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Mechanisms of Energy Balance in Obesity

Mark R. McMinn
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The proper understanding of obesity requires a multifaceted approach. Behavioral considerations of eating and activity patterns do not account for the large between- and within-subjects variance associated with the energy-balance equation. Sources of adaptive and dispositional variance in metabolic rates are reviewed and suggested to be a likely source of importance for the proper conceptualization and intervention of obesity. Five proposed mechanisms of metabolic variation are reviewed with consideration of the supporting evidence for each mechanism. The generalizability of some of the proposed mechanisms is limited because of the scope of past research. However, the roles of lipoprotein lipase in fat storage and brown adipose tissue in thermogenesis are intriguing possibilities for future research with humans.

By tradition, weight management programs have focused only on one element of the energy-balance equation—that of energy intake (Wilson, 1978). It now appears that a singular approach to weight management is inadequate. Obesity is the product of intake, activity, and metabolism, each of which may be influenced by a host of psychosocial and physiological factors. As such, its understanding and its treatment are best perceived as a multifaceted endeavor (Katahn & McMinn, *in press*).

Metabolism varies within individuals, depending on energy intake and expenditure, and between individuals, which leads to dispositional tendencies toward obesity. The within-individuals variance of maintenance metabolism is an adaptive metabolic influence which is affected by energy intake and expenditure. This variance is subsequently referred to as adaptive metabolic variance. The between-individuals variance is a dispositional metabolic influence which is determined largely by heredity. This variance is subsequently referred to as dispositional metabolic variance.

Adaptive metabolic variance is evidenced by an asymptotic slowing of diet-produced weight loss over time (Stuart, Jensen, & Guire, 1979; Wooley, Wooley, & Dyrenforth, 1979). Apfelbaum, Bostsarron, and Lacatis (1971) reported that the basal metabolic rate (BMR) of subjects on a very low calorie diet (220 kcal/day) decreased from 12% to 17% within the first 15 days of the diet. Bray (1969, 1970) reported a similar 15% reduction in BMR during the first 2 weeks of caloric restriction. Flatt (1980) estimated that the actual metabolic adaptation may be in excess of 30% when the decrease in the rise of heat production that normally follows a meal is considered. Krotkiewski et al. (1980) stated that "in the long term perspective, mechanisms for the control of caloric storage, even if abnormal in obesity, seem to counteract measures aimed at altering the energy balance" (p. 1003).

An analogous metabolic adaptation is observed in human overfeeding studies (Apfelbaum et al., 1971; Miller, Mumford, & Stock, 1967; Sims et al., 1973). Caloric expenditure increases with overfeeding, so that less weight is gained than would be expected from strict energy-balance computations. It may be reasonable to assume that the same physiological mechanisms account for metabolic adaptation in both overfeeding and underfeeding, an assumption that is of significance in evaluating a current model of metabolic adaptation which is discussed later.

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Dispositional metabolic variance is evidenced by past research indicating that obesity runs in family lines (cf. Bakwin, 1973; Garn & Clark, 1976; Hartz, Giefer, & Rimm, 1977; Mueller & Reid, 1979). Of course, a familial tendency toward obesity does not necessitate the existence of a dispositional (i.e., genetic) predisposition because heredity or environment or both may contribute to familial obesity, yet several studies implicate the importance of heredity in familial obesity (Borjeson, 1976; Brook, 1977; Brook, Huntley, & Slack, 1975). Animal studies have also shown that genetically obese rodents have metabolic defects that contribute to obesity (Gruen, Hietanen, & Greenwood, 1978; Lin, Romosos, Akeru, & Leveille, 1979; Trayhurn, Thurlby, & James, 1977). After reviewing the literature on humans and animals, Greenwood, Cleary, and Hirsch (1979) concluded that some genetic tendency for human obesity is present at birth. Apfelbaum et al. (1980) presented preliminary evidence for a genetic form of obesity that is passed on by a dominant gene. A certain antigen (B18) appeared in four of five families with at least two obese siblings. In contrast, the same antigen appeared in only one of five families with one obese sibling.

Nature of the Metabolic Component

Thermogenesis systematically varies with the availability of fuel substrates. Thus, adaptive metabolic changes may be mediated by changes in the proportion of energy supplies being used to generate heat. Similarly, thermogenesis may also be a primary mechanism of genetic variation. If some individuals are born with a lower propensity toward thermogenesis than others, then more food energy would be diverted into fat storage and obesity might develop. James and Trayhurn (1976) suggested that genetically preobese individuals may be born with a tendency toward lower levels of thermogenesis. As a compensation to the decreased energy expenditure in these preobese individuals, obesity develops. Because basal metabolism increases with obesity, an equilibrium level is eventually reached at which energy intake is balanced by energy expenditure. Thus, the preobese

individual compensates for a low rate of thermogenesis by increasing body mass and, thereby, basal metabolism. Mechanisms that attribute metabolic variation to changes in heat production are herein referred to as *thermogenic mechanisms*.

