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Brown Adipose Tissue - a Short Historical Perspective

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Abstract

Brown adipose tissue (BAT) was first identified by Conrad Gessner in 1551, but it was only in 1961 that it was firmly identified as a thermogenic organ. Key developments in the subsequent two decades demonstrated that: (i) BAT is quantitatively important to non-shivering thermogenesis in rodents, (ii) uncoupling of oxidative phosphorylation through a mitochondrial proton conductance pathway is the central mechanism by which heat is generated, (iii) uncoupling protein-1 is the critical factor regulating proton leakage in BAT mitochondria. Following pivotal studies on cafeteria-fed rats and obese *ob/ob* mice, BAT was then shown to have a central role in the regulation of energy balance and the aetiology of obesity. The application of fluorodeoxyglucose positron emission tomography in the late 2000s confirmed that BAT is present and active in adults, resulting in renewed interest in the tissue in human energetics and obesity. Subsequent studies have demonstrated a broad metabolic role for BAT, the tissue being an important site of glucose disposal and triglyceride clearance, as well as of insulin action. BAT continues to be a potential target for the treatment of obesity and related metabolic disorders.

Key words Brown adipose tissue, Diet-induced thermogenesis, Energy metabolism, Mitochondria, Non-shivering thermogenesis, Nutritional energetics, Obesity, Uncoupling protein-1 (UCP1), White adipose tissue

1 Introduction

Many tissues have their dedicated enthusiasts, but those who study brown adipose tissue (BAT) exhibit a particularly strong devotion to their chosen subject. This may at first have been partly because the tissue defies what was considered as a central axiom of metabolic systems – that they operate to minimise energy leakage and to maximise energetic efficiency. It may also be due partly to the considerable adaptive capacity of BAT with the direct and immediate influence of the external environment in the form of the ambient temperature. In the 1970's, the community of researchers who focused on brown fat was both small and relatively localised with much of the pioneering work being performed by scientists based in Canada, France, Sweden and the UK. These are, of course, northern countries with cold winter climates, as David Nicholls and I noted in the Preface to the volume on 'Brown Adipose Tissue' (1986) that we had edited [1]. This book was in effect a successor to the volume of the same name edited by Lindberg and published in 1970 [2], the appearance of the 1986 book reflecting the extensive developments that had occurred during the 1970's and early 1980's.

The Swiss naturalist Conrad Gessner is credited with being the first to describe brown fat. In 1551 he identified BAT in marmots, a species which has large quantities of the tissue [3]. Since marmots are hibernators, BAT was described as the 'hibernating gland', a descriptor that prevailed for a considerable period. The subsequent evolving perspectives on the functions of this fascinating tissue are described here, highlighting the major developments over the past 50 years.

2 Early History

Views on the central function(s) of brown fat have changed several times over the nearly five hundred years since the discovery of the tissue [4]. Between 1670 and 1817 it was considered to be part of the thymus, while from 1817 to 1863 it was thought to be an endocrine gland and active in the formation of blood (Table 1). This was followed (1863-1902) by the view that BAT was a modified form of fat tissue which acted as a reservoir for food substances. From 1902 until 1961 it was once more considered to be an endocrine organ – a role which has subsequently been shown to be true in part, as noted later (section 6.2). There were also suggestions during this period that BAT is involved in thermoregulation [5].

The central function of BAT was finally identified in 1961 when Smith in California demonstrated that the tissue is thermogenic - generating heat for the maintenance of body

temperature by non-shivering mechanisms [6, 7]. All tissues produce heat, of course, as a by-product of normal metabolic processes, but heat is recognised as being the primary – desired – endpoint of the metabolic activity of BAT.

