Uncoupling protein modulates muscle energetics and body weight

BIOLOGIE & SANTÉ 2011

Project "**MetUCP3**" - **ANR-07-BLAN-0354**

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Context

Body energy consumption has always been a matter of interest. Given that skeletal muscle accounts for 50 to 60 % of the total body mass, muscle energy consumption has received a particular attention regarding muscle efficiency during exercise and possible mechanisms of energy dissipation through uncoupling processes that could play an important role in the control of body weight. The third member of the uncoupling protein family, i.e., the uncoupling protein-3 (UCP3), is a mitochondrial inner membrane protein which is highly and preferentially expressed in skeletal muscle. Based on its close sequence homology with UCP1, a protein which uncouples respiration from ATP production in brown adipose tissue thereby promoting heat production in response to cold or overfeeding, it has been suggested that UCP3 could be involved in the control of muscle energy expenditure via the oxidation of body fat.

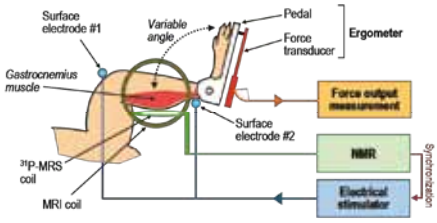
Objective and experimental approach

The aim of this integrative project was to determine the physiological role that UCP3 could play in energy production at skeletal muscle and whole body levels, using murine models.

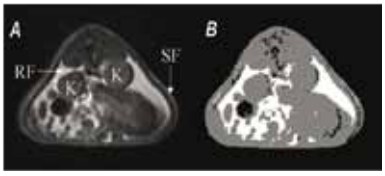
This project combined in vivo and in vitro experiments in small animals through an integrative approach investigating muscle function and energetics using muscular performance and ^{31}Phosphorus Magnetic Resonance Spectroscopy (^{31}P-MRS) measurements, whole body fat accumulation with MR imaging, UCP3 gene expression via quantitative PCR analysis, and mitochondrial electron chain transport activity on the basis of oxygraphic measurements in biopsy samples. UCP3 gene expression was modulated chemically by oral administration of capsiate, a natural compound that has been shown to decrease and increase UCP3 gene expression, in rat and mouse, respectively. Ultimately, the use of transgenic knock-out mice for UCP3 will allow us to shed additional light on the role of UCP3. It is noteworthy that this project included the development of an original and unique experimental setup allowing a complete noninvasive investigation of mechanical performance and energetics in mouse skeletal muscle using MR techniques[1].

Results

Our results indicate that both down- and up-regulation of UCP3 gene expression lead to a reduced whole body fat accumulation[2,3]. Although the underlying mechanisms are likely different, the reduction in whole body fat accumulation in response to the downregulation of UCP3 gene expression is probably caused by an acceleration of muscular energy metabolism associated to a decreased energetic efficiency[2]. On the contrary, the effect of upregulation seems rather to be due to an improvement of muscle efficiency[3].



Schematic representation of the experimental setup allowing the noninvasive investigation of mouse gastrocnemius muscle function and energetics.



Magnetic resonance image of rat abdominal region (A). Computer-processing of the image (B) using "segmentation" method allows to highlight fat accumulation regions for their quantification. *RF, retroperineal fat; SF, subcutaneous fat; K, kidney.*

Conclusion and perspectives

These data demonstrate the key role of UCP3 in the control of energy expenditure. Based on a better understanding of the regulation of energy expenditure in relation to UCP3 expression, future potential applications related to body weight control and obesity might be developed.

Publications

(1) Giannesini B et al. A strictly noninvasive MR setup dedicated to longitudinal studies of mechanical performance, bioenergetics, anatomy, and muscle recruitment in contracting mouse skeletal muscle. Magn Reson Med 2010;64:262-270.
(2) Faraut B et al. Capsiate administration results in an uncoupling protein-3 downregulation, an enhanced muscle oxidative capacity and a decreased abdominal fat content in vivo. Int J Obes (Lond) 2009;33:1348-1355.
(3) Yashiro Y et al. Capsiate supplementation promotes energy metabolism and supresses body fat accumulation in mice. In preparation.

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