Alternatively, an adaptive or genetic predisposition to obesity may be described as an increased propensity toward fat storage. Thermogenic differences might still be noticed, because energy would be "stolen" away from heat production in order to store fat in the preobese, yet such thermogenic differences would be secondary to fat storage differences. Mechanisms that attribute metabolic variation to differences in fat storage is referred to as *fat storage mechanisms*. It should be noted that both thermogenesis and fat storage may be affected by either thermogenic or fat storage mechanisms. The distinction is that thermogenic mechanisms have a primary effect on thermogenesis and only a secondary effect on fat storage. The inverse is true for fat storage mechanisms.

Five theoretical formulations of the mechanistic nature of the metabolic component of energy expenditure are considered subsequent to a description of three types of thermogenesis. Three of these mechanisms are thermogenic mechanisms, one is a fat storage mechanism, and one is both a thermogenic and a fat storage mechanism.

Types of 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 (Hochachka, 1974). Thus, shivering thermogenesis is a means of maintaining body temperature in a cold environment.

As an alternative to the uncomfortable and mechanically restrictive act of shivering, many mammals are capable of nonshivering thermogenesis. Nonshivering thermogenesis can be found in new-born

mammals and also in mammals adapted to living in a cold environment and in hibernating animals. A tissue known as brown adipose tissue "is present in all mammals capable of nonshivering thermogenesis" (Nicholls, 1979, pp. 2-3).

Metabolic adaptation of heat production due to energy intake is known as diet-induced thermogenesis. Rothwell and Stock (1979) 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 because oxygen is a component of the respiratory chain) were noted for the experimental rats.

As was previously noted, diet-induced thermogenesis has been suggested as an important variable in the metabolic component of the energy equation. The relevance of diet-induced thermogenesis in the understanding of weight management is intimated by findings that genetic obesity in mice is at least partly due to a failure of diet-induced thermogenesis (Cox & Powley, 1977; Trayhurn & James, 1978).

Glycerol Phosphate Shuttle

Mechanism. Nicotinamide adenine dinucleotide—reduced form (NADH) is a biomolecule that carries energy in the body. NADH can be oxidized in the mitochondria to yield three molecules of adenosine triphosphate (ATP) from adenosine diphosphate (ADP). The ATP can then be used in cellular work production. NADH is formed during glycolysis (the cellular breakdown of glucose) from nicotinamide dinucleotide—oxidized form (NAD^+). When supplies of NAD^+ are depleted, therefore, glycolysis halts because of a lack of that substrate. It is essential that NADH be converted back to NAD^+ so that glycolysis can continue. Mitochondrial oxidation of NADH does yield NAD^+ .

A second metabolic pathway, known as the glycerol phosphate shuttle, also serves the purpose of converting NADH back to NAD^+ for subsequent use in glycolysis. At the same time that the high-energy NADH is being converted to the lower energy NAD^+ , another molecule, flavin adenine

dinucleotide—oxidized form (FAD; low energy), is converted to the reduced form (FADH_2 ; higher energy). FADH_2 can then be oxidized in the mitochondria to produce two molecules of ATP.

So a NADH molecule has two possible routes available in order to be converted back to NAD^+ . Direct mitochondrial oxidation results in three ATP molecules. Alternatively, the energy in NADH can be transferred to FADH_2 which, in turn, is oxidized to form two ATP molecules. The former route of NADH leads to more work (three ATP) and therefore less heat than the latter route (see Figure 1). Obversely, the latter route yields more heat.

The glycerol phosphate shuttle functions as a thermogenic mechanism in the manner described above. The shuttle also serves as a source of fat storage variance. During the glycerol phosphate shuttle, dihydroxyacetone is first converted to glycerol 3-phosphate. The glycerol 3-phosphate may then be converted back to dihydroxyacetone at the mitochondrial membrane. Glycerol 3-phosphate is also a precursor for triglyceride (fat) formation, however. Therefore, a glycerol 3-phosphate molecule has two possible routes: to a mitochondrion to continue in the shuttle pathway or to fat storage (see Figure 2).

Dispositional metabolic variance. By measuring enzyme levels, Galton and Bray (1967) inferred an increased availability of glycerol 3-phosphate for triglyceride formation in obese subjects. The study was only suggestive of a possible genetic difference in the obese because it was a retrospective study and therefore could have been influenced by the adaptive changes of obesity. The investigators noted that causation should not be inferred from their results.

The possible role of the glycerol phosphate shuttle in dispositional metabolic variance has not been followed up with other reported research. Largely, this may reflect the methodological difficulties of a relevant prospective study.

