*Proceedings of the Nutrition Society* (2005), **64**, 47–52 DOI:10.1079/PNS2004408


# Respiration uncoupling and metabolism in the control of energy expenditure

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Metabolic energy expenditure negatively regulates energy balance. Metabolic and catabolic pathways contribute to energy expenditure. Catabolic pathways split C-containing molecules into small molecules and generate reduced coenzymes and ATP. For a given amount of substrate, any increase in energy expenditure requires either increased ATP hydrolysis or decreased ATP synthesis. In skeletal muscles substrate utilisation is coupled to ATP production, whereas ATP hydrolysis is activated during physical exercise and increases energy expenditure. In brown adipose tissue activation of cells during exposure to cold increases substrate utilisation in such a way that glucose and fatty acid oxidation detach from the orthodox coupling to ATP synthesis and result in thermogenesis. The unique mechanism of uncoupling respiration that occurs in brown adipocyte mitochondria represents an attractive strategy for promoting energy expenditure and decreasing the fat content of the body. Moreover, ectopic expression of brown fat uncoupling protein (UCP) 1 in mouse skeletal muscle and induction of UCP1 in mouse or human white adipocytes promote fatty acid oxidation and resistance to obesity. In normal conditions UCP2 and UCP3 do not seem to contribute substantially to energy expenditure. Whether the induction of UCP1, the induction of other UCP or chemical mild uncoupling represent promising strategies for attenuating nutrient efficiency and counteracting obesity should be considered.

**Respiration uncoupling: Energy expenditure: Uncoupling protein 1: Brown adipose tissue**

## Metabolism and control of energy expenditure: a cooperation between cytoplasm and oxidative organelles leading to catabolism

Living cells comprise complex energy-producing and energy-utilising chemical reactions termed metabolism. Energy expenditure is strongly dependent on the activities of metabolic pathways. The stimulation of energy expenditure is observed either during physical exercise or during periods committed to control of body temperature such as arousal of hibernators or adaptation to cold of non-hibernators. Whether energy expenditure can be activated sufficiently in response to food intake to buffer excess energy intake remains controversial.

Energy expenditure results from catabolism of C-containing molecules and ATP hydrolysis. Catabolism involves degradation of ingested foodstuffs or stored fuels such as carbohydrate, lipid and protein. Catabolic pathways operate in the cytoplasm (glycolysis, pentose phosphate pathway), mitochondria (fatty acid oxidation, re-oxidation of reduced coenzymes), lysosomes (oligosaccharide degradation, protein degradation) and peroxysomes (degradation of fatty acids). The catabolic pathways split C-containing molecules such as glucose and fatty acids or amino acids into small molecules such as pyruvate, acetyl-CoA precursors and intermediary substrates of the tricarboxylic acid cycle, and generate reduced coenzymes (NADH, $FADH_2$). Concomitantly, catabolic reactions promote ADP phosphorylation and ATP synthesis, since the reactions in metabolic pathways contributing to energy expenditure are exergonic reactions coupled to endergonic reactions. However, such reactions are clearly catabolic, as the coupling of exergonic and endergonic reactions is far below 100% and most synthesised ATP molecules are hydrolysed.

## Contribution of mitochondria to energy expenditure

Although mitochondria are involved in urea synthesis, gluconeogenesis, Ca homeostasis, radical production, protein

**Abbreviation:** UCP, uncoupling protein.

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synthesis and apoptosis, their major function is cellular respiration and oxidation of reducing equivalents. These organelles contain two compartments bounded by inner and outer membranes. The outer membrane is permeable to small metabolites whereas the permeability of the inner membrane is strongly controlled. This inner membrane possesses specific transporters for ADP–ATP exchange, phosphate, pyruvate, oxoglutarate, citrate, glutamate and malate. The inner membrane maintains a high electrochemical gradient generated by the respiratory chain (see Nicholls & Ferguson, 2002).

Mitochondria participate in energy expenditure through fatty acid oxidation and oxidation of reduced NADH and $FADH_2$. In fact, the final steps of oxidation of fatty acids, carbohydrates and amino acids result in the formation of NADH and $FADH_2$. The electron transport chain oxidises these reduced cofactors by transferring electrons in a series of steps to $O_2$, which is the terminal electron acceptor. Simultaneously, the free energy of the oxidation–reduction reactions is used to drive ATP synthesis. This overall process is referred to as mitochondrial oxidative phosphorylation. The mechanism of coupling respiration to ADP phosphorylation was elucidated by Peter Mitchell (see Nicholls & Ferguson, 2002). Complexes I, II and III of the respiratory chain pump protons to the outer surface of the inner membrane during re-oxidation and electron transfer. This proton pump generates a proton gradient that is made use of by mitochondrial ATP synthase. Thus, the ability of mitochondria to phosphorylate ADP to ATP limits the rate of respiration. Under such conditions a large proportion of oxidation energy is converted to ATP. However, the coupling of respiration to ATP synthesis is not 100% efficient and some of the energy is dissipated as heat. The partial coupling of respiration to ATP synthesis prevents the inhibition of respiration by exaggerated levels of ATP.

