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ABSTRACT: Approaches to weight management which consider only energy intake and/or expenditure do not consistently lead to favorable outcomes. A third variable, thermogenesis, must also be considered in a comprehensive understanding of obesity. Three types of thermogenesis have been outlined—shivering thermogenesis, nonshivering thermogenesis (NST), and diet-induced thermogenesis (DIT). The latter two types of thermogenesis, NST and DIT, may share a common biochemical mechanism which leads to heat production in brown adipose tissue (BAT) which is unchecked by energy needs. Four categories of studies are reviewed which implicate BAT as an important factor in DIT and point to commonalities in NST and DIT. More research is necessary to fully understand the role of BAT in human obesity.

Treatments of obesity have traditionally included two variables in their conceptualization of the energy equation. The title of the article which introduced behavioral methods to weight management was, "The control of eating."[1] This approach to modifying energy intake has continued to be the most widely considered variable in the energy equation and has reached what Jeffery, Wing, and Stunkard[2] call a "popularity verging on fadism (p. 189)."

Although it is not common,[3] a second variable in the energy equation has also been a subject of investigation. Physical activity, an output variable, has been included in several studies.[4-8] Davis and Roncari[9] conclude, "A combination of behavioral techniques and other measures such as intensive long-term programs of physical activity has shown promise of success (p. 1425)."

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A THIRD VARIABLE

A brief look into the obesity literature will show that these two variables, energy intake and physical activity, do not account for all the variance in weight management. In their statement of a behavioral weight management outcome, Jeffery, Wing, and Stunkard[2] note:

> If behavioral approaches achieve their results through incremental learning, weight losses should accelerate. Initially, when few changes have been made, losses should be slow; later, with the learning of additional skills, losses should be more rapid (p. 192).

As these investigators note, accelerating weight losses are not observed. Instead an asymptotic slowing of weight loss over time is observed.[10]

Obversely, overfeeding studies have shown a smaller weight gain than that expected from energy intake and physical activity alone.[11-13] These studies suggest the existence of a wide range of diet-induced energy costs for weight maintenance or weight gain.

Taken together, the overfeeding studies and the decelerated weight loss observation provide evidence for a third variable in weight management—a metabolic variable (see Figure 1). The phenomenon of metabolic adaptation has been reported both in behavioral literature[14] and in medical literature.[15-17]

The existence of metabolic adaptation is no longer in question. Rather, the nature of metabolic adaptation is the subject of current investigation. There is not uniform agreement,[18] but many investigators suggest that thermogenesis—heat production—is responsible for a major portion of metabolic adaptation.[19-21] Much as the first law of thermodynamics states that total

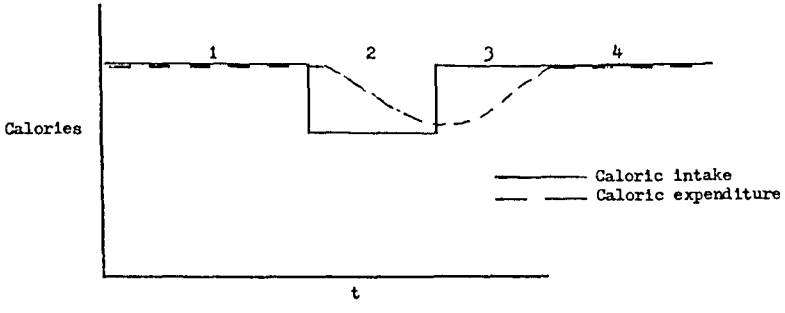

Figure 1. Metabolic adaptation. During phase 1, intake and expenditure are balanced. During phase 2, intake is restricted and weight loss results. Metabolic adaptation causes gradual slowing of loss. During phase 3, intake is returned to pre-diet level, metabolic adaptation gradually returns expenditure to original level also, but weight gain results because of positive energy balance. During phase 4, intake and expenditure are again balanced.

energy must be equivalent to work plus heat production, human energy expenditure may depend both upon work output and thermogenesis; the latter factor being quite variable, depending on energy intake. In his review of the medical obesity literature, Mann[19] states, "The energy-balance formulation has at least three elements—intake, thermogenesis, and work expenditure (p. 180)."