Adaptive metabolic variance. Evidence has also been reported that implicates the role of the glycerol phosphate shuttle in adaptive metabolic variance. Bray (1969) observed metabolic adaptation in obese

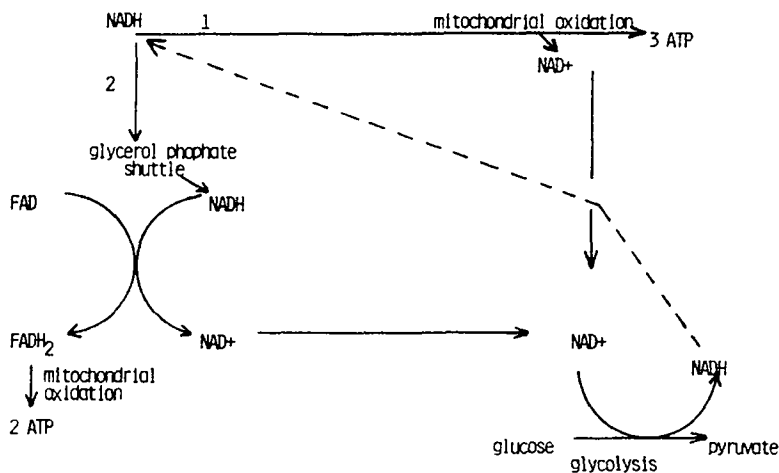


Figure 1 Two alternate routes for NADH. (High work results if NADH is directly oxidized to form ATP. Greater thermogenesis results if the energy in NADH is first transferred to FADH_2 which is, in turn, oxidized to 2 ATP. NADH = nicotinamide adenine dinucleotide—reduced form; ATP = adenosine tri-phosphate; NAD^+ = nicotinamide dinucleotide—oxidized form; FAD = flavin adenine dinucleotide—oxidized form; FADH_2 = reduced form of FAD.)

subjects on a low-calorie diet. Enzyme measurements indicated that the activity of the glycerol phosphate shuttle was reduced concurrent with metabolic adaption. That is to say, NADH was presumably using the energy-efficient route of direct mitochondrial oxidation, and thermogene-

sis was reduced. Moreover, there is a later report of thyroid hormone, an agent known to increase thermogenic activity, administered to subjects, with the result of increased glycerol phosphate shuttle activity (Bray, 1970), a result consistent with the model suggested above.

The glycerol phosphate shuttle in obesity has received little or no research attention since Bray's reports in 1969 and 1970. Although the mechanism may play a role in metabolic adaptation, it is also possible that the magnitude of thermogenic change due to the glycerol phosphate shuttle is minimal.

Brown Adipose Tissue

Another thermogenic mechanism for the metabolic component of energy balance has been suggested recently (see McMinn, 1981, for review). Brown adipose tissue¹ has been implicated as the organ primarily involved in rat thermogenesis (James, Trayhurn, & Garlick, 1981). Foster and Frydman (1978) concluded that although brown adipose tissue accounts for only 1% or 2%

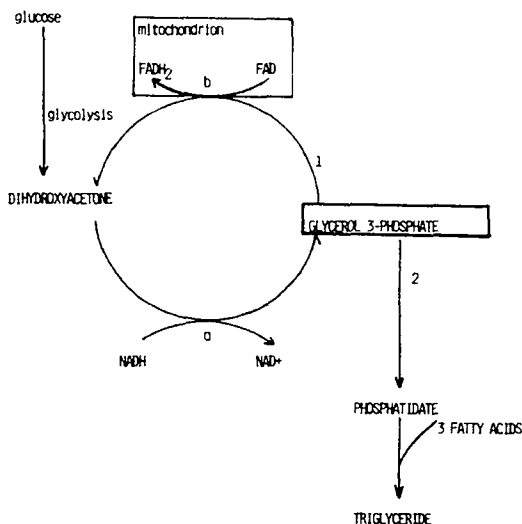


Figure 2 Two pathways of glycerol 3-phosphate. (One pathway leads to the transfer of energy from NADH to FADH_2 . The other, more active in obese subjects, leads to fat production. See caption to Figure 1 for abbreviations.)

¹ Brown adipose tissue appears brown because of the high cytochrome concentration in the tissue. It is located in the thoracic and cervical regions of the back (Heaton, 1972).

of body weight in the cold-adapted rat, it accounts for as much as 60% of nonshivering thermogenesis. A series of animal studies has demonstrated a connection between thermogenesis, obesity, and brown adipose tissue.

Mechanism. A model in the medical literature accounts for the rapid heat production of brown adipose tissue (Nicholls, 1979). This model is a variation of a more general model proposed by Mitchell (1976). Mitchell's chemiosmotic theory is meant to apply to virtually all cells, whereas Nicholls's model applies only to brown adipose tissue cells. An understanding of Mitchell's chemiosmotic theory is necessary before any discussion of Nicholl's proton conductance model.

The mitochondria of all cells are capable of ATP production through a chain process called oxidative phosphorylation. During this process, heat is released, and ATP is produced from the lower energy ADP molecule. Mitchell's chemiosmotic theory postulates strict coupling between heat production and ATP production. In other words, only as ADP molecules are available for conversion to ATP will the respiratory chain be active. This provides a control mechanism for the activity of oxidative phosphorylation. If no energy is needed (i.e., the ADP is already converted to ATP), then oxidative phosphorylation will cease.

During the respiratory chain activity, several hydrogen atoms (H^+) are expelled from the mitochondria. As more atoms are expelled, the potential difference across the membrane increases. Once the potential difference across the membrane is sufficiently high, no more protons can be extruded, which causes a cessation of oxidative phosphorylation. This potential across the membrane can be relieved only by the H^+ ions reentering the mitochondria through the translocase enzyme. The translocase enzyme accepts H^+ passage only if an ADP molecule is also available. This is so because concurrent with the proton reentry, ATP is made from ADP, being fueled by the energy provided by relieving the potential across the membrane. Once the potential difference is relieved, the respiratory chain can continue, which results in more heat production.

