The existence of fat deposits of a brownish colour, distinct from white adipose tissue deposits, located at various sites in the body of mammals has been recognized for many years. This tissue has been referred to as brown adipose tissue (BAT), and its multilocular lipid storing cells have been referred to as brown adipocytes. The thermogenic function of BAT in newborn rabbits, cold acclimated rats and arousing hibernators was discovered in 1965 (reviewed in [1]). Since this date, intensive research, the main aims of which were the appreciation of the physiological role of BAT and the elucidation of the biochemical mechanisms of heat production, has been carried out.

Research on BAT demonstrated that the brown adipocytes are different from white adipocytes and consist of specialized thermogenic cells. The brown adipocytes have particular locations in the body and they are characterized by

Abbreviations used: BAT, brown adipose tissue; UCP, uncoupling protein; AR, adrenoreceptor.
abundant and highly thermogenic mitochondria. These mitochondria are activated when the brown adipocytes themselves are triggered by noradrenaline released at their surface. This neuromediator interacts with α1, β1 and β3 adrenoceptors. The increased production of cAMP activates lipolysis in brown adipocytes, and free fatty acids activate the uncoupling protein (UCP) present in the inner membrane of brown adipocyte mitochondria. Uncoupling protein activation results in increased respiration which is uncoupled from ADP phosphorylation and promotes the dissipation of energy as heat [2]. The production of heat by BAT is important for thermoregulation and in particular for cold-induced thermogenesis. BAT is also an effector of diet-induced thermogenesis. Both cold-induced thermogenesis and diet-induced thermogenesis in BAT refer to a sympathetically mediated activation of brown adipocytes [1,3–5]. Although a role for a defect in thermogenesis in the aetiology of human obesity is debated, experiments with different types of obese rodents demonstrated that a decreased BAT thermogenesis was associated with fat gain. In agreement with these observations, an increased thermogenic activity of BAT was demonstrated in animals exhibiting increased diet-induced thermogenesis and decreased fat gain [3–5]. It is assumed that any activation of cellular thermogenesis will facilitate resistance to weight gain. However, the weak development of BAT in human adults suggests that any BAT activator may have a limited effect. Research on BAT has led also to the discovery of two interesting proteins: UCP, and the β3-adrenoceptor; these may be used as targets for new anti-obesity drugs.

**Brown fat UCP**

A major clue was the discovery of the brown fat UCP [2,6], recently renamed UCP1 [7]. This protein is a component of the inner mitochondrial membrane that is specifically expressed in brown adipocytes. In basal conditions, the respiratory activity of BAT mitochondria is rather low and is coupled to ADP phosphorylation; moreover UCP is inhibited by nucleotides. The low number of ATP-synthase molecules in BAT mitochondria restrict respiration to a low level. When brown adipocytes are activated, the free fatty acids activate UCP, which promotes the dissipation of the mitochondrial proton gradient through the membrane and short-circuits the ATP-synthase. The activation of respiration and the short-circuiting of the ATP-synthase result in energy dissipation as heat.

**β3-adrenoceptor**

Pharmacological studies of catecholamine-induced lipolysis in isolated brown adipocytes identified an atypical β-adrenoceptor (AR) present at the surface of these cells. Later, this atypical receptor, now referred to as β3-AR, was cloned. Such a receptor is not, in fact, specific for brown adipocytes, but these cells contain a very high number of β3-AR. It prompted many laboratories and pharmacological companies to search for agonists specific for the receptor, including potential thermogenic compounds stimulating energy expenditure. Such agonists active in rodents were obtained; it still remains to isolate compounds active in humans [1].

**BAT in neonates**

BAT is present during the whole life-span in most rodents (hibernators or non-hibernators) and small mammals. BAT is present in the newborn or young of most species, and in most species it differentiates during fetal life. In guinea-pigs, BAT has already reached its full development at birth. In rats, full development is observed during the first days following birth, whereas it takes several weeks in the golden hamster. Morphological differentiation of brown adipocytes occurs during the last week of fetal development in the mouse [8]. The UCP appears 2 days before birth and its level increases during the next few days [1]. Just before birth, or at birth, high levels of UCP can be detected in the BAT of calves or lambs. UCP is present in adipose tissue of fetal Rhesus monkeys 30 days before birth, and in adipose tissues of fetal reindeer 2 weeks before birth. In the human fetus, typical brown adipocytes containing UCP are present during the third trimester of gestation [1]. In human neonates, BAT depots are in cervical, axillary, perirenal, periadrenal, and pericardiac regions, as well as along thoracic aorta, intercostal arteries, abdominal aorta, and in the omentum. With increasing age, an increasing proportion of the cell populations in BAT become unilocular and most BAT depots are replaced by white adipose tissue.

