"Response of autophagy and ubiquitin-proteasome pathways to ultra-endurance running"

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Abstract
AIMS: Modulation of ubiquitin-proteasome pathway (UPP), autophagy-lysosomal pathway (ALP) and mitochondrial remodelling were assessed by measuring protein markers during ultra-endurance exercise in human skeletal muscle.

METHODS: Eleven male ultra-endurance athletes ran for 24 hours on a treadmill. Biopsies were taken from the vastus lateralis muscle two hours before starting and immediately after finishing exercise.

RESULTS: The phosphorylation state of Akt (-74%), FoxO3a (-49%), mTOR Ser2448 (-32%) and 4E-BP1 (-34%) decreased significantly whereas AMPK phosphorylation state increased by 247%. Proteasome β2 subunit activity and MuRF1 protein level increased by 95% and 55%, respectively. LC3bII and the form of ATG12 conjugated to ATG5 increased by 554% and 36%, respectively. The mitochondrial fission marker phospho-DRP1 increased by 110% whereas the fusion marker Mfn1 and the mitophagy markers Parkin and PINK1 remained unchanged.

CONCLUSION: These results fit well with a coordinated...

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Référence bibliographique
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Experiments on more conventional forms of endurance exercise with controlled intensity, duration and food intake should be conducted for identifying the physiological mechanisms implicated in the modulation of autophagy markers that we observed.

Efficient protein degradation systems are needed

- Two main proteolytic pathways in skeletal muscle:
  - the ubiquitin-proteasome pathway (UPP) (Fig.1)
  - the autophagy-lysosomal pathway (ALP) (Fig.2)

Introduction

- Ultra-endurance running:
  - deficit in food and fluid intake leading to negative energy and protein balances (Pikosky et al., 2008.;)
  - cell stresses leading to accumulation of damaged and/or misfolded proteins (Sahlin et al., 2010);
  - repeated eccentric contractions damaging muscle cells (Kuipers, 1994).

Methods

- 11 trained subjects:
  - age: 42 ± 7.8 y.o.;
  - VO\(_{\text{max}}\): 53.0 ± 5.4 ml·kg\(^{-1}\)·min\(^{-1}\);
  - V\(_{\text{E}1}\): 18.4 ± 1.4 km·h\(^{-1}\).
- 24 hours running on a treadmill (24TR) (food and water intake recorded)
- Muscle biopsies: vastus lateralis, before and just after the end of exercise
- Plasma insulin: radioimmunoassay
- Protein expression and phosphorylation states: western blot
- Enzymatic activities: fluorimetry

Results

- Fig.1: The ubiquitin-proteasome pathway. Adapted from Jackman and Kandarian (2004).
- Fig.2: The autophagy-lysosomal pathway. Adapted from Cell Signalling Technology website (http://www.cellsignal.com – consulted June 1, 2012).
- Fig.3: Raced distance (A) and caloric intake (B) over time during the 24TR. Values are means ± SEM. *\(P < 0.05\); **\(P < 0.01\); ***\(P < 0.001\).
- Fig.4: ALP markers (A), CATH L relative activity (B) and mitochondrial remodelling markers (C). Values are expressed as percentage of change (mean ± SEM) in comparison to the pre-exercise condition. *\(P < 0.05\); **\(P < 0.01\); ***\(P < 0.001\).
- Fig.5: Proteasome 26S relative activities (A) and protein expression level of MAFbx, MuRF1 and UCP (B). Values are expressed as percentage of change (mean ± SEM) in comparison to the pre-exercise condition. *\(P < 0.05\).
- Fig.6: Phosphorylation state of kinases implicated in signalling pathways regulating protein balance. Values are means ± SEM. *\(P < 0.05\); **\(P < 0.01\); ***\(P < 0.001\).
- Fig.7: Time-course of plasma glucose and insulin concentration during the 24TR. Values are means ± SEM. *\(P < 0.05\).
- Fig.8: Proposed model for signalling pathways regulating protein balance in skeletal muscle in response to ultra-endurance exercise.

Conclusion

The purpose of this study was to assess the activation of protein markers for autophagy, mitophagy and mitochondrial network remodelling during ultra-endurance running exercise in humans. A second goal was to evaluate if this activation was coordinated with the UPP and to highlight the signalling pathways implicated in these regulations.

Perspectives

Experiments on more conventional forms of endurance exercise with controlled intensity, duration and food intake should be conducted for identifying the physiological mechanisms implicated in the modulation of autophagy markers that we observed.