## Respiration uncoupling and energy expenditure: the example of the mitochondrial uncoupling protein 1 of brown adipose tissue

Mitchell's theory predicted that any proton leak in the inner membrane not coupled with ATP synthesis would provoke the uncoupling of respiration and thermogenesis (see Nicholls & Ferguson, 2002). Interestingly, this prediction has been validated by David Nicholls and by other researchers studying the thermogenic machinery of brown adipose tissue (Nicholls & Locke, 1984; Ricquier & Bouillaud, 2000; Cannon & Nedergaard, 2004).

The brown adipose tissue is a particular form of adipose tissue found in infants at birth, rodents, small mammals and hibernators (Nicholls & Locke, 1984; Kozak & Harper, 2000; Ricquier & Kozak, 2003; Cannon & Nedergaard, 2004). In fact, the thermogenic activity of this organ has been observed at birth, during exposure to the cold or during arousal from hibernation. Brown adipocytes differ from white adipocytes by the presence of numerous mitochondria. These mitochondria exhibit a spontaneous uncoupling of respiration. Consequently, approximately 100% of the fatty acid oxidation is dissipated as heat instead, contributing to ATP synthesis. When brown adipocytes are activated, NEFA produced by the lipolysis of triacylglycerols activate a unique system of proton conductance present in the inner mitochondrial membrane. This system has been characterised as a specific membrane transporter termed uncoupling protein (UCP) and recently renamed UCP1. UCP1 belongs to the family of mitochondrial anion transporters that includes the adenine nucleotide translocator, the phosphate carrier, the citrate carrier, the oxoglutarate carrier and the acylcarnitine transporter (Kozak & Harper, 2000; Ricquier & Bouillaud, 2000; Ricquier & Kozak, 2003).

The respiration-uncoupling activity and the thermogenic activity of UCP1 have been clearly demonstrated using different experimental approaches such as transport reconstitution in liposomes and inhibition or activation of its expression in cells or transgenic mice. UCP1 functions as a futile cycle, similarly to a shunt bypassing ATP synthase and making use of the electrochemical gradient. When UCP1 is functional, the utilisation of the proton gradient decreases the mitochondrial membrane potential, which in turn facilitates extrusion of protons and stimulates respiration (Nicholls & Locke, 1984; Garlid & Jaburek, 1998). Thermogenesis is associated with mitochondria and also results from a general activation of catabolic pathways in activated brown adipocytes.

## The mitochondrial uncoupling proteins 2 and 3

The mitochondrial membrane transporters form a family comprising forty proteins. Recent studies have led to the identification of several proteins more similar to UCP1 than to other mitochondrial transporters and referred to as UCP2 and UCP3 (Kozak & Harper, 2000; Ricquier & Bouillaud, 2000; Boss *et al*. 2001; Ricquier & Kozak, 2003). UCP2 and UCP3 are adjacent on human chromosome 11 and mouse chromosome 7 and may represent ancestral forms of UCP1. UCP2 and UCP3 share 58% of their amino acid identity with UCP1 but differ markedly from the brown fat UCP as they have a different tissue distribution and physiological regulation. UCP1 is unique to brown adipocytes, UCP2 is expressed in numerous tissues, whereas UCP3 is predominantly expressed in skeletal muscles. It is also interesting that the expression of UCP2 or UCP3 is not induced during exposure to cold, in contrast to UCP1 expression. Another major difference between the three UCP is that UCP2 and UCP3 are normally expressed at a level that is 200-fold lower than that of UCP1 in brown adipocytes.