Following the identification of brown fat as a specific thermogenic organ, three physiological states were recognised in which the tissue is prominent and active in the generation of thermoregulatory heat. These are: (i) the arousal from hibernation, (ii) cold-stressed mammalian neonates where 'normal' environmental temperatures in effect represent a considerable thermal challenge, and (iii) small adult rodents in response to cold environments [8, 9, 7]. The association with arousing hibernators is, of course, congruent with the original observations of Gessner and the subsequent use of the descriptor 'hibernating gland'.

2.1 Brown Fat as the Major Thermogenic Organ

Two key questions were under consideration in the early-mid 1970's, a decade after the functional role of BAT had been established. One was the quantitative importance of BAT to the total capacity for non-shivering thermogenesis (NST), while the other was the molecular mechanisms by which heat is generated in the tissue. In small mammals adapted to the cold, the energy expenditure on thermoregulatory NST can be 2-3 times, or more, than the resting metabolic rate at thermoneutrality, with concomitant increases in food intake [10]. However, BAT was seen to comprise only a few percent of body mass at most, a value of 0.5-2% being common in rodents [4]. Thus the extent to which such a small tissue could account for NST was viewed as problematic.

The importance of BAT to the capacity for NST was addressed directly by Foster and Frydman in Ottawa in a series of studies measuring regional blood flow in rats. Previous work employing what was then the widely used approach to determining blood distribution involving soluble indicators - particularly $^{86}Rb^{+}$ - had indicated that blood flow to BAT increased following exposure to cold or the administration of noradrenaline. Nevertheless, the scale of the increase was such that BAT could not make more than a minor contribution to NST. Foster and Frydman [11] demonstrated that studies with $^{86}Rb^{+}$ seriously under-estimated the blood flow to BAT, while over-estimating that to skeletal muscle, compared to what had become the gold standard for measuring blood distribution - the radioactively labelled microsphere technique. In further studies using $^{86}Rb^{+}$-labelled microspheres (15 μM in diameter), together with measurements of cardiac output and oxygen extraction, BAT was shown to be the dominant site

of NST in rats acclimated to the cold [12]. Furthermore, when thermogenesis was maximally stimulated following the administration of noradrenaline, a figure of 60% was calculated as the contribution of BAT to NST in rats [13].

Subsequent studies employing similar experimental techniques, including in mice [14], supported the view that BAT is the key site of NST in small rodents. However, a smaller contribution to NST was suggested for warm-acclimated, as opposed to cold-acclimated, rats [15].

2.2 How Heat is Generated in Brown Adipose Tissue

Understanding how heat is generated in BAT was a major focus of Lindberg and his group at the Wenner-Gren Institute in Stockholm. Rapid progress in determining the central molecular mechanism occurred following the application of Mitchell's chemiosmosis concept by Nicholls (initially in Stockholm and then Dundee). During normal oxidative phosphorylation the proton gradient generated across the inner mitochondrial membrane is harnessed to the synthesis of ATP. In marked contrast, in a series of studies the proton gradient was shown to be dissipated in BAT as heat rather than being coupled to ATP synthesis. This proton conductance pathway acts in effect to short circuit the mitochondrial proton gradient [16, 17].

The proton conductance across the inner mitochondrial membrane is regulated by a tissue-specific protein, now termed uncoupling protein-1. It was first identified as a 32,000 M_r band on SDS-polyacrylamide gels of brown fat mitochondria by Ricquier in Paris, the level being markedly increased in rats exposed to the cold [18, 19]. This cold-inducible protein was subsequently shown to be the factor regulating proton conductance and the uncoupling of BAT mitochondria [20, 19]. The protein was initially known by two different names – uncoupling protein and thermogenin. The former is more literal, while the latter, which was introduced by Cannon and Nedergaard in Stockholm, is more literary. Uncoupling protein (UCP) became the name of choice, but this was itself later modified to uncoupling protein-1 (UCP1) when two new uncoupling proteins (UCP2, UCP3) were discovered in the late 1990s [21, 22].