Nicholls (1979) proposed the existence of "proton leaks," called proton conductance pathways, in brown adipose tissue mitochondria which do not exist in other tissues. According to this model, instead of coming back into the mitochondria through the translocase enzyme, hydrogen ions can enter through the conductance pathways without generating ATP. This provides for a mechanism of continued respiratory chain activity without the coupling of ATP production. Thus, the brown adipose tissue can produce heat rapidly without being checked by energy needs (ADP supplies).

Nicholls drew support for his theory by citing, among others, a study showing mitochondrial respiration without ATP production in brown adipose tissue of rats (Smith, Roberts, & Hittelman, 1966) and another study demonstrating proton extrusion in brown adipose tissue mitochondria of hamsters (Nicholls, 1974). This latter study indicated that the link between respiration and proton extrusion is not broken in brown adipose tissue; rather, a later link must be broken, such as the one suggested in the uncoupling model.

Since Nicholls's model of brown adipose tissue activity is based on the premise that there are conductance pathways for protons in the mitochondrial membranes of brown adipose tissue, the number of these pathways is thought to be proportional to the heat-producing capacity of the tissue. Guanosine di-phosphate (GDP) binds to the membrane at a position that apparently blocks the conductance pathway (Brooks, Rothwell, Stock, Goodbody, & Trayhurn, 1980; Hogan & Himms-Hagen, 1980). By measuring the amount of GDP binding to the membranes, an estimate of the relative number of conductance pathways, and thereby thermogenic capacity, can be arrived at.

Dispositional metabolic variance. Recent investigations have implicated a possible role of brown adipose tissue in the dispositional metabolic variance of obesity in rodents. Several studies have been designed to investigate the relation between brown adipose tissue activity and the hypothalamus, a brain structure previously implicated for its role in obesity (Bray & York, 1979).

Perkins, Rothwell, Stock, and Stone (1981) applied electrical stimulation to the ventromedial hypothalamus of rats and measured interscapular brown adipose tissue temperature concurrently. They found that an increased temperature accompanied ventromedial hypothalamic stimulation. From their data and those of past research, Perkins et al. concluded that the ventromedial hypothalamus may serve the dual functions of reducing food intake and stimulating brown adipose tissue thermogenesis. It should be noted that the role of the ventromedial hypothalamus in causing satiety is not accepted by all researchers in the area.

Other investigators noted increased lipid metabolism in brown adipose tissue, but not in white adipose tissue, with electrical stimulation of the ventromedial hypothalamus in rats (Shimazu & Takahashi, 1980). These investigators reported that brown adipose tissue has adrenergic fibers connected to it, so that it responds to sympathetic nervous system innervation. In contrast, white adipose tissue has no such fibers except those related to blood vessels.

Also, rats with ventromedial hypothalamus lesions have been found to have brown adipose tissue that is metabolically less reactive to nerve stimulation and noradrenaline than that of control rats (Seydoux, Rohner-Jeanrenaud, Assimacopoulos-Jeannet, Jeanrenaud, & Girardier, 1981). From their data, the investigators suggested that obesity in rodents may be due to a functional disconnection of brown adipose tissue from neural control.

The above studies demonstrate a relation between brown adipose tissue and the sympathetic nervous system which differs in lean and genetically obese rodents. Noradrenaline, a sympathetic nervous system activator, has also been empirically linked to brown adipose tissue and genetic obesity. Thurlby and Trayhurn (1980) compared blood flow to brown adipose tissue of a strain of genetically obese (*ob/ob*) mice 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. Whereas there were no major differences under basal con-

ditions, marked differences were noted with noradrenaline administration. Brown adipose tissue of lean mice received more blood than brown adipose tissue of obese mice. Thurlby and Trayhurn estimated that 93% of the diminished metabolic response to noradrenaline in obese mice can be explained by lower oxygen consumption of brown adipose tissue. They concluded that there is "no evidence to implicate any other tissue" (p. 200).

These studies provide evidence for a functional relation between brown adipose tissue and the central nervous system. Specifically, catecholamines, brown adipose tissue, and the hypothalamus appear to be interrelated in the control of thermogenesis in rodents.

In theory, the site responsible for reduced sympathetic innervation of brown adipose tissue could be either the central nervous system or the brown adipose tissue itself. The former possibility has not been researched. Some evidence exists which indicates that the brown adipose tissue is abnormal in obese rodents. Guanosine diphosphate binding studies (described earlier) have indicated that genetically obese mice have fewer brown adipose tissue proton conductance pathways than do controls (Himms-Hagen & Desautels, 1978; Hogan & Himms-Hagen, 1980). Accordingly, obese rodents have a decreased metabolic rate relative to controls (Boissonneault, Hornshuh, Simons, Romsos, & Leveille, 1978) and are less able to adapt to a cold environment (Davis & Mayer, 1954). Taken together, these results suggest a defect of brown adipose tissue thermogenesis in obese rodents.