Recent medical investigations have implicated brown adipose tissue (BAT) (Brown adipose tissue appears brown because of the high cytochrome concentration. It is generally located in the thoracic and cervical regions of the back.) as the organ primarily involved in thermogenic metabolic adaptation. The evidence for this connection will be reviewed subsequent to a description of three types of thermogenesis.

TYPES OF THERMOGENESIS

Shivering Thermogenesis

Perhaps the most familiar means of heat production is shivering thermogenesis. As skeletal muscle randomly contracts, adenosine tri-phosphate (ATP) supplies are depleted. In order to restore ATP supplies, mitochondrial respiration increases which results in heat production because of the exothermic (heat yielding) nature of the reactions.[22] Thus, shivering thermogenesis is a means of maintaining body temperature in a cold environment.

Non-shivering Thermogenesis

As an alternative to the uncomfortable and mechanically restrictive act of shivering, many mammals are capable of non-shivering thermogenesis (NST). NST can be found in new-born mammals and also in mammals adapted to living in a cold environment and in hibernating animals.

It is evident that BAT is a functional organ involved in NST. Nicholls[23] cites several investigations showing that BAT "is present in all mammals capable of NST (pp. 2, 3)." Foster and Frydman[24] conclude that although BAT accounts for only one or two percent of body weight in the cold-adapted rat, it accounts for as much as 60% of NST.

There is a model in the medical literature to account for the rapid heat production by BAT.[23] Mitchell's[25] chemiosmotic theory postulates strict coupling between demand for ATP and respiratory chain activity of the mitochondria. The respiratory chain (and thus heat production) is only active when ATP is needed. Thus ATP production and heat production (via the respiratory chain) must occur concurrently according to Mitchell's model. If ATP is not needed,

then heat will not be produced. Nicholls[23] has suggested that an uncoupling model operates in BAT which can produce heat via the respiratory chain even in the absence of a need for ATP.

The coupling theory of Mitchell is represented in Figure 2. The product of the respiratory chain (RC) is the expulsion of hydrogen (H^+) ions from the mitochondria. Once the potential difference across the mitochondrial membrane is sufficiently high, no more protons can be extruded, causing a cessation of the respiratory chain. This potential across the membrane can be relieved by the H^+ ions reentering the mitochondria through a translocase enzyme (TL). Concurrent to proton reentry, ATP is made from adenosine diphosphate (ADP), being fueled by the energy provided by relieving the potential difference. Once the potential is relieved, the respiratory chain can continue, resulting in heat production.

Nicholls has proposed the existence of "proton leaks," called proton conductance pathways, in BAT mitochondria which do not exist in other tissue. According to this model, instead of coming back into the mitochondria through the translocase enzyme, hydrogen ions can enter through the conductance pathway (CP) without generating ATP. This provides for a mechanism of continued respiratory chain activity without the coupling of ATP production (see Figure 3). Thus, the BAT can produce heat rapidly without being checked by energy need.

Nicholls draws support for his theory by citing, among others, a study by Smith, Roberts, & Hittelman[26] showing mitochondrial respiration without ATP production in BAT of rats, and by his own study[27] demonstrating proton extrusion in BAT mitochondria of hamsters (indicating the link between respiration and proton extrusion is not broken in BAT; rather, a later link must be broken, such as the one suggested in the uncoupling model). A second mechanism of BAT activity has been suggested[28,29] which involves the protein