As animals adapt to a cold environment the total amount of UCP1 in brown fat depots increases, thereby raising the thermogenic capacity of the depot and of the animal as a whole. This occurs both through the recruitment of new brown adipocytes and by increases in the quantity of UCP1 in pre-existing brown fat cells [23]. Within individual brown adipocytes there are in turn two distinct mechanisms by which the total UCP1 rises: (i) increases in concentration per unit

mitochondrial mass (protein), and (ii) mitochondriogenesis, there being mitochondrial proliferation as part of the adaptive response to cold [23].

The profound effect of cold on the total UCP1 content of BAT depots is illustrated by data from 1987 by my own group in Cambridge (Fig. 1) in which rats were acclimated for three weeks at different temperatures between thermoneutrality (29°C) and 4°C [24]. A stepwise increase in the mitochondrial content of the interscapular depot (as assessed from measurements of cytochrome *c* oxidase activity) and of the UCP1 content per mg of mitochondrial protein is evident, the values in the animals at 4°C being 11.2 and 9.3 times higher, respectively, than those at thermoneutrality [24]. Similarly, the total UCP1 content in the depot, calculated from the changes in cytochrome *c* oxidase activity and the UCP1 concentration per mg mitochondrial protein, follows a similar pattern. The total amount of UCP1 in the interscapular depot of animals at 4°C was 104-fold higher than those at 29°C (Fig. 1) [24]. These, and other, studies in which UCP1 was measured immunologically were enabled by the relative ease with which antibodies could be raised against the protein [25-27]. This in turn had been facilitated by the publication of a method for the isolation and purification of UCP1 from BAT mitochondria of rats and hamsters [28].

The sympathetic nervous system was recognised to play a central role in the regulation of BAT thermogenesis [29]. Brown fat is densely innervated by sympathetic nerve endings with the release of noradrenaline leading to the direct stimulation of heat production, both acutely and chronically [29, 23]. The sympathetic system is also central to the increases in thermogenic capacity that occur with chronic stimulation of thermogenesis, driving the increases in the amount of UCP1. One of the key developments in the mid 1980s was the report that BAT contains what was a novel – or 'atypical' as it was originally described – β-adrenoceptor [30]. This was subsequently named the β_3-adrenoceptor, distinguishing it from the then recognised β_1- and β_2-subtypes [31].

The β_3-adrenoceptor provided a defined target for the development of specific agents to increase energy expenditure based on the stimulation of BAT thermogenesis. Several selective β_3-agonists were developed, including BRL35135 and 37344, L-796568 and CL316243, each of which was effective in rodents [31]. However, they were ineffective, or not sufficiently effective, in humans and this is in part because of sequence differences between the rodent and human β_3-

adreonceptor genes [31]. In addition, in some cases such as L-796568 which has good selectivity to the human receptor, poor oral bioavailability has limited the effectiveness.

2.3 UCP1 in the Identification of BAT

The presence of UCP1 in a tissue has been regarded as the critical diagnostic feature of whether that tissue is brown fat, or contains brown adipocytes. This has usually been a question primarily in relation to differentiating between brown and white adipose tissue depots. However, with the discovery of beige adipocytes (see section 6.1) the situation has become less clear-cut. UCP1, and by implication BAT, has been identified in a wide range of mammalian species [32]. In many cases the tissue is present and active throughout life, while in others it is relatively transient being detectable only in the early post-natal period. Neonates of some large agricultural species, such as cattle and sheep, provide potent examples of where BAT is evident at birth and for only a short period post-natally. The perirenal fat in cattle, lambs, goats and reindeer is rich in UCP1 at birth, but by approximately 1-2 months of post-natal life immunoreactive UCP1 cannot be detected, and the tissue takes on the appearance and properties of white fat [33-36].

Following the identification of UCP1 and the rapid development of molecular genetics, the UCP1 gene was cloned in the early 1980s by Ricquier and colleagues [37, 38]. Several studies were soon reported examining the key factors that modulate expression of the UCP1 gene, with both acute cold exposure and the administration of noradrenaline being shown to lead to a rapid and substantial increase in mRNA level [39].

