Acute hypoxia reduces plasma myostatin independent of hypoxic dose


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Acute hypoxia reduces plasma myostatin independent of hypoxic dose
Bradley T. Elliott¹, Tatum S. Simonson², Stephen J. Getting¹, Derek Renshaw¹, Peter D Wagner³, & Richard W.A. Mackenzie⁴
1. Faculty of Science & Technology, University of Westminster. 2. Division of Physiology, University of California San Diego & 3. Centre of Applied Biological & Exercise Sciences, Coventry University & 4. Department of Life Sciences, University of Roehampton.

Introduction
Muscle is the largest tissue in the human body and the size and mass of muscle is significantly regulated by the protein myostatin. Chronic hypoxemia in vivo induces muscle atrophy in both healthy mountain dwellers and patients with COPD (figure 1). However, both COPD patients and mountain dwellers are difficult models to study due to several confounding factors. Chronic hypoxia in mice and COPD patients co-presents with elevated myostatin, suggestive of a causative role. We previously showed that acute hypoxia (12 % O₂) induced a decrease expression of myostatin in both muscle and plasma of otherwise healthy individuals (n=8). We therefore aimed to determine the effect of hypoxic dose, hypothesizing that increasing hypoxic dose would result in further reductions in myostatin concentration.

Methods
Healthy males (N = 9, 27.5 [8.1] years of age) visited the laboratory twice, in a fasted state. Participants gave a venous plasma sample, were placed in a normobaric hypoxic chamber (10.7 or 12.3 % O₂, blinded, random order) for 2 hours, with a second plasma sample taken following hypoxia, and a 3rd sample 2 hours following hypoxic exposure (figure 2). During recruitment, one Sherpa participant, native to the Tibetan Plateau (4,500 altitude), was identified. This individual is herein characterized separately.

Results
Table 1: Subject characteristics (N = 9). Expressed as mean [SD].

<table>
<thead>
<tr>
<th>Lowlander (n = 8)</th>
<th>Sherpa (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.5 (8.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.6 (7.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.9 (12.9)</td>
</tr>
<tr>
<td>BMI (kg.m⁻²)</td>
<td>22.3 (8.7)</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>130.8 / 75.1</td>
</tr>
<tr>
<td>Resting SpO₂ (%)</td>
<td>98.8 (1.0)</td>
</tr>
</tbody>
</table>

Besides a notably low blood pressure, the Sherpa participant characteristics were unremarkable relative to the lowlander cohort (table 1).

Plasma myostatin was unchanged between 0 and 2 hours (p = 0.338), but significantly reduced at 4 hours, relative to 0 hours (p = 0.01) and 2 hours (p < 0.01; Figure 2A). This finding is maintained if results are expressed relative to baseline (Figure 2B). No difference is noted between the Sherpa individual and the lowlander cohort.

SpO₂ was reduced during hypoxic exposure, and this reduction was greater in the 10.7 % condition compared with the 12.3 % condition (Figure 3). The Sherpa individual did not desaturate at 12.3 % O₂, but showed the lowest measured SpO₂ at 10.7 % O₂.

Discussion
Here we show a decreased concentration of plasma myostatin following acute hypoxic exposure in healthy young male participants. This work aligns with our previous findings, reduced plasma myostatin after 10 hours of hypoxia (12 %) and extends this, suggesting dose of hypoxia (within the range measured here), does not alter the myostatin response. Further, differences in the SpO₂ desaturation response are not reflected in the changes in plasma myostatin.

What physiological meaning can be ascribed this reduction in myostatin concentration in plasma? Myostatin acts in an endocrine manner, systemic concentration correlates with muscle mass across cachexic and healthy individuals. However, myostatin activity is extracellular, binding myofibers surface receptors to induce an atrophic signalling cascade. Thus, it is tempting to speculate decreases in plasma myostatin may represent a shift towards extracellular space; this needs to be confirmed by microdialysis studies in small animal or human models. Alternatively, myostatin in plasma may be degraded or sequestered in an as yet undescribed manner, as a protective response against an acute catabolic insult.

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References

Figure 2: Absolute myostatin concentration (µg.mL⁻¹) as a function of time (hours). B) relative myostatin concentration (% of 0 hours) as a function of time (hours). Black indicates lowlander population (n = 8), red indicates Sherpa (n = 1). * indicates differences between groups as marked, y indicates difference from baseline (n = 0 hours).

Figure 3: SpO₂ as a function of time. Black indicates lowlander population (n = 8), red indicates Sherpa (n = 1). * indicates difference between lowlander groups. Error bars represent se.

Figure 4: Proposed model of myostatin movement in response to hypoxic stimulus.