and VO$_{2\text{max}}$ reaches a plateau after 6–8 wk (41, 42).
Expression of regulatory and metabolic genes tends to occur within few hours after exercise and often returns to baseline within 24 h (7, 32). Sample collection after 8 wk of exercise training, 48 h after the last exercise bout, means that we miss several of the differentially expressed genes. However, this was intended, since we were interested in the long-term adaptations to exercise. Even so, 58 transcripts were found upregulated by exercise in the HCR group, whereas one transcript was upregulated in the LCR group. In both HCR and LCR, exercise training upregulated a transcript similar to a subunit in complex IV. Increased expression of complex IV subunits is a common feature of exercise training and a marker of mitochondrial

<table>
<thead>
<tr>
<th>GO</th>
<th>Name</th>
<th>Master List</th>
<th>HCR-T/LCR-T</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO:0008150</td>
<td>Biological process</td>
<td>8586</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>GO:0048523</td>
<td>negative regulation of cellular process</td>
<td>936</td>
<td>11</td>
<td>0.001</td>
</tr>
<tr>
<td>GO:0009892</td>
<td>negative regulation of metabolism</td>
<td>358</td>
<td>6</td>
<td>0.003</td>
</tr>
<tr>
<td>GO:0043170</td>
<td>macromolecule metabolism</td>
<td>2674</td>
<td>19</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Calculated in GeneTools (eGOn) by a Master-Target test (based on Fisher’s exact test) \((P < 0.05)\). The table only shows categories with more than one associated transcript.

Fig. 3. Heat map of the most significant transcripts. Transcripts with a high expression are shown in red and transcripts with a low expression are shown in yellow.
content and biogenesis (2, 33). From the physiological data, it appears that the endurance training led to a “normalization” of the LCR phenotype to the baseline of the HCR in terms of VO$_{2\text{max}}$ and running speed. However, as only one skeletal muscle transcript was differentially expressed after exercise training in LCR, the improvements in VO$_{2\text{max}}$ and running speed are likely to involve changes in other organ systems, e.g., the heart (4).

In HCR, adaptation to exercise involved increased expression of genes involved in lipid/fatty acid metabolism (e.g., Crot, Auh) and fatty acid elongation in the mitochondria (e.g., Pecr). Moreover, the peroxisomes seemed to be of particular importance for the adaptations to exercise in the soleus muscle of HCR. Previously, peroxisomes have largely been overlooked with respect to maintaining a healthy cellular lipid environment in the cells, although they are ubiquitously expressed and have a wide range of cellular functions, including a primary role in FAO (40). Since very long chained fatty acids exclusively can be oxidized by the peroxisomes, increased peroxisomal activity might be important for enhanced FAO and energy production in exercise-trained muscle. In this study, exercise training triggered expression of the peroxisomal gene Crot in HCR, which may indicate accelerated FAO by increased transfer of chain-shortened fatty acids from the peroxisomes to the mitochondria (38). Furthermore, increased expression of the FAO enzyme Auh suggested increased energy production in the mitochondria. In line with the indications from our data, previous studies have shown that exercise trained muscles oxidize more fatty acids (18, 35). Consequently, glycogen stores are spared, hypoglycemia-induced fatigue is delayed, and exercise capacity is increased (18, 35). Mechanisms responsible for enhanced FAO in exercise-trained muscle are not completely elucidated; however, increased expression of Crot and Auh might be important mediators.

Surprisingly, the Myh4 transcript was 34 times upregulated after exercise training in the HCR group. Upregulation of this fast-twitch myosin heavy chain might shift the fiber type in HCR-T toward more fast fibers. However, it may also reflect a repair of damaged fast fibers after exercise training or a switch between different forms of fast fibers. When performing fiber-typing of formalin-fixed soleus muscles, we found no signs of an increased number of fast fibers in HCR-T, but rather a trend toward fewer fast fibers in HCR-T ($P = 0.07$). In line with our results from the fiber typing, stimuli like endurance training most often result in a shift from fast to slow fibers. The reason for the Myh4 mRNA upregulation in HCR-T remains therefore uncertain.