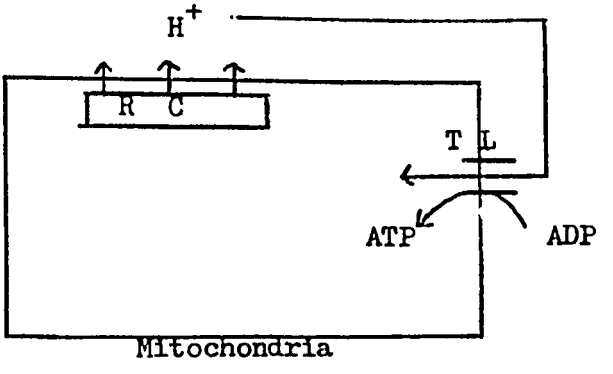

Figure 2: Mitchell's chemiosmotic theory

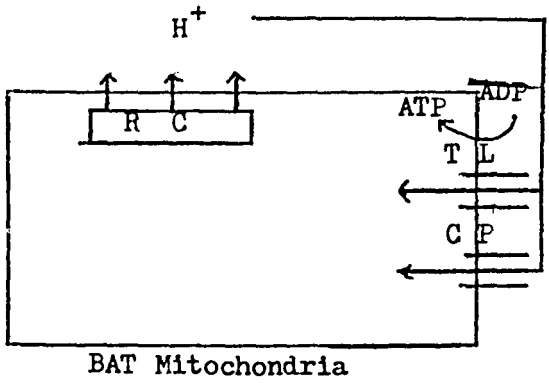

Figure 3: Nicholls's uncoupling model

Na^+-K^+-ATPase. This mechanism has been supported by one study[30] in which a strong correlation was found between BAT Na^+-K^+-ATPase activity and resting oxygen consumption.

The response of BAT in NST is mediated by catecholamines.[31] Within one minute of noradrenaline binding to the adipose cell membrane, the breakdown of lipids (Noradrenaline binds and increases cyclic-AMP concentrations[32-34] which in a cascade series activates hormone sensitive lipase.[35] A rapid release of free fatty acids[36] and glycerol[33] is then observed with fatty acid oxidation simultaneously stimulated.[36]) and mitochondrial respiration increase.[34,36-38] In addition to this acute sympathetic nervous system response in NST, there is a long-term adaptive process which may be due to an increase in BAT mass.[39]

Diet-induced Thermogenesis

Metabolic adaptation of heat production due to energy intake is known as diet-induced thermogenesis (DIT). For example, Rothwell and Stock[40] fed an experimental group of rats 80% more calories than controls, but the former group gained only 27% more weight. Concurrent increases in oxygen consumption (indicative of heat production since O_2 is a component of the respiratory chain) were noted for the experimental group.

As was previously noted, DIT has been suggested as an important third variable in the energy equation. The relevance of DIT to the understanding of weight management is intimated by findings that genetic obesity in mice is at least partly due to a failure of DIT.[41,42]

While the role of BAT in NST is well established, its role in DIT has only recently been studied. It now appears that BAT may be involved in DIT via the same proton conductance mechanism with which it contributes to NST.[43] Evidence for this connection will be reviewed next.

BROWN ADIPOSE TISSUE IN DIET-INDUCED THERMOGENESIS

Although the existence of BAT has been known for many years, only recent attempts have been made to delineate the role of BAT in DIT. These studies will first be reviewed, then the implications of the role of BAT in DIT and obesity will be discussed.

BAT Mass and Oxygen Consumption Studies

Although rats are typically able to precisely control food intake to maintain normal developmental body weight, Rothwell and Stock[40] were able to rapidly increase rats' body weight by introducing four new palatable food items each day (cafeteria diet). All animals in the cafeteria-fed group showed hyperphagia, but the degree of obesity differed among animals. The experimenters interpreted this differential obesity as anecdotal evidence for variations of thermogenesis among animals.

Resting oxygen consumption was 20-30% higher in cafeteria animals, showing increased thermogenesis. This increased thermogenesis persisted when animals were taken off cafeteria feeding despite marked hypophagia. Only as body weights declined to normal did the oxygen consumption decline to the control level.

Effects of noradrenaline injections also differed between groups. The thermogenic effect (increase in resting oxygen consumption) in cafeteria animals was two times what it was in controls. It was also noted that the interscapular temperature increased after the injection in the cafeteria animals, but not in the control animals. This indicates that the interscapular region (where BAT is typically located) was either receiving an elevated blood flow or was producing more heat or both.