From the studies reviewed so far, there are three empirical connections between brown adipose tissue and genetic obesity in rodents. First, Thurlby and Trayhurn (1980) showed that genetically obese mice had a smaller proportion of the cardiac output sent to brown adipose tissue when noradrenaline was administered than did 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 did lean rats (Rothwell & Stock, 1981a). The genetic tendency toward obes-

ity in rodents may therefore be due to a failure in the capacity to metabolically adapt to caloric intake by "burning" the excess as heat.

Second, obese mice have fewer proton conductance pathways, as measured by GDP binding, than normal mice (Himms-Hagen & Desautels, 1978; Hogan & Himms-Hagen, 1980). According to Nicholl's (1979) model, this implies that obese mice have a decreased capacity for thermogenesis. Taken together, the cardiac output studies and the GDP binding studies suggest that some rodents are constitutionally obese because of a decreased tendency for brown adipose tissue thermogenesis.

Third, the ventromedial hypothalamus, a brain region related to obesity in past research, has been shown to affect brown adipose tissue activity (Perkins et al., 1981; Shimazu & Takahashi, 1980) and its sensitivity to noradrenaline (Seydoux et al., 1981). In sum, rodent obesity is affected by the thermogenic activity of brown adipose tissue which, in turn, may be affected by the sympathetic nervous system.

Adaptive metabolic variance. Brown adipose tissue has also been implicated for its role in adaptive metabolic variance in obesity. In order to evaluate the effects of brown adipose tissue in adaptive metabolic changes, Rothwell and Stock (1979) were able to rapidly increase rats' body weights 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.

Resting oxygen consumption (a measure of metabolic rate) was higher in cafeteria-fed animals than in stock-fed controls, a result showing increased thermogenesis in the cafeteria-fed animals. This metabolic adaptation to overfeeding 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 levels.

Effects of noradrenaline injections also differed between groups. The thermogenic effect (increase in resting oxygen consumption) in cafeteria-fed animals was twice that in controls. It was also noted that the interscapular temperature increased after

the injection in the cafeteria-fed animals, but not in the control animals. This indicated that the interscapular region (where brown adipose tissue is typically located) was either receiving an elevated blood flow or was hyperthermogenic, or both.

After 21 days, the animals were sacrificed, and brown fat mass was determined. Mass of the brown adipose tissue in cafeteria-fed animals was more than twice that of controls. Although the composition of brown adipose tissue in both groups was similar, the cafeteria-fed group yielded brown adipose tissue that was much more sensitive to noradrenaline. Among cafeteria-fed animals, resting oxygen consumption correlated highly with interscapular brown adipose tissue mass ($r = .8$), whereas the same correlation with control animals was not significant.

Rothwell and Stock (1980) later 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 discriminated between nonshivering thermogenesis (for cold-adapted animals) and diet-induced thermogenesis (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, roughly equivalent in the warm-adapted, cafeteria-fed group and the cold-adapted, stock-fed group, and lowest in the warm-adapted, stock-fed group (control). A similar pattern was found for sensitivity to noradrenaline and for brown adipose tissue mass in sacrificed animals. Rothwell and Stock (1980) concluded that diet-induced thermogenesis and nonshivering thermogenesis are associated with brown adipose tissue in a similar way and that the effects of the two forms of thermogenesis are additive.

Glick, Teague, and Bray (1981) demonstrated that metabolic activity and brown adipose tissue 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 those in a control group were exposed to an identical dietary regimen for 2 weeks. On the experimental day, the former group was given access to a 2.5-hr meal, while the control group did not have access to food. The results implicated brown adipose tissue as an important organ in the metabolically adaptive specific dynamic effect. Brown adipose tissue weighed 38% more in meal-fed animals, on the average, than in controls. The oxygen consumption of brown adipose tissue for the experimental animals was twice that for controls even after controlling for the increased brown adipose tissue mass.

Rothwell and Stock (1981a) also investigated metabolic activity by measuring blood flow to brown adipose tissue of cafeteria-fed and stock-fed animals. Blood flow is a measure of metabolic activity because the mitochondria need the oxygen carried by the blood in order to oxidize high-energy substrates. The investigators reported no difference between groups in blood flow to other tissues, but the cafeteria-fed group did show more blood flow to brown adipose tissue than did the stock-fed group, especially in response to noradrenaline stimulation (see Table 1). Rothwell and Stock (1981a) concluded that "results indicate that brown adipose tissue can account for all of the enhanced thermogenic response of cafeteria rats to noradrenaline" (p. 240).

Finally, Brooks et al. (1980) used the GDP binding procedure on cafeteria- and stock-fed rats. As expected, the cafeteria-fed animals showed higher GDP binding, a result indicating an increase in proton conductance pathways and, therefore, in thermogenesis. A similar increase was observed in cold-adapted animals (Desautels, Zaror-Behrens, & Himms-Hagen, 1978).