Despite many biochemical, genetic and physiological studies the exact functions of UCP2 and UCP3 remain unclear. Insertion of UCP2 or UCP3 in liposomes or their expression in cellular systems has led to conflicting data in relation to their proton-translocating activity and their respiration-uncoupling activity (Garlid & Jaburek, 1998; Clapham *et al*. 2000; Garcia-Martinez *et al*. 2001; Klingenberg & Echtay, 2001; Ledesma *et al*. 2002). Clapham *et al*. (2000) have reported that overexpression of UCP3 in skeletal muscle strongly decreases food efficiency in relation to the uncoupling of respiration. However, the same authors have also concluded that the uncoupling of respiration in these mice is artifactual (Cadenas *et al*. 2002). Analogous to the proposed role for UCP1, it has

https://doi.org/10.1079/PNS2004408 Published online by Cambridge University Press

been suggested that the function of UCP3 could be to export excess fatty acids out of mitochondria in a situation of elevated mitochondrial fatty acid oxidation (Kozak & Harper, 2000). It has also been proposed that UCP2 and UCP3 translocate either superoxide (Echtay *et al*. 2002) or fatty acid peroxides (Goglia & Skulachev, 2003). UCP1 activity is strongly regulated by GDP (inhibition) and NEFA (activation). There is no consensus about the regulation of UCP2 and UCP3 by these ligands (Nègre-Salvayre *et al*. 1997; Garlid & Jaburek, 1998; Couplan *et al*. 2002*b*; Krauss *et al*. 2002; Echtay *et al*. 2003). Echtay *et al*. (2002) and Krauss *et al*. (2002) have reported that superoxide is able to activate UCP1, UCP2 and UCP3. It has also been reported that ubiquinone contributes to the activation of the UCP (Klingenberg & Echtay, 2001).

Studies of UCP2 or UCP3 variants have provided evidence both in support and against their contribution to diet-induced expenditure, body fat content, obesity or type 2 diabetes. Genetic studies have also suggested a role for the UCP2–UCP3 locus in resting metabolic rate (Bouchard *et al*. 1997) and anorexia nervosa (Hu *et al*. 2002).

Most physiological studies have not enhanced the understanding of the roles of UCP2 and UCP3. These UCP do not contribute to the control of body temperature in response to the cold, and a study of Ucp2-/- and Ucp3-/- mice receiving a high-fat diet has demonstrated that they do not contribute to diet-induced energy expenditure (Ricquier & Kozak, 2003). Transgenic mice overexpressing a high and pharmacological level of UCP3 in their skeletal muscles are resistant to an obesity-inducing high-fat diet (Clapham *et al*. 2000). The metabolic roles of UCP2 and UCP3 are unclear, although nutritional and hormonal changes (starvation, high-fat diet, thyroid hormone status) have been shown to markedly alter UCP2 and UCP3 expression (Diehl & Hoek, 1999; de Lange *et al*. 2001; Lanouette *et al*. 2001; Collins *et al*. 2002; Hesselink *et al*. 2003). It has been proposed that these transporters are involved in fatty acid metabolism and in metabolic adaptation linked to the transition from glucose oxidation to fatty acid oxidation (Dulloo & Samec, 2001).

More specifically, UCP2 and UCP3 down regulate the mitochondrial production of reactive oxygen species (Ricquier & Bouillaud, 2000) and UCP2 is a negative regulator of insulin secretion in response to glucose (Boss *et al*. 2001; Chan *et al*. 2004). Interestingly, these findings, derived from mice made null for *ucp2* or *ucp3*, provide some support for respiration-uncoupling activity of UCP2 and UCP3. Based on the role of UCP2 in the limitation of reactive oxygen species and the relatively high level of UCP2 in macrophages it has been demonstrated that UCP2 protects against atherosclerosis (Alves-Guerra *et al*. 2003; Blanc *et al*. 2003). The importance of UCP2 in macrophages and in protection against atherosclerosis has been confirmed by Ryu *et al*. (2004). These authors have demonstrated that overexpression of UCP2 in monocytes inhibits trans-endothelial migration and adhesion to endothelial cells. A role for UCP2 in protection against chronic inflammatory diseases has been suggested (Pecqueur *et al*. 2001). Whether UCP2 directly affects levels of reactive oxygen species, or regulates glutathione, which in turn affects the levels of reactive oxygen species, has been the subject of discussion (de Bilbao *et al*. 2004). More recently, several studies (Bechmann *et al*. 2002; Clavel *et al*. 2003; Mattiasson *et al*. 2003; Paradis *et al*. 2003; Sullivan *et al*. 2003) have indicated a role for UCP2 in neuroprotection, while Ibrahim *et al*. (2000) have suggested that UCP2 contributes to autoimmune encephalomyelitis. It has also been reported that mice deficient in UCP3 are protected from hyperthermia induced by the drug N-methyl-D-aspartate (Mills *et al*. 2003). Other proposed roles for UCP2 are: activation of NO production (Kizaki *et al*. 2002); regulation of apoptosis (Voehringer *et al*. 2000; Teshima *et al*. 2003); activation of oncosis (Mills *et al*. 2002). Table 1 summarises the demonstrated and proposed roles of the UCP.