3 BAT in Nutritional Energetics and Obesity

By the end of the 1970s/early 1980s the central role of BAT in NST had been demonstrated and the mechanism by which heat is generated established with UCP1 identified as the critical regulator of the process. In the last two years of the 1970s, a new dimension to the functional role of BAT emerged – in nutritional energetics.

The background to this radical development was that there had been increasing interest in the concept, advanced principally by Miller and Stock in London, that adaptive thermogenesis plays a significant role in energy balance and the aetiology of obesity. This was itself a revitalisation of the 'Luxuskonsumption' proposal from Neumann in 1901. The core proposition was that reduced energy expenditure on thermogenesis – particularly diet-induced – was an important factor in the initiation and development of obesity. Evidence in favour of this view included the

observation that rats induced to overeat when fed a palatable 'cafeteria' diet retained less of the excess energy than would be expected and that this was through the activation of facultative diet-induced thermogenesis [40, 41]. The second line of evidence was that obese animals - particularly the obese (*ob*/*ob*) mouse and other rodent models - exhibit reduced energy expenditure and are able to develop obesity on a normal energy intake, this being attributable to a reduction in expenditure on NST [42, 43].

An important question for those exploring thermogenesis in the context of nutritional energetics and obesity was the tissue localisation and molecular mechanism of adaptive heat production – the same issues as previously for those concerned with thermoregulation and adaptation to the cold. Several mechanisms had been considered: these included Na+ transport across the plasma membrane, tissue protein turnover, and futile (substrate) cycles such as that between fructose-6-phosphate and fructose-1,6-bisphosphate [44-47]. However, none appeared to meet the central criteria: (i) of being specific, or relatively specific, in terms of the tissue(s) involved, and (ii) having the potential to provide sufficient quantities of heat [48]. Furthermore, fundamental processes such as protein turnover and Na+ transport could not readily be viewed as having the capacity to change by the scale that would be required (orders of magnitude) without disrupting normal physiological function.

As a consequence of the recognition of BAT as the major site of NST, and the mitochondrial proton conductance pathway as the process by which heat is generated, the tissue emerged as a new locus for those concerned with energy balance and obesity. Two seminal observations quickly linked BAT to nutritional energetics. In the first, Himms-Hagen and Desautels in Ottawa found that GDP binding was reduced in BAT mitochondria of *ob*/*ob* mice relative to lean siblings [49] – at the time GDP binding was the key tool for assessing the activity of the proton conductance pathway [50]. These authors also demonstrated that the response to cold was attenuated in the obese mutants, there being a reduced increase in GDP binding [49].

In the second seminal report, Stock and Rothwell in London presented evidence for expansion and increased activity of BAT in cafeteria-fed rats exhibiting diet-induced thermogenesis [40]. This was accompanied by an increase in the maximum capacity for noradrenaline-stimulated thermogenesis, resting O_2 consumption in response to administration of the catecholamine being elevated in cafeteria-fed animals compared with controls on a normal diet. A follow-up study demonstrated a greater mitochondrial content (cytochrome *c* oxidase activity), and increased

mitochondrial GDP binding and GDP-sensitive respiration in BAT of cafeteria-fed rats [51]. Subsequent work during the 1980s was consistent with BAT being a locus of facultative diet-induced thermogenesis in rodents. Among the further changes documented in the tissue in cafeteria-fed rats was an increase in the total amount of UCP1 and in the expression of the UCP1 gene [52, 53].

These initial observations were quickly followed by a series of studies in which the activity of BAT was assessed in a range of physiological and pathological conditions in which energy flux and energy balance are altered [42, 54, 48]. These encompassed various types of rodent obesity, including dietary and that induced hormonally and through hypothalamic lesioning, as well as different types of obese mutation. Physiological and nutritional states in which changes in the thermogenic activity and capacity of BAT were demonstrated included fasting-refeeding, modifications to diet composition, lactation, the hibernation cycle, and seasonality-induced alterations in body fat driven by photoperiod [42, 54, 48].