So the role of brown adipose tissue in adaptive metabolic thermogenesis is potentially quite important. Increased thermogenesis was noted in rats exposed to excessive caloric intake over a prolonged period (Rothwell & Stock, 1979, 1980, 1981a) and for a single meal (Glick et al., 1981). Concurrent increases in brown adipose tissue mass (Rothwell & Stock, 1979, 1980), brown adipose tissue sensitivity to noradrenaline (Rothwell & Stock, 1979), and

Table 1
Blood Flow to Brown Adipose Tissue With Saline or Noradrenaline Injections

Injection	% cardiac output	
	Stock-fed subjects	Cafeteria-fed subjects
Saline	1	2.2
Noradrenaline	7	15.5

Note This is a tabular presentation of the results reported by Rothwell and Stock (1981a).

proton conductance pathways (Brooks et al., 1980) have been reported as well. Moreover, the nature of brown adipose tissue metabolic adaptation is similar or identical to the nature of heat production (nonshivering thermogenesis) by an animal in a cold environment (Rothwell & Stock, 1980). It is apparently the thermogenic activity of brown adipose tissue that is altered in both cold adaptation and metabolic adaptation in rats (Himms-Hagen, 1979).

These results suggest that brown adipose tissue is involved in the metabolic adaptation of overfed rats. No studies have yet been reported that consider the effects on brown adipose tissue of caloric restriction rather than caloric excess. It seems reasonable to predict that brown adipose tissue activity and mass would decrease with a negative metabolic adaptation in the same way as they increase with positive metabolic adaptation. More research is needed to understand the role of brown adipose tissue in metabolic adaptation to caloric deficits.

None of the studies reviewed have included human subjects; therefore caution should be exercised in making inferences to human metabolic adaptation (Rothwell & Stock, 1981b). Only one study has been reported that begins to extend this research to humans.² Rothwell and Stock (1979) gave human subjects ephedrine—an agent that increases metabolic rate—and measured skin-temperature increases. The largest increases were noted in the neck and upper back, areas corresponding to brown

² Another study, not directly related to brown adipose tissue, showed a decreased thermogenic response to noradrenaline stimulation in obese human subjects (Jung, Shetty, James, Barrand, & Callingham, 1979).

adipose tissue locations in humans (Heaton, 1972). Rothwell and Stock (1979) reported that "these findings can be interpreted as evidence for functional brown adipose tissue in man" (p. 34). Of course, further research is necessary to understand the role of brown adipose tissue in humans.

Sodium, Potassium, -ATPase

Another proposed thermogenic mechanism for the metabolic component involves the action of sodium, potassium, -ATPase ($\text{Na}^+, \text{K}^+, \text{-ATPase}$), the enzyme responsible for the action of the sodium pump (see McMinn, 1982/83, for review). Estimates of the proportion of body thermogenesis dependent upon the sodium pump range from 5% (Chinet, Clausen, & Girardier, 1977) to 40% (Edelman, 1976).

The activity of the sodium pump as it relates to obesity has been studied predominantly in rodents. As is the case with brown adipose tissue research, there is some question of the generalizability of $\text{Na}^+, \text{K}^+, \text{-ATPase}$ studies to human subjects.

Dispositional metabolic variance. The amount of $\text{Na}^+, \text{K}^+, \text{-ATPase}$ enzyme, as measured by a technique with ouabain binding,³ is reduced in the skeletal muscle of obese (*ob/ob*) mice relative to lean controls (Lin, Romsos, Akera, & Leveille, 1978). No differences in $\text{Na}^+, \text{K}^+, \text{-ATPase}$ levels were observed in the livers and kidneys of obese and lean mice in one study (Lin, Vander Tuig, Romsos, Akera, & Leveille, 1979), although another study demonstrated that obese mice had lower $\text{Na}^+, \text{K}^+, \text{-ATPase}$ activities in these tissues (York, Bray, & Yukimura, 1978).

From these studies, two points are important to note. First, obesity in mice may be related in some way to the lower thermogenic activity of the sodium pump in muscle. Each time the $\text{Na}^+, \text{K}^+, \text{-ATPase}$ enzyme operates, three molecules of sodium are removed from the cell, two molecules of potassium enter the cell, and one molecule of ATP is converted to ADP. The overall reaction is heat yielding and therefore contributes to thermogenesis. For obese mice to have reduced amounts of the $\text{Na}^+, \text{K}^+, \text{-ATPase}$ enzyme intimates a thermogenic mechanism for obesity which relates to

$\text{Na}^+, \text{K}^+, \text{-ATPase}$ activity. Second, it is noteworthy that not all tissues differed in enzyme levels between obese and lean mice. If there is a thermogenic defect related to the sodium pump, it may be manifested only in a subset of the body. The importance of this point will become clear as the research on the sodium pump in humans is subsequently reviewed.

Other studies have added support to the notion that sodium pump activity is reduced in the skeletal muscle of obese mice. Lin et al. (1981) observed lower levels of potassium and higher levels of sodium in the muscle of obese mice than in the muscle of lean mice. The sodium pump activity of the lean mice was apparently higher than that of obese mice because sodium and potassium were more distinctly separated across the cell membranes of the lean mice.

The phenotype of lean versus obese mice can be predicted with great accuracy before the obesity develops by measuring thermogenesis (Trayhurn et al., 1977). At this point in the development of mice, there are already differences in $\text{Na}^+, \text{K}^+, \text{-ATPase}$ levels of skeletal muscle which may cause the lower thermogenesis in preobese mice (Lin, Romsos, Akera, & Leveille, 1979).