Exercise training was accompanied by increased expression of ATPase, Ca$^{2+}$ transporting, membrane 3 (Atp2b3) in HCR soleus muscle, which encodes one of four mammalian proteins constituting the plasma membrane Ca$^{2+}$ ATPases that mediates the extrusion of intracellular Ca$^{2+}$. These pumps are responsible for the resetting and maintenance of resting levels of intracellular [Ca$^{2+}$] and are involved in local regulation of Ca$^{2+}$ signaling. Increased expression of Atp2b3 may indicate increased abundance of plasma membrane Ca$^{2+}$ ATPases after exercise training in the HCR group and should be further studied. To our knowledge, increased expression of Atp2b3 has not previously been associated with exercise training.

Fatty acid elongation in mitochondria was significantly upregulated in the HCR group and was mediated by Pecr, a key enzyme in the chain elongation pathway (6). The pathway involves elongation of either palmitate or other dietary fatty acids to give rise to longer fatty acids. Fatty acid elongation is important to store energy and to synthesize lipids important for cellular functions, as for instance membrane components.

Regarding different responses to exercise training in terms of gene expression between HCR and LCR, we cannot rule out the possibility that biological noise such as activity levels in the cages may contribute.

**Differences between soleus muscle of HCR and LCR after the exercise intervention.** Eight weeks of exercise training produced differences between the strains for regulation of metabolism, particularly in macromolecular metabolism. Igf1 was significantly more expressed in LCR-T than HCR-T. Igf1 plays a major role in exercise-induced skeletal muscle hypertrophy and strength improvements. Igf1 is highly inducible with exercise, and the level often keeps increasing for 2 days after just a single bout of exercise (13). At first, a higher exercise-induced increase in Igf1 mRNA in the LCR group
compared with the HCR group was not easily explained. However, when performing Western blot, we found twice as much IGF1 in the HCR-S compared with the LCR-S. That is, the LCR had a considerably lower basis of IGF1 before the exercise intervention. Reduced levels of IGF1 are also reported in animals and humans with HF (14, 36). Skeletal muscle IGF1 level correlates with muscle cross-sectional area, and low levels of IGF1 may contribute to the development of muscular dysfunction and muscle atrophy (14). The low level of IGF1 in LCR-S might be explained by a potential growth hormone (GH) deficiency, and is probably a contributing factor to impaired exercise capacity. The ability of exercise to increase IGF1, by means of increased work overload and passive stretch, does however seem to be maintained in LCR. The reason why exercise training had no impact on the IGF1 levels in the HCR group remains unknown.

Interestingly, the negative regulator of growth, Adamts1 (A disintegrin and metalloproteinase with thrombospondin motifs 1) was more expressed in LCR-T than HCR-T. Upregulation of Adamts1 is associated with muscle weakness, muscle wasting, and various inflammatory processes (25). High expression of Adamts1 in LCR-T suggests an ongoing inflammatory process in the soleus and impaired muscle growth, compared with HCR-T.

Increased fibrinolytic potential is a well-known beneficial effect of long-term endurance training (44). Fgll2, a recently discovered prothrombinase, was less expressed in the soleus muscle of HCR-T compared with LCR-T (45). Due to superior fitness in HCR-T, it seems likely that HCR-T has a superior antithrombotic status. To our knowledge, regulation of Fgll2 in skeletal muscle has not previously been associated with exercise training.

Conclusion

Gene expression profiling of rats with inborn high or low VO2max indicated only minor differences in soleus muscle gene expression at a sedentary state. This implies that the stimulus for gene expression is about the same for the extremities in VO2max as long as the animals remain sedentary. However, the inborn level of fitness seems to affect the transcriptional adaption to exercise, as more genes were upregulated in the HCR group than in the LCR group after similar exercise programs. HCR seem to adapt well to exercise training, as more genes were upregulated in the inborn level of fitness seems to affect the transcriptional VO2max as long as the animals remain sedentary. However, the expression at a sedentary state. This implies that the stimulus in response to exercise training in humans. Eflügers Arch 443: 61–66, 2001.

ACKNOWLEDGMENTS

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GRANTS

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