Lactation was of particular interest to my group since this condition is associated, certainly in rodents and other small mammals, with substantial hyperphagia, the energy costs of milk production being high. In rats, for example, food intake at peak lactation is increased 3-fold relative to virgin siblings [55, 56]. However, in contrast to animals exhibiting hyperphagia on a cafeteria diet, BAT is characterised by a substantial atrophy during lactation. Mitochondrial content, GDP binding, and the mitochondrial concentration and total tissue amount of UCP1 are each markedly reduced [57, 58]. The scale of the alteration can be illustrated (Fig. 2) by the total tissue UCP1 content which at peak lactation is <10% of that in virgin mice [43]. The consequence of this suppression of BAT during lactation – which is rapidly reversed following weaning – is a substantial energy saving that results in a significant contribution to the energy costs of milk production. However, this is unlikely to be a specific strategy to conserve energy, but rather a reflection of the limited capacity to dissipate excess heat given the large amount of metabolic heat generated through the synthesis of milk [59].

4 Brown Fat in Humans

By the middle of the 1980's it was clear that BAT is involved in nutritional energetics and obesity, as well as in thermoregulation, at least in rodent species. Concern with the growing public health problem of obesity in both the developed and developing world had become a significant driver behind much of the work on BAT. However, by the end of the 1980s the

prevailing view was that while BAT is important to energetics in laboratory rodents it was of little, or no, relevance to energy metabolism in adult humans. This in part echoed the often cited line of Alexander Pope - "*the proper study of Mankind is Man*" - from his poem "Essay on Man".

The general view was that although BAT is present in human neonates and infants, particularly from the work of Hull in Oxford [60, 61], the tissue atrophies after the early years of life to be replaced by white fat. Such a conclusion was based essentially on anatomical and histological appearance – primarily the presence of multilocular adipocytes of a 'brownish appearance', replacement being by unilocular fat cells of a pale yellow/white colour. However, by 1983 UCP1 had been detected in adult humans as well as in infants [62, 25]. Indeed the protein had been isolated from infants and antibodies raised against it [25]. A subsequent survey of different age groups observed the presence of UCP1 even in some elderly individuals, although lower concentrations were evident in adults compared with infants and children [63]. Thus there was clear evidence on the basis of the critical diagnostic feature of BAT that the tissue is present throughout much of life [64].

That BAT was in practise active, or had the plasticity to be activated, was demonstrated from studies on patients with phaeochromocytoma, these being characterised by a hypersecretion of catecholamines. Adipose tissue from around the kidneys and the adrenals of phaeochromocytoma patients was shown to be rich in mitochondria, these mitochondria exhibiting a well-developed cristae structure and GDP-sensitive respiration [65]. The concentration of UCP1 was also found to be increased in (perirenal) adipose tissue in those with phaeochromocytoma [66]. As a further indication of active BAT in this condition, UCP1 mRNA was detected in the tissue [67].

Despite the substantial evidence for active BAT in adults, it is not clear why the tissue was generally deemed to be of little relevance to human physiology. One explanation may be the limited acceptance at the time that reduced energy expenditure, and thermogenesis in particular, was a significant factor in the aetiology of obesity in humans. Indeed, this remains an issue of continuing debate. Clearly, if energy expenditure on thermogenesis is not considered relevant to the development of human obesity, then there appears little reason for any focus on BAT. Nevertheless, it can be argued that augmenting energy expenditure through BAT thermogenesis, whether by selective β_3-adrenoceptor agonists or via other means, is an appropriate strategy to treat obesity irrespective of whether reduced energy expenditure as such is aetiologically

important. Furthermore, in principle BAT thermogenesis need not be more than a trivial component of total energy expenditure under normal conditions for its stimulation to be a potential therapeutic route.