Other investigators have considered the activity of $\text{Na}^+, \text{K}^+, \text{-ATPase}$ rather than the amount of enzyme in the tissue. Because ouabain binds to and inhibits the action of $\text{Na}^+, \text{K}^+, \text{-ATPase}$, Guernsey and Morishige (1979) were able to derive the activity of the sodium pump by measuring the cellular respiration that could be inhibited by ouabain. As expected, the obese mice showed lower sodium pump activity than lean mice.

From the animal studies that have been reviewed, it appears that the number of sodium pump units and the activity of the sodium pump are reduced in the skeletal muscle of obese mice. This reduction of $\text{Na}^+, \text{K}^+, \text{-ATPase}$ is apparently present at an early developmental age, even before obesity is observable.

Whereas the studies with obese (*ob/ob*)

³ Ouabain binds to $\text{Na}^+, \text{K}^+, \text{-ATPase}$. By determining that amount of ouabain binding, an estimate of the amount of $\text{Na}^+, \text{K}^+, \text{-ATPase}$ enzyme can be arrived at.

mice⁴ are quite consistent and yield straightforward conclusions, studies with humans are rare and difficult to interpret. In the studies that used human subjects to evaluate Na⁺,K⁺,ATPase activity in the obese, the investigators have come to differing conclusions.

DeLuise, Blackburn, and Flier (1980) reported evidence of decreased sodium pump activity in obese humans. Three measurements were taken on the red blood cells of each subject. Ouabain binding was used as an index of the number of Na⁺,K⁺,ATPase units. Rubidium transport was used to measure potassium influx into red cells, and intracellular electrolytes were measured to assess sodium and potassium levels. Ouabain-binding results showed that obese subjects had 22% fewer sodium pump units than controls and that the amount of Na⁺,K⁺,ATPase enzyme correlated negatively with percentage of ideal body weight to account for 31% of the variance. Red cells from obese subjects took up less rubidium than red cells from lean subjects, a result indicating less activity of the sodium pump. Finally, intracellular sodium levels were higher in obese subjects than in lean subjects. The higher sodium levels also indicated lower sodium pump activity.

These results were interpreted as possible evidence for a metabolic defect of thermogenesis in obese subjects due to reduced activity of the sodium pump. However, the study has been criticized on several grounds since its publication. One subsequent study did replicate the findings (Klimes, Nagulesparan, Unger, Arnoff, & Mott, 1982), but another did not (Mir, Charalambous, Morgan, & Evans, 1981).

Kaji (1981) suggested that the evidence of DeLuise et al. (1980) for a reduced number of sodium pump units may be due to a lower binding affinity for ouabain in obese subjects. Others suggested that the relevant issue may not be the number of sodium pumps but rather the stoichiometry of their action (three sodium out, two potassium in, one ATP used). If, as was assumed, the stoichiometry is the same for obese and lean subjects, then the energy output (and therefore thermogenesis) depends on the

steady-state operation of the cell and not on the number of pumps doing the work (Hilton, Jones, Poston, Johnson, & Jones, 1981). In other words, the overall activity of the sodium pump may be more relevant than the number of Na⁺,K⁺,ATPase units.

Bray, Kral, and Bjorntorp (1981) compared the results of DeLuise et al. with analogous research on obese (*ob/ob*) mice. Bray et al. noted that there is evidence for fewer sodium pumps in obese mice as well as evidence for a lower resting metabolic rate and an increased sensitivity to cold. In human obesity research, however, only the sodium pump deficit has been documented. There is currently no evidence of a lower metabolic rate or an increased sensitivity to cold in obese humans, according to Bray et al. (1981). Cold tolerance may be reduced in obese subjects (Buskirk, Thompson, & Whedon, 1963). One investigation suggests that obese humans have a higher resting metabolic rate than controls because of their increased lean body mass (James, Bailes, Davies, & Dauncey, 1978). To account for this discrepancy in animal and human research, Bray et al. (1981) suggested that the red cell was an inappropriate site of sodium pump measurement. To support this assertion, they cited research showing that the activity of Na⁺,K⁺,ATPase in red cells is decreased with hyperthyroidism, which is the inversion of the response of other cells because thyroid stimulates the sodium pump in general.

Bray et al. (1981) reported a study similar to that of DeLuise et al. (1980), but instead of measuring sodium pump activity in red cells, they measured activity in liver cells. Instead of replicating the findings of Na⁺,K⁺,ATPase activity in red cells, they found more Na⁺,K⁺,ATPase activity in obese subjects than in controls. They reported a positive correlation between body mass index (weight/height squared) and sodium pump activity which accounted for 56% of the variance.

⁴It should be noted that other obese rodents (e.g., fatty rats) have normal Na⁺,K⁺,ATPase activities (Bray, York, & Yukimura, 1978).

So evidence from human obesity and sodium pump research is inconclusive. It appears to be likely that red cell sodium pump activity is dissimilar to liver sodium pump activity in obesity. If sodium pump activities throughout the human body react differently, depending on the tissue that they are part of, then the issue becomes one of determining which tissue, if any, is most responsible for thermogenic deficits in obesity and how the sodium pump of that tissue can be characterized.

