Acute endotoxaemia does not impair voluntary or electrically stimulated human quadriceps femoris contractions.

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Respiratory failure is a serious feature of sepsis, and animal studies suggest this is due to skeletal muscle dysfunction (e.g. Hussain et al., 1985). The effects of sepsis on human muscle contractility are unclear, and patient studies are likely to be confounded by malnutrition and therapeutic neuromuscular blockade. This Local Research Ethics Committee-approved study used an in vivo sepsis model to assess the effects of this, and the resulting systemic inflammatory response, on quadriceps contractile function. Eight healthy males, mean (SD) age 32.0 (4.4) yr were examined twice, in random order and 2 weeks apart. On one occasion they received 4 ng/kg i.v E.coli lipopolysaccharide (LPS), and on the other the same volume of i.v sterile normal saline. Pulse rate, rectal temperature and oxygen consumption (VO₂), and arterialized venous plasma concentrations of cortisol, growth hormone (GH), IL-6 and TNF-α were monitored/measured hourly for one hour before and 6 hours following i.v LPS/saline. Also assessed hourly were isometric quadriceps contractile properties: maximum voluntary contractile force (MVC), and 10:50 and 20:50 Hz force ratios and maximum relaxation rate (MRR) determined from computer-controlled electrically stimulated contractions (6s trains comprising 10, 20 and 50Hz, arranged contiguously). Statistical comparisons used repeated measures ANOVA and, where applicable, the experiments described here conform with Physiological Society ethical requirements.

Muscle stiffness transiently exceeds its steady-state value following a rapid shortening/re-stretch protocol

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When contracting muscle fibres are allowed to shorten and then rapidly re-stretched, tension often transiently exceeds the steady-state isometric level during the recovery process. The effect is particularly prominent in permeabilized muscle fibres at sub-maximal levels of Ca²⁺ activation. We have used stiffness measurements to investigate whether this transient overshoot may reflect a temporary increase in the number of attached cross-bridges. Bundles of soleus fibres were isolated from a rat (anaesthetized by inhalation of 3-4% isofluorane and subsequently killed by a pneumothorax) and skinned using 1% Triton X-100. Individual fibres (n=7, initial sarcomere length 2.55 ± 0.04 μm) were connected between a motor (Aurora 312B, step-time ~0.5 ms) and a force transducer (AE801, resonant frequency 2.5 kHz). Fibres were activated in solutions with pCa (= -log10[Ca²⁺]) values in the range 9.0 to 4.5. Once tension had stabilized in each solution, ten trials, each of the form shown schematically in Fig 1A were imposed at regular 18 s intervals. The fibre was subjected to two 1% length changes during each trial. A large shortening/re-stretch perturbation (20% muscle length, 20 ms duration) was applied 60 ms after the first length change. The time interval τ (Fig 1A) was adjusted between pre-set values in a pseudo-random manner in successive trials. The muscle was returned to its initial length at the end of each 8 s recording. Experiments were performed using SLControl software (Campbell & Moss, 2003). The P2/P1 ratio (Fig 1A) is a measure of the muscle’s relative stiffness. Fig 1B shows this ratio plotted as a function of the time interval τ at a sub-maximal level of Ca²⁺ activation. A double exponential function (which transiently exceeds unity) fits the experimental data significantly better (F-test, p<0.001) than a single exponential function (which approaches unity asymptotically). This result suggests that the number of attached cross-bridges temporarily exceeds the steady-state value following release and re-stretch of the muscle. Possible mechanisms include transient cooperative recruitment of new force-generating cross-bridges or a combination of new cross-bridge attachments at the longer lengths and slower detachment of cross-bridges strained by the stretch.

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Effects of N-benzyl-p-toluene sulphonamide (BTS) on tension responses in intact mammalian skeletal muscle.

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The present study examined stretch-induced tension responses in muscle when its active tension was significantly reduced using N-benzyl-p-toluene sulphonamide (BTS), a compound known to inhibit myosin-II ATPase without affecting calcium release (Cheung, et al., 2002). Adult male rats were humanely killed with an intra-peritoneal injection (>200 mg kg⁻¹) of an overdose of sodium pentobarbitone (Euthatal). Bundles of ~5 intact (fast) fibres (fibre length, L₀, ~2 mm) were isolated from the flexor hallucis brevis muscle of the rat and mounted horizontally between a force transducer and a servomotor (initial sarcomere length = 2.5 μm; 20 °C). Fibre bundles were tetanized and a ramp stretch of 5% L₀ applied on the tension plateau. Stimulation was maintained for a further 500 ms where residual force enhancement (RFE; see Edman & Tsuchiya, 1996) was measured. Experiments (n=5) show that 10 μM BTS produced a reversible depression of tetanic tension. Mean ± S.E.M. (kN m⁻²) for peak twitch tension (P), tetanic tension before stretch (P₀), peak tension during stretch (P_k), and steady tension at the maintained stretch length (i.e. RFE) are shown in the table. Student’s paired t-tests revealed significant decreases in P, P₀, and P_k whereas RFE was not significantly different, in the presence of BTS, suggesting the involvement of non-crossbridge mechanism(s) in the tension response to stretch. To further investigate these findings, additional experiments were conducted at different initial muscle lengths. RFE was clearly seen on the ascending limb, plateau and descending limb of the length-tension relationship in both the presence and absence of BTS. To our knowledge, these are the first data to indicate the reversible suppression of active tension in intact mammalian skeletal muscle by BTS. Our findings indicate that RFE does not vary in proportion to steady active tension. Similar observations have been made in frog fibres (Bagni, et al., 2002); however, the exact mechanism of non-crossbridge contributions to the stretch-induced tension response remains unclear.

<table>
<thead>
<tr>
<th></th>
<th>P (kN m⁻²)</th>
<th>P₀ (kN m⁻²)</th>
<th>P_k (kN m⁻²)</th>
<th>RFE (kN m⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>32.3 ± 3.0</td>
<td>209 ± 23.4</td>
<td>164 ± 20.1</td>
<td>26.6 ± 4.9</td>
</tr>
<tr>
<td>10 μM BTS</td>
<td>2.9 ± 0.6</td>
<td>42.7 ± 6.5</td>
<td>111 ± 17.2</td>
<td>35.8 ± 7.3</td>
</tr>
<tr>
<td>(BTS/Control) %</td>
<td>8.9 ± 1.4 (P&lt;0.001)</td>
<td>20.9 ± 3.3 (P&lt;0.001)</td>
<td>70.2 ± 7.3 (P=0.02)</td>
<td>158 ± 34.6 (P&lt;0.005)</td>
</tr>
</tbody>
</table>


We thank The Wellcome Trust for financial support.

Where applicable, the experiments described here conform with Physiological Society ethical requirements.