**Function of BAT in neonates**

The most obvious role for BAT is related to thermogenesis and thermoregulation. BAT of
newborn infants has a thermogenic function similar to that in animals [9]. In newborn rats, the activation of BAT is characterized by an acute increased UCP synthesis. The newborn infant can increase its energy expenditure by more than 2-fold when it is exposed to very mild cold. Since the newborn infant is unable to shiver, it is assumed that this increase in thermogenesis occurs primarily in BAT [10]. There is some evidence for more active BAT in infants kept at 22-25°C than those kept at 34°C. Increased BAT thermogenesis has been suggested in infants dying from sudden infant death syndrome, and in infants with malignant disease [3]. It has been proposed also that certain volatile anaesthetic agents that inhibit the thermogenesis in animal BAT contribute to hypothermia in infants [11]. Although it remains difficult to quantitate the contribution of BAT to neonatal non-shivering thermogenesis, it has been calculated by Hull that 30 g of brown adipose tissue is required to cope with all observed non-shivering thermogenesis in a newborn baby (reviewed in [12]).

**Hypothesis: a role for BAT in thermoregulatory feeding in newborn infants**

It was recently proposed by Dr. J. Himms-Hagen that BAT thermogenesis may have a central role in control of both onset and termination of a feeding episode in rats. This author suggested that a feeding episode occurs during an episode of increased sympathetic nervous system activity that stimulates BAT thermogenesis [13]. More recently, Dr. Himms-Hagen proposed a role for BAT thermogenesis in the control of food intake in newborn infants: initiation of feeding is attributed to transient dip in blood glucose concentration that is due to stimulation of glucose utilization in the BAT; termination of feeding is attributed to increased temperature brought about by the stimulated BAT thermogenesis [9]. In other respects, it was shown that the interscapular BAT of newborn rats express leptin which may also regulate feeding behaviour at birth [14].

**The novel uncoupling proteins UCP2 and UCP3**

Recently, a UCP homologue was cloned using a brown-fat-UCP-cDNA as a probe [7,15]. This newly identified UCP, now termed UCP2, is present in many rodent and human cell types including white and brown adipocytes, muscular cells, bone marrow cells, macrophages and lymphocytes. It is 59% identical to brown fat UCP, which is now referred to as UCP1. Functional studies support an uncoupling activity for UCP2, which therefore constitutes a thermogenic system. Interestingly, it was shown that the UCP2 gene maps to a chromosomal region linked to obesity, hyperinsulinism and glucose intolerance. UCP2 mRNA is also overexpressed in mice that are resistant to obesity induced by a hyperlipidic diet. Another UCP homologue, referred to as UCP3 was also identified [16,17]. UCP3 seems to be dominantly expressed in skeletal muscles. In rodents, UCP2 and UCP3 mRNAs are present in BAT in addition to UCP1 mRNA. UCP−/− mice are less resistant to cold but survive at room temperature; these animals overexpress UCP2 mRNA in their BAT [18].

Recent data show that these novel uncoupling proteins are related to thermogenesis induced by cold exposure, diet, infection, thyroid hormones etc. Although it is not yet known if such novel UCPS are involved in homeothermy of neonates, it may be postulated that they contribute to neonatal thermoregulation.

The author's research is supported by the Centre National de la Recherche Scientifique, Direction des Recherches, Etudes et Techniques and Association de Recherches sur le Cancer.


Volume 26
Neonatal metabolic adaptation after preterm delivery or intra-uterine growth retardation

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In utero, the fetus receives a constant supply of nutrients via the placenta. These nutrients provide energy for basal metabolism, substrates and energy for growth, and fuel stores. After birth, the neonate must adapt to an independent existence in many ways. One of the adaptive mechanisms is metabolic adaptation whereby the neonate releases fuels from body stores and utilizes substrates in milk feeds in order to meet the body's energy needs, so that blood glucose control is achieved and alternative fuels to glucose are mobilized if necessary. The infant must adapt first to the abrupt cessation of placental nutrition and the subsequent fast-feed cycle, secondly to the change from intravenous to enteral nutrition, and third to the change of major substrate from glucose to fat.

This process, which can be likened to the adult counter-regulatory response has two main components — hormonal and metabolic. During fetal life, insulin enhances growth and the laying down of fuel stores as liver glycogen and fat in adipose tissue. After birth, the action of insulin diminishes and there is a surge in the secretion of counter-regulatory hormones — glucagon, cortisol and the catecholamines. These hormonal changes induce the enzymes responsible for the metabolic changes which release substrate from body stores: glycogenolysis, gluconeogenesis, lipolysis, and \( \beta \)-oxidation of fatty acids to form ketone bodies. These ketone bodies are important alternative fuels to glucose, particularly in the neonatal brain, and this contributes to total fuel availability [1,2].

Patterns of metabolic adaptation in infants

Healthy, full-term infants

First, a cross-sectional study was performed of the patterns of metabolic adaptation in 156 healthy, appropriate weight for gestational age (AGA), full-term infants [3]. Many of these babies had low pre-feed blood glucose levels although they demonstrated no clinical signs of hypoglycaemia. The same babies had high ketone body concentrations (up to 3 mmol/l), representing alternative fuel production which is thought to protect them from the neurological effects of hypoglycaemia. A close negative relationship was found between blood ketone body (log value) and glucose concentrations on the second and third postnatal days \((r, -0.57; P <0.001)\). Although there was the expected positive relationship between plasma non-esterified fatty acid and blood ketone body concentrations, the relationship varied amongst full-term babies more than amongst older subjects.

Feeding patterns affected metabolism in that breast-fed infants had low blood glucose