As a consequence of the presumption that BAT is not relevant to energy metabolism in adult humans, general interest in the tissue declined from the end of the 1980s. BAT continued, of course, to be the focus of considerable activity by those concerned with the fundamental biology of the tissue.

5 Renaissance – Brown Fat in Humans

Renewed interest in BAT in humans, particularly in relation to obesity, was catalysed in 2009 when a trio of papers on the tissue appeared in the 'New England Journal of Medicine' [68-70]. These reported the application of fluorodeoxyglucose positron emission tomography (FDG-PET) in adults, a procedure that is customarily used to track the metastasis of tumours in cancer investigations by identifying localised areas of high glucose uptake. Adipose tissue areas exhibiting a high level of glucose uptake were observed, and these were associated with positive immunostaining for UCP1, demonstrating that they represented BAT [68-70]. That FDG-PET was serendipitously identifying BAT in adult humans had been highlighted two years previously in a review by Cannon and Nedergaard [71]. The sites of BAT identified by FDG-PET include the supraclavicular and neck regions, as well as the suprarenal area.

Importantly, the initial group of FDG-PET studies, together with the several subsequent follow-up reports, demonstrated variations in the metabolic activity of BAT in response to environmental stimuli, age and body fat – broadly similar to rodents. For example, BAT in humans is activated by exposure to cold and by insulin, and decreases with age and with BMI (body mass index) [68-70, 72, 73]. Indeed, there is an inverse relationship between apparent BAT activity and BMI. Thus three decades after BAT was first linked to energy balance and obesity from rodent studies, it was now evident that this is also true for humans – Alexander Pope's aphorism notwithstanding. This has led to fresh interest in ways of increasing the amount and thermogenic activity of BAT in the treatment not only of obesity, but also more widely in metabolic disease. Although the β_3-adrenoceptor continues to be a target, with mirabregon (originally developed to treat an overactive bladder) being a recent selective agonist [74], more radical routes for the augmentation of BAT thermogenesis have been proposed such as stem cell therapy, brown fat transplantation and the central stimulation of sympathetic activity [75, 76].

6 Cellular Heterogeneity and Metabolic Roles

6.1 Cells

In addition to the demonstration that BAT is present and functionally active in adult humans, there have been other key developments over the past decade. These relate to cellular origin, cell heterogeneity and additional metabolic functions. With respect to cellular origin, brown adipocytes were found, unexpectedly, to be derived from myogenic precursors in skeletal muscle indicating that they and white adipocytes have a different origin [77].

Although, traditionally, there were thought to be only two types of mature adipocyte – brown and white – with different ultrastructural and functional characteristics, a third type of fat cell has been discovered [78-80]. These cells, termed beige or brite (BRown in whITE), express the critical feature of brown adipocytes - UCP1. Beige adipocytes, this having become the most widely used name (reflecting their 'intermediate' status/colour between white and brown fat cells), express in addition to UCP1 some, but not all, of the other molecular signatures of brown adipocytes [78, 79]. They are found particularly in what have customarily been regarded as white fat depots and can be recruited by cold exposure - a process described as 'browning' [81]. Different fat depots appear to vary with respect to the presence of, and ability to recruit, beige adipocytes.

The extent to which beige adipocytes can contribute to the overall thermogenic capacity is unclear, but a number of factors ranging from specific hormones to food components are reported to induce browning [82, 83]. These factors and conditions encompass adrenergic stress, apelin, thyroid hormones and dietary polyphenols [84-88].