Mechanism. Brown adipose tissue should be considered as a tissue potentially responsible for a great deal of thermogenesis because it is the major site of thermogenesis in mice (Thurlby & Trayhurn, 1980). Horwitz (1979) suggested that heat is produced in brown adipose tissue by the sodium pump activity itself ($\text{ATP} \rightarrow \text{ADP} + \text{P}_i + \text{heat}$) and, most important, by increased cellular respiration which is stimulated by a signal generated from the activity of the sodium pump (see Figure 3). The nature of this signal is uncertain. Nonetheless, Horwitz suggested several possibilities of what the intracellular signal may be. The signal may be the ADP molecule resulting from the sodium pump action (Path 1 in Figure 3). The ADP molecule could stimulate mitochondrial respiration by providing substrate for the translocase enzyme on the surface of the mitochondria. It will be recalled that translocase allows hydrogen ions to reenter the mitochondria while concurrently converting ADP to ATP.

Alternatively, the activity of the sodium pump may stimulate the activity of the energy-producing tricarboxylic acid cycle. As ATP levels are depleted with the action of the sodium pump, guanosine tri-phosphate (GTP) and ADP are converted to ATP and GDP by an enzyme called nucleoside diphosphokinase. The resulting GDP molecule then stimulates the action of the tricarboxylic acid cycle and thereby heat production (Path 2 in Figure 3).

A third possibility of the nature of the signal is that the sodium pump may alter alkaline levels in the cytosol (Path 3 in Figure 3) and result in altered coupling of mitochondrial respiration (i.e., heat pro-

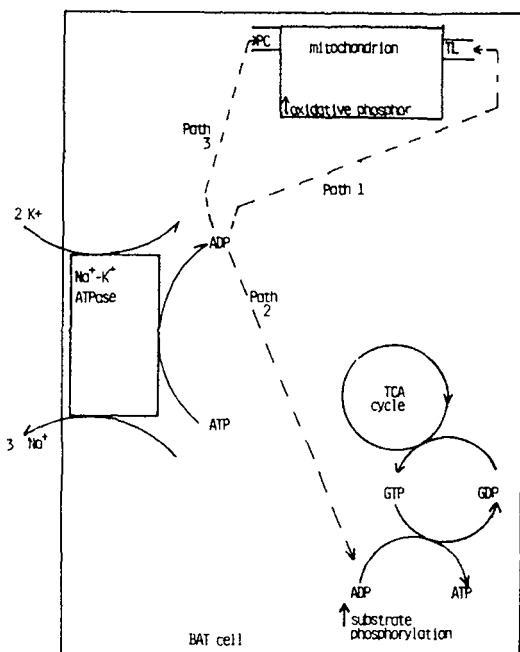


Figure 3 Intercellular signals of sodium pump that increase cellular respiration based on Horwitz's (1979) description of possible activating factors of thermogenesis in brown adipocytes. (PC = proton conductance pathway; TL = translocase enzyme; ADP = adenosine di-phosphate; ATP = adenosine tri-phosphate; TCA = tricarboxylic acid cycle; GTP = guanosine tri-phosphate; GDP = guanosine di-phosphate; BAT = brown adipose tissue.)

duction not strictly coupled to ATP needs). This latter possibility is compatible with Nicholls's (1979) model of altered coupling in brown adipose tissue mitochondria which was discussed previously.

Horwitz's model of brown adipose tissue thermogenesis can be supported in several ways. First, noradrenaline administration leads to an increase in brown adipose tissue thermogenesis concurrent with an increase in $\text{Na}^+, \text{K}^+, \text{-ATPase}$ activity (Horwitz & Eaton, 1975) and membrane depolarization. The membrane depolarization may cause the sodium pump to be activated which, in turn, may result in increased thermogenesis.

Second, ouabain inhibits cellular respiration (about 30%) and lipid breakdown (about 60%) in noradrenaline-stimulated brown adipose tissue of rats (Herd, Ham-

mond, & Hamolsky, 1973). Thus, by inhibiting the sodium pump, ouabain effectively inhibits brown adipose tissue thermogenesis in rats.

Third, Rothwell, Stock, and Wyllie (1981) found a .97 correlation between oxygen consumption (measure of cellular respiration) of rats in vivo and $\text{Na}^+, \text{K}^+, \text{ATPase}$ activity of brown adipose tissue in vitro. Taken together, these three pieces of evidence are suggestive of a relation between brown adipose tissue sodium pump activity and thermogenesis. It is unclear whether this relation holds only in rodents or holds also in humans.

Because brown adipose tissue may play an important role in obesity, the sodium pump activity of brown adipose tissue is an important issue in this area of research. Horwitz's model delineates the role of the sodium pump in brown adipose tissue, but no research has been reported that directly assesses the applicability of the model to obese and nonobese humans. The difficulties of performing such an investigation are significant and perhaps prohibitive, yet resolution of the question of the involvement of $\text{Na}^+, \text{K}^+, \text{ATPase}$ in human obesity awaits such research.

Adaptive metabolic variance. Although the effects of the sodium