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Review

UCP1, the mitochondrial uncoupling protein of brown adipocyte: A personal contribution and a historical perspective

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ABSTRACT

The present text summarizes what was my contribution, starting in 1975, to the research on the uncoupling protein 1 (UCP1), the mitochondrial uncoupler of brown adipocytes. The research on UCP1 aimed at identifying the mechanisms of heat production by brown adipocytes that occurs in mammals either at birth or during cold exposure and arousal in hibernators. With others and in particular Dr. David Nicholls, I participated in the first experiments that contributed to the identification of UCP1. Important steps were the obtention of UCP1 antibodies followed with my main collaborator and friend Frédéric Bouillaud with the initial cloning of the UCP1 cDNA and gene from rats and humans. These molecular tools were then used not only to analyse UCP1 uncoupling activity and to investigate the effects of mutagenesis on the uncoupling function of this protein, but also to decipher the transcriptional regulation of the UCP1 gene. In addition to experiments carried out in rodents, we could identify UCP1 and thermogenic brown adipocytes in humans. A more recent outcome of our research on this uncoupling protein was the identification of a second isoform of UCP, that we named UCP2, and of several UCP homologues in mammals, chicken and plants. UCP1 is certainly a unique mitochondrial transporter able to uncouple respiration from ADP phosphorylation in mitochondria. The discovery of this protein has opened new avenues for studying energy expenditure in relation to overweight, obesity and related pathologies.

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1. Introduction

The history of the identification of the uncoupling protein 1 (UCP1), a mitochondrial transporter of the inner membrane, is directly linked to the search for the unique thermogenic mechanism operating in brown adipocytes. In all types of mitochondria (except in brown fat mitochondria), respiration is coupled to ATP synthesis. This process is generally referred to as respiration coupling, meaning that energy released during re-oxidation of reduced coenzymes and oxygen consumption is in large part used to phosphorylate ADP into ATP. Ninety percent of ATP produced in most cells is generated in this manner. Meanwhile, in any type of mitochondria, besides energy recovered as ATP, a part of respiration energy is lost as heat. Since the sixties, physiologists observed that specific cells referred to as brown adipocytes possess a spectacular ability to release heat in order to maintain body temperature around 37 °C. The heat production ability of brown adipocytes was described in new-born animals, in cold-exposed rats and in arousing hibernators between 1962 and 1965. Around 1976–1978, biochemists aiming to understand the molecular basis of this thermogenic mechanism identified a specific mitochondrial protein present in the inner membrane of brown adipocyte mitochondria. This protein allows the brown fat mitochondria to actively respire without being obliged to phosphorylate ADP: in such an exceptional situation energy is dissipated as heat [1–3].

This manuscript is very particular for me since I was asked to summarize the research developed in my team about the brown adipocyte UCP since the beginning of the story in the early seventies. Although I will focus here on what we did, I do not forget and I admire what was done by my distinguished foreign colleagues, collaborators, competitors and friends and among them in particular: Drs J. Arch, C. Bouchard, B. Cannon, M. Cawthorne, S. Cinti, J-P. Giacobino, B. Holloway, J. Himms-Hagen, M. Klingenberg, L. Kozak, O. Lindberg, Jan Nedergaard, D. Nicholls, L. Perusse, E. Rial, D. Richard, E. Silva, M. Saito, B. Spiegelman.

I was unable to refer herein to all the papers published by many laboratories and I decide to only quote papers from my team and a few review manuscripts.

2. The brown adipocyte mitochondria before 1970: a thermogenic loose coupling of respiration to ATP synthesis

Since the sixties, brown adipocytes were recognized as cells forming the Brown Adipose Tissue (BAT) and dedicated to regulatory thermogenesis but he question of the nature of the thermogenic mechanism was open. A series of experiments carried out with newborn rabbits, rats exposed to the cold and arousing hibernators between 1962 and 1965 had established the ability of BAT depots to produce heat in specific situations and to dispatch it towards the brain, the heart, the kidneys through blood vessels transporting the warm blood [4,5]. The brown adipocytes contained many lipid droplets and were considered as a peculiar subtype of adipocytes, i.e. cells synthesizing and storing triglycerides and also able to perform lipolysis in response to catecholamines released by sympathetic fibres at the surface of the cells. However, a major difference between brown and white adipocytes, revealed by electron microscopy analyses and confirmed by biochemical investigations, was the presence of an unusual and enormous number of mitochondria in brown adipocytes. In addition, these mitochondria were striated by cristae of the hyperdeveloped inner mitochondrial membrane that traverse the whole width of the mitochondrion, conferring these mitochondria and brown adipocytes a huge ability to respire and oxidise carbonated substrates and reduced coenzymes. This particular morphology of brown adipocytes suggested the existence of a link between the chondrioma and the mechanism of heat production.

In the sixties, several leading researchers, the “fathers” of mitochondria bioenergetics, had established that respiration of mitochondria was obligatory coupled to ADP phosphorylation. The dogma was that mitochondria respire and obligatorily synthesize ATP in such a manner that respiration ceased when ADP phosphorylation was slowed or blocked. In the case of BAT mitochondria, it was postulated that the high level of respiration due to the high number of mitochondria triggered an elevated production of ATP that was then hydrolysed in a reaction releasing heat. However, the search for a particular ATP-ase hydrolysing ATP in brown adipocytes was unsuccessful.

The explanation came from a couple of independent researchers, Drs Bob Smith at the University of California Davis and Olov Lindberg at the Wenner Gren Institute of Stockholm University. They published pioneering experimental analysis in 1966 and 1967 and cleared up the question. They reported that, in contrast to what was observed in all types of mammalian mitochondria, respiration of BAT mitochondria was non-coupled or loosely coupled to ADP phosphorylation [6,7]. The existence of this uncoupling was *a priori* the mechanism explaining why BAT mitochondria dissipated a significant part of respiration energy as heat since, in the presence of an uncoupling mechanism, energy of coenzyme re-oxidation was not used to phosphorylate ADP, similarly to what was observed when a respiration uncoupler (2,4-DNP, FCCP…) was artificially added to coupled respiring liver or skeletal muscle mitochondria. Actually, the 2 laboratories were right and made a fundamental discovery showing the inability of BAT mitochondria to exhibit energy conservation. In other words, BAT mitochondria can respire actively without having to phosphorylate ADP, contrary to the dogma of energy conservation in mitochondria. Smith and Lindberg were the first authors to propose a mechanistic explanation for the thermogenic activity of brown adipocytes. However, these authors were discussing whether the procedure of the isolation of BAT mitochondria might have induced an artefactual uncoupling of respiration mediated by fatty acids during the isolation of mitochondria (see Table 1).

3. Mitochondrial mechanism of thermogenesis in BAT: nucleotides, fatty acids and proton leak

Several biochemical mechanisms of thermogenesis are known. They include the action of ATP-ases, accelerated ATP turnover, futile cycles and changes in mitochondrial bioenergetics [6]. Many studies confirmed the coupling between oxygen consumption and ATP synthesis in mitochondria, meaning that any change in respiration modifies the production of ATP by mitochondria and, conversely and importantly, that any change in ATP synthesis alters the respiration rate. Different mechanisms explaining the coupling between respiration and ADP phosphorylation in mitochondria were proposed and were a matter of intense dispute over 20 years