6.2 Metabolic Roles

In addition to its direct thermogenic function, BAT has been shown to have a broader metabolic role. Specifically, it is a major site of glucose disposal, insulin action and of triglyceride clearance [89-91, 82]. That it is important in glucose disposal is perhaps not surprising given that the FDG-PET studies identifying the tissue in adult humans are based on the high levels of glucose uptake. Indeed, some of the studies in rodents in the early 1980s indicated that BAT is an important site of glucose uptake. This was shown through measurements of the activity of glycolytic enzymes, which increased on cold-acclimation, and by studies on 2-deoxy-D-glucose uptake which was stimulated by both noradrenaline and insulin [92, 93]. In addition, evidence was presented at the

time that insulin resistance in BAT leads to an impairment in the capacity to activate cold-induced thermogenesis [94, 95].

A further, wider metabolic role for BAT, as an endocrine organ, has recently been highlighted [96, 97], although this was again suggested in earlier studies where leptin and interleukin-6, for example, were shown to be expressed and secreted by brown adipocytes [98, 99]. Brown fat cells synthesise and secrete a series of protein factors and signals – 'batokines' or 'brown adipokines' – in addition to leptin and interleukin-6, including insulin-like growth factor I, fibroblast growth factor-21 and the chemokine CXCL14 (C-X-C motif chemokine ligand-14) [97, 100]. White adipocytes, of course, secrete an extensive range (several hundred) of adipokines with both local and distal actions [101, 48], but the secretome of brown adipocytes appears more limited. Certainly, brown adipokines are unlikely to make a significant contribution to circulating levels when these same factors are released by white adipocytes and other cells.

The ability of brown adipocytes to secrete protein signals parallels the secretory actions of a growing diversity of cell types – from myocytes (secreting myokines) to hepatocytes (secreting hepatokines).

7 Concluding comments

Perspectives on BAT have evolved markedly and continuously over the past 50+ years. While both BAT itself and particularly brown adipocytes appear highly specialised for heat production, it is evident that there is in effect not inconsiderable multi-functionality. A central action in the generation of thermoregulatory heat, through a unique mechanism for uncoupling mitochondrial oxidative phosphorylation, has extended to a direct role in energy balance and nutritional energetics. These functions have been further amplified by the recognition that BAT has a broad role in metabolic homeostasis. The brown adipocyte is far from unique in having a more extensive set of actions than was initially envisaged. White adipocytes, for example, are now recognised as complex endocrine and signalling cells in a manner that far transcends the earlier assumption that they were simply passive vehicles for lipid storage.

An emerging area of interest is the interaction between brown adipocytes and the other types of cell within BAT, particularly the immune cells [102]. This also has parallels with white adipose tissue, where the importance of the different cell types and especially the various cells of the

immune system has been a growing focus - beginning from when macrophages were shown to be key players in the inflammatory response of white fat in obesity [103, 104].

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Conflicts of Interest

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Table 1. Evolving views on the physiological role and functions of brown adipose tissue

Year	Function
1551	Formal description by Conrad Gessner – the 'hibernating gland'
1670-1817	Considered part of the thymus
1817-63	An endocrine gland - active in the formation of blood
1863-1902	A form of fat tissue serving as a reservoir for food substances
1902-61	An endocrine gland - again
1912-59	Some references of a link to thermoregulation
1961-	A thermogenic organ – thermoregulatory non-shivering thermogenesis
1974-8	Mechanism of heat generation identified - uncoupling of mitochondrial oxidative phosphorylation - through application of chemiosmosis
1976-8	Discovery of uncoupling protein – subsequently named uncoupling protein-1 (UCP1)
1978	Demonstration of quantitative importance to non-shivering thermogenesis in cold-acclimated rodents
1978/9-	Involved in energy balance (diet-induced thermogenesis) and obesity
2009-	Definitive identification of BAT in adult humans, and its metabolic plasticity, by FDG-PET and immunostaining for UCP1
2010/12	Discovery of 'beige'/'brite' adipocytes
2011/12	Role in metabolic homeostasis - glucose disposal, triglyceride clearance and insulin sensitivity

Modified and updated from [4].