After 21 days, the animals were sacrificed and brown fat mass was determined. Mass of the BAT in cafeteria animals was more than twice that of controls. While the composition of BAT in both groups was similar, the cafeteria-fed group yielded BAT which was much more sensitive to noradrenaline. Among cafeteria animals, resting oxygen consumption correlated highly with interscapular BAT mass ($r = 0.8$; $p < .001$) while the same correlation with control animals was not significant.

In summary, Rothwell and Stock[40] showed that cafeteria-fed animals showed increased thermogenesis, increased thermogenic sensitivity to noradrenaline, increased BAT mass, and a strong linear relationship between BAT mass and thermogenesis.

In a subsequent experiment, Rothwell and Stock[39] introduced a second independent variable into a similar experimental design. Cafeteria versus stock diet was crossed with cold climate (4°C) or warm climate (24°C) conditions. In effect, this design discriminates between NST (for cold-adapted animals) and DIT (for cafeteria-fed animals) and the interaction of the two (cold-adapted, cafeteria-fed animals).

Results showed that thermogenesis (as measured by resting oxygen consumption) was highest in the cold-adapted, cafeteria-fed group (DIT and NST), roughly equivalent in the warm-adapted cafeteria group (DIT) and the cold-adapted stock-fed group (NST), and lowest in the warm-adapted, stock-fed group (control). A similar pattern was found for sensitivity to noradrenaline and for BAT mass in sacrificed animals. Rothwell and Stock[39] conclude that DIT and NST are associated with BAT in a similar way, and that the effects of the two forms of thermogenesis are additive.

Glick, Teague, and Bray[44] demonstrated that oxygen consumption and BAT mass can be influenced by a single meal (an increase in thermogenesis following a meal, called the specific dynamic effect, has been observed for many years, but the organ responsible has been unclear). Rats in an experimental group and a control group were exposed to an identical dietary regime for two weeks. On the experimental day, the former group was given access to a 2½ hour meal while the control group did not have access to food.

The results implicated BAT as an important organ in the specific dynamic effect. BAT weighed 38% more in meal-fed animals than in controls, and the oxygen consumption of BAT for the experimental animals was twice that of controls after controlling for the increased BAT mass.

Table 1: Rothwell & Stock's (1980) experimental design crossing the effects of non-shivering thermogenesis (NST) and diet-induced thermogenesis (DIT).

	Stock	Cafeteria
cold adapted	NST	NST DIT
warm adapted	Control	DIT

Rothwell and Stock[39,40] have implicated BAT as the important tissue in both NST and DIT. Glick et al.[44] have demonstrated that the same tissue may be important in the specific dynamic effect.

Blood Flow Studies

Thurlby and Trayhurn[45] compared blood flow to BAT of a strain of genetically obese mice (ob/ob) to that of lean mice. The amount of blood flowing to the tissue is a measure of thermogenesis because the oxygen needed for thermogenesis (mitochondrial respiration) is carried by the blood. While there were no major differences under basal conditions, marked differences were noted with noradrenaline administration. BAT of lean mice received more blood than BAT of obese mice. Thurlby and Trayhurn estimate that 93% of the diminished metabolic response to noradrenaline in obese mice can be explained by lower oxygen consumption of BAT. They conclude that there is "no evidence to implicate any other tissue (p. 200)."

Rather than using genetically obese animals as Thurlby and Trayhurn did, Rothwell and Stock[46] investigated blood flow to BAT of cafeteria-fed and stock-fed animals. While they found no difference between groups in blood flow to other tissues, the cafeteria-fed groups did show more blood flow to BAT than did the stock-fed group, especially under noradrenaline stimulation (Table 2). Rothwell and Stock[46] conclude that "the present results indicate that BAT can account for all of the enhanced thermogenic response of cafeteria rats to noradrenaline (p. 240)."

Hypothalamus Studies

The studies reviewed so far have not only suggested that BAT differs in quantity depending upon intake, but have also suggested that BAT differs in its reactivity to sympathetic nervous system stimulation. Several studies have attempted to investigate the relationship between BAT activity and the hypothalamus, a brain structure previously implicated for its role in obesity.[47]

Table 2: Rothwell & Stock's (1981) results of blood flow to BAT in percentage of cardiac output.