## Can induction or activation of uncoupling proteins stimulate fatty acid oxidation and promote energy expenditure?

The chemical uncoupler of respiration, 2–4-dinitrophenol, has in the past been prescribed in the treatment of obese patients. The effects of such a toxin have been dramatic and extremely negative. It has severe metabolic effects and causes hyperpyrexia and death. An interesting observation, referred to as the Luft syndrome (Luft, 1992), has been reported. A patient was found to exhibit a catabolic state characterised by hypermetabolism of non-thyroid origin and a defect in the maintenance of mitochondrial respiratory control in skeletal muscle. Although the molecular mechanism was not identified, this observation highlights the contribution of respiration uncoupling to increased energy expenditure.

Following the characterisation of the brown adipocyte UCP, the ectopic expression of this UCP has been directed either to white adipose tissue or skeletal muscle of transgenic mice (Kopecky *et al*. 1995; Kozak & Harper, 2000). As expected, these animals develop a resistance to diet-induced obesity. In particular, the expression of UCP1 in skeletal muscles induces a marked uncoupling of respiration and a stimulation of fatty acid oxidation (Li *et al*. 2000). However, UCP1 expression in skeletal muscles also modifies the ratio between the subtypes of muscular fibres and increases the proportion of type IIa oxidative fibres at the expense of glycolytic type IIb fibres (Couplan *et al*. 2002*a*). As mentioned earlier, transgenic mice overexpressing UCP3 in their skeletal muscles are also resistant to diet-induced obesity and type 2 diabetes (Clapham *et al*. 2000). However, in this study the amount of UCP3 was very large, and it seems improbable that such a level of induction can be obtained using any pharmacological approach.

More recently, Tiraby and colleagues (Tiraby & Langin, 2003; Tiraby *et al*. 2003) have reported the induction of UCP1 in differentiating cultured human white adipocytes. Instead of using an expression vector for UCP1, they tried to obtain a physiological expression of UCP1 using transfection of preadipocytes by an adenoviral expression vector encoding the co-activator PPARγ co-activator-1. A moderate induction of UCP1 and mitochondrial proteins was observed. Interestingly, such a small induction of UCP1 was shown to result in a doubling of the oxidation of

https://doi.org/10.1079/PNS2004408 Published online by Cambridge University Press

**Table 1.** Demonstrated and proposed roles for the mitochondrial uncoupling proteins (UCP) 1, 2 and 3

| | UCP1 | UCP2 | UCP3 |
|---|---|---|---|
| Biochemical role | Proton transport* | Proton transport | Proton transport |
| | Export of deprotonated fatty acids | Export of deprotonated fatty acids | Export of deprotonated fatty acids |
| | Transport of ROS | Transport of ROS | Transport of ROS |
| | | Glutathione transport | Translocation of peroxidised fatty acids |
| | | Translocation of peroxidised fatty acids | |
| Activator | NEFA* | NEFA | NEFA |
| | Retinoic acid | Retinoic acid | |
| | Superoxide | Superoxide | Superoxide |
| | Ubiquinone | Ubiquinone | Ubiquinone |
| | Hydroxynonenal | Hydroxynonenal | Hydroxynonenal |
| Inhibitor | GDP, GTP, ADP, ATP* | GDP, ATP | GDP, ATP |
| Physiological role | Cold-induced thermogenesis* | Resting metabolic rate | Resting metabolic rate |
| | Diet-induced thermogenesis | Adaptation to increased fatty acid oxidation | Adaptation to increased fatty acid oxidation |
| | | Limitation of ROS* | Limitation of ROS* |
| | | Control of NO* | NMDA-induced hyperthermia* |
| | | Regulation of glutathione level | |
| | | Protection against atherosclerosis* | |
| | | Inhibition of insulin secretion* | |
| | | Neuro-protection* | |
| | | Anti-inflammatory activity | |
| | | Inhibition of macrophage adhesion* | |
| | | Apoptosis regulation | |
| | | Oncosis activation | |

ROS, reactive oxygen species; NMDA, N-methyl-D-aspartate.
*Demonstrated roles for mitochondrial UCP.

palmitic acid by human adipocytes. It was also observed that the administration of PPARγ co-activator-1adenovirus to the inguinal fat map of mice induces UCP1 expression. These data suggest that a moderate induction of UCP1 in white fat may be used to increase metabolic energy expenditure in obese human subjects. Thus, specific uncoupling of adipocyte mitochondria remains an attractive target for the development of anti-obesity drugs.

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