Legends to Figures

Fig. 1 Illustration of the effect of cold-acclimation on the amount of UCP1 in brown adipose tissue (interscapular) of rats. The rats were acclimated at either thermoneutrality (29°C) or 4°C for three weeks. Total tissue cytochrome *c* oxidase activity (CO activity) is given as an indicator of mitochondrial content, and mitochondrial GDP binding (per mg mitochondrial protein) as an index of thermogenic 'activity' (GDP bind). UCP1 conc, UCP1 per mg of mitochondrial protein; UCP1 total, UCP1 in the interscapular fat depot. The fold changes at 4°C are shown relative to the values at 29°C. Data is derived from [24].

Fig. 2 Illustration of changes in the amount of UCP1 in brown adipose tissue (interscapular) of lactating mice. The mice were taken at late (peak) lactation and compared with virgin mice as controls. Total tissue cytochrome *c* oxidase activity (CO activity) is given as an indicator of mitochondrial content, and mitochondrial GDP binding (per mg mitochondrial protein) as an index of thermogenic 'activity' (GDP bind). UCP1 conc, UCP1 per mg of mitochondrial protein; UCP1 total, UCP1 in the interscapular fat depot. The fold changes at late lactation are shown relative to the values in the virgin mice. Data is derived from [58].

Fig. 1

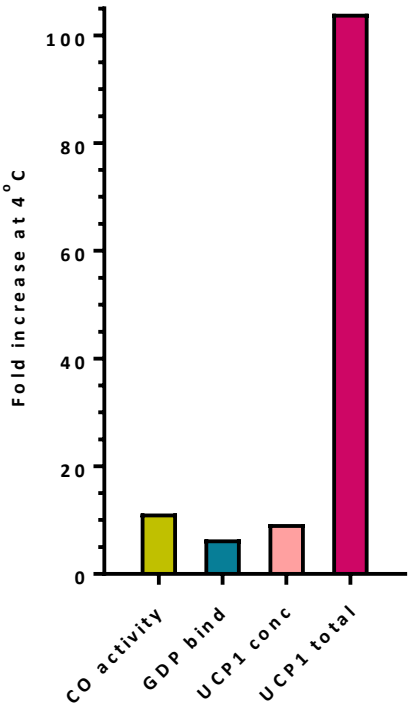
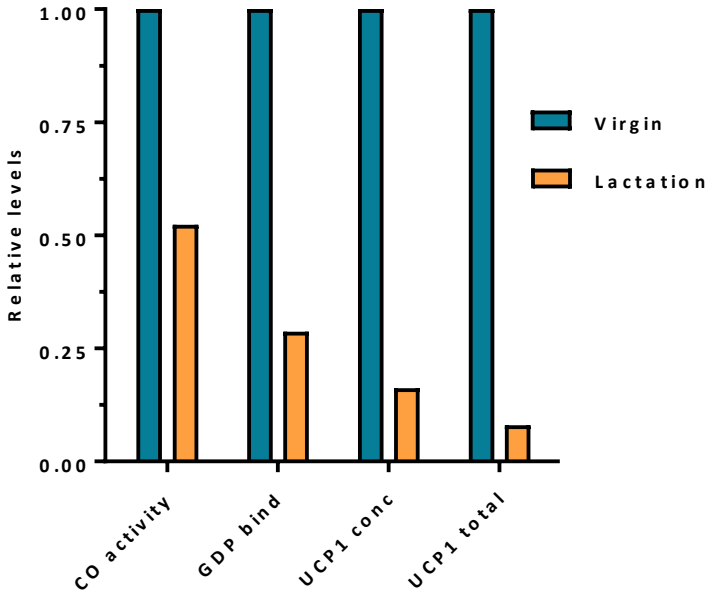

Fold increase at 4 °C
100
80
60
40
20
0
CO activity
GDP bind
UCP1 conc
UCP1 total

Fig. 2


1.00
0.75
0.50
0.25
0.00
Relative levels
CO activity
GDP bind
UCP1 conc
UCP1 total
Virgin
Lactation