	Stock	Cafeteria
saline	1 %	2.2 %
NA	7 %	15.5 %

Perkins, Rothwell, Stock, and Stone[48] applied electrical stimulation to the ventromedial hypothalamus (VMH) of rats and measured interscapular BAT temperature concurrently. They found that an increased temperature accompanied VMH stimulation. From their data and past research, Perkins et al. concluded that the VMH may serve the dual functions of reducing food intake (hypophagia) and stimulating thermogenesis.

Shimazu and Takahashi[49] noted an increased turnover of lipids in BAT, but not white adipose tissue, with electrical stimulation of the VMH in rats. These investigators reported that BAT has adrenergic fibers connected so that it responds to sympathetic innervation. In contrast, white adipose tissue has no such fibers except those related to blood vessels.

Seydoux, Rohner-Jeanrenaud, Assimacopoulos-Jeannet, Jeanrenaud, and Girardier[50] found that rats with VMH lesions had metabolically less reactive BAT to nerve stimulation and noradrenaline than controls. From their data, they suggest that obesity in rodents may be due to functional disconnection of BAT from neural control.

These studies provide evidence for a functional relationship between BAT and the central nervous system. Specifically, catecholamines, BAT, and the hypothalamus appear to be interrelated in the control of thermogenesis.

GDP Binding Studies

Nicholls's[23] model of BAT activity is based on the premise that there are conductance pathways for protons in the mitochondrial membrane of BAT. The number of these pathways is thought to be proportional to the heat producing capacity of the tissue. Guanosine di-phosphate (GDP) and other puridine nucleotides bind to the membrane at a position which presumably blocks the conductance pathway.[51,52] By measuring the amount of GDP binding to the membranes, an estimate of the relative number of conductance pathways, and thus uncoupled thermogenic capacity, can be arrived at.

Brooks et al.[51] used the GDP binding procedure on cafeteria- and stock-fed rats. As expected, the cafeteria-fed animals showed higher GDP binding, indicating an increase in proton conductance pathways. A similar increase is observed in cold-adapted animals.[53]

In contrast, genetically obese mice bind less GDP than controls.[54] This is consistent with the lower body temperature[42] and the decreased metabolic rate[55] of the genetically obese rodent observed at cold temperatures relative to non-obese rodents. In fact, genetically obese mice cannot be readily cold-adapted to 4° C because they die after 3 hours of the cold exposure.[56] The decreased GDP binding suggests a defect in BAT thermogenesis in these obese rodents.

Hogan and Himms-Hagen[52] first acclimated obese mice to 14° C for 2 weeks, then successfully acclimated the same mice to 4° C. GDP binding at 4° C in the 14° C adapted animals was increased 3-fold from baseline values. The results of this study imply that the successful adaptation of obese mice to 4° C was due to an increased thermogenic capacity of BAT achieved during the intermediated cold adaptation at 14° C.

The GDP binding study results are consistent with expectation for both cafeteria-feeding studies (DIT) and cold-adaptation studies (NST). The common tie of NST and DIT to BAT is again implicated.

DISCUSSION

Table 3 summarized the studies reviewed. Three lines of evidence argue for commonalities in NST and DIT. First, Rothwell and Stock[39] showed that increased oxygen consumption (measure of thermogenesis) was observed in cold-adapted animals (NST) as well as cafeteria-fed animals (DIT). Similar increases in oxygen consumption were noted for cafeteria-fed animals by Rothwell and Stock in an earlier study.[40] Glick et al.[44] found increased oxygen consumption after a single meal and concluded that the specific dynamic effect and DIT "may be one phenomenon (p. 1126)."

