Health Innovations Research Institute
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Metabolism, Exercise and Disease (MED)

Skeletal muscle in health and disease

John A. Hawley, Ph.D.
Exercise Metabolism Group
School of Medical Sciences
<table>
<thead>
<tr>
<th>Healthy, non-diseased populations</th>
<th>Populations with lifestyle-related disease states</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise training interventions</td>
<td>Nutritional and pharmacological interventions</td>
</tr>
</tbody>
</table>
Skeletal muscle: The locus of control for whole-body metabolic health

- Deterioration of muscle quality & quantity
  - ↓ Protein synthesis
  - ↓ Fat accumulation
  - ↓ Basal metabolic rate
  - ↑ Insulin resistance

- ↑ Lifestyle-related Chronic diseases
- ↓ Functional capacity

- Inappropriate level of physical activity
Chronic metabolic diseases: The product of gene-environment interactions
An increase in physical inactivity parallels the rise in modern chronic disease states.
The best research model to study inactivity-related diseases are humans!
Risk factors for cardiovascular disease emerge after natural selection for low intrinsic running capacity

Research models to study ‘metabolic inflexibility’ and inactivity-related diseases must have translational value
Risk factors for cardiovascular disease emerge after natural selection for low intrinsic running capacity

Table 1. LCR and HCR rats differed significantly for carbohydrate and lipid metabolic measures. Measurements were taken from male LCR (n = 8) and HCR (n = 8) rats. Blood was drawn at 0900 hours with food and water ad libitum to measure random blood sugar. Other metabolic measures were made on blood drawn after 12 hours of food and water deprivation.

<table>
<thead>
<tr>
<th>Measure</th>
<th>LCR</th>
<th>HCR</th>
<th>% Difference LCR vs. HCR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random glucose (mg/dl)</td>
<td>86 ± 6</td>
<td>75 ± 12</td>
<td>15%</td>
<td>0.036</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>110 ± 9</td>
<td>92 ± 5</td>
<td>20%</td>
<td>0.0007</td>
</tr>
<tr>
<td>Insulin (pM)</td>
<td>684 ± 195</td>
<td>296 ± 172</td>
<td>131%</td>
<td>0.002</td>
</tr>
<tr>
<td>C-peptide (pM)</td>
<td>1590 ± 338</td>
<td>1077 ± 565</td>
<td>46%</td>
<td>0.061</td>
</tr>
<tr>
<td>C-peptide/insulin</td>
<td>2.4 ± 0.4</td>
<td>3.8 ± 1.2</td>
<td>-58%</td>
<td>0.013</td>
</tr>
<tr>
<td>Visceral adiposity/body weight (%)</td>
<td>1.55 ± 0.39</td>
<td>0.95 ± 0.32</td>
<td>63%</td>
<td>0.005</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>67 ± 24</td>
<td>25 ± 4</td>
<td>168%</td>
<td>0.013</td>
</tr>
<tr>
<td>Free fatty acids (meq/l)</td>
<td>0.64 ± 0.22</td>
<td>0.33 ± 0.04</td>
<td>94%</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Two-way artificial selection for intrinsic fitness is an appropriate model to study metabolic diseases

1. Direct selection for disease states is unfeasible approach because such selection is based on symptoms and not on mechanisms

2. Chemical and physical interventions inevitably fail to consider the life-long interactions between numerous genetic and environmental factors

3. Single or multiple gene knockout approaches are insufficient because complex diseases result from expression of combinations of allelic variations sensitive to a given environment

4. Gene knockout approaches only reveal the essentiality of a gene and biological reorganisation subsequent to its loss

5. Mutagenic approaches are random and provide indirect information as to the identity of the allelic variants or gene combinations that comprise a given disease
Metabolic inflexibility:
The manifestation of an ‘exercise-deficient’ phenotype
‘Metabolic inflexibility’ of skeletal muscle oxidative fuel selection in chronic metabolic disease states

Hind-limb perfusion technique to assess for oxidative fuel selection in skeletal muscle

3-O-methyl glucose transport
$^{14}$C-Palmitate uptake and oxidation rates
‘Metabolic inflexibility’ in skeletal muscle of rats selectively bred for low intrinsic running capacity

A true mitochondrial ‘dysfunction’ implies an inherent abnormality within the mitochondrial machinery rather than a decline in mitochondrial number or density. One question that remains to be answered is ‘Do individuals with type 2 diabetes have a genetic predisposition to low muscle oxidative capacity, or does impaired mitochondrial capacity arise from environmental and/or lifestyle related factors?’

Low intrinsic running capacity is associated with lower mitochondrial content in ‘white’ muscle

What are the potential mechanisms conferring metabolic health in rats with high intrinsic aerobic capacity?
Nuclear hormone receptor signalling: Useful therapeutic target for metabolic diseases?

Nur77 and target proteins are down-regulated in muscle from rats with low intrinsic running capacity.

Exercise training completely reverses impaired metabolism induced by artificial selection for low running capacity.

Where to from here?

The Future

NEXT EXIT
FNDC5 (Irisin): The circulating exercise factor?

Increase in PGC-1α and FNDC5 in white skeletal muscle from animals with high-intrinsic running capacity

Fig. 6

Stephensen EJ et al. (In review)
Primary myotubes from LCR and HCR rats for ‘gain of function’ and ‘loss of function’ studies