Table 3 -- Studies of BAT in DIT

Study	Subjects	Experimental Condition	Results
BAT mass & O_2 uptake			
Rothwell & Stock (1979a)	Rats	Cafeteria-fed	Increased O_2 uptake Increased sensitivity--NA Increased BAT mass
Rothwell & Stock (1980)	Rats	Cafeteria-fed Cold-adapted	as above for both experimental conditions
Glick et al. (1981)	Rats	Single meal fed	Increased O_2 uptake Increased BAT mass
Blood flow			
Thurlby & Trayhorn (1980)	Mice	Genetically obese	Decreased blood flow--NA
Rothwell & Stock (1981)	Rats	Cafeteria-fed	Increased blood flow Increased blood flow--NA
Hypothalamus			
Perkins et al (1981)	Rats	VMH stimulation	Increased BAT temperature
Shimazu & Takahashi (1980)	Rats	VMH stimulation	Increased BAT lipid turnover
Seydoux et al. (1981)	Rats	VMH lesion	Decreased reactivity--NA
GDP binding			
Brooks et al. (1980)	Rats	Cafeteria-fed	Increased GDP binding
Hogan & Himms-Hagen (1980)	Mice	Genetically obese Gradual cold adaptation	Increased GDP binding following 14° adaptation

Second, BAT mass is increased in cold-adapted animals.[39] Similar increases are noted in cafeteria-fed animals,[39,40] and in animals fed a single meal before being sacrificed.[44]

Third, sensitivity to noradrenaline by BAT is noted in cold-adapted animals[39] as well as in cafeteria-fed animals.[39,40,46] Taken together, these three commonalities suggest the likelihood of a common mechanism of NST and DIT. The most likely mechanism is the activity of BAT.

Further, there are implications that the BAT involvement in DIT is a relevant consideration in the etiology and maintenance of obesity. From the studies reviewed, there are three empirical connections between BAT and obesity in rodents.

First, Thurlby and Trayhurn[45] showed that genetically obese mice had a smaller proportion of the cardiac output sent to BAT when noradrenaline was administered than lean mice. This suggests a decreased thermogenesis in the obese animals. In contrast, normal rats made obese by overeating showed greater receipt of cardiac output than normal rats,[46] showing greater heat production. The genetic tendency toward obesity in rodents may be due to a failure in the capacity to metabolically adapt to excess caloric intake by "burning" the excess as heat.

Second, obese mice have fewer proton conductance pathways, as measured by GDP binding, than normal mice.[52] According to Nicholl's[23] model, this implies that the obese mice have a decrease capacity for thermogenesis. Again in contrast, cafeteria-fed animals have more pathways than normals.[51] Taken together, the cardiac output studies and the GDP binding studies suggest that some rodents avoid obesity by increasing BAT activity while others are constitutionally obese because of a decreased tendency for BAT thermogenesis.

Third, the VMH, a brain region related to obesity in past research, has been shown to affect BAT activity[48,49] and its sensitivity to noradrenaline.[50] In sum, rodent obesity is affected by the thermogenic activity of BAT which, in turn, is affected by neural stimulation.

Thus, the studies reviewed are consistent with the interpretation that DIT and NST are mediated by the same tissue, BAT, and that this tissue is relevant in the development of obesity.

> The extreme rapid development of obesity in the weanling ob/ob mouse could thus be seen as a consequence of a failure of two distinct mechanisms involved in energy balance, namely non-shivering thermogenesis and diet-induced thermogenesis, both of which work through the same end organ, brown adipose tissue (p. E308).[52]

None of the studies reviewed have included human subjects, therefore caution must be taken in making any inference for human obesity. Only one (Another study, not directly related to BAT, has shown a decreased thermogenic response to noradrenaline stimulation in obese human subjects.[57])

study has been reported which begins to extend this research to humans. Rothwell and Stock[40] gave human subjects ephedrine—an agent which increases metabolic rate—and measured skin temperature increases. The largest increases were noted in the neck and upper back, areas corresponding to BAT locations in humans.[58] Rothwell and Stock[40] report that "these findings can be interpreted as evidence for functional BAT in man (p. 34)." Of course, further research is necessary to understand the role of BAT in humans.

The insufficient results of weight management efforts aimed at intake regulation do not necessarily need to be attributed to poor adherence or to ineffective strategies. Rather, a third variable in the energy-balance equation, metabolic adaptation, may be affecting outcome. Evidence that connects thermogenesis, a commonly suggested means of metabolic adaptation, to BAT has been presented in this review. As research on BAT is extended to humans, an increased understanding of the etiology and prevention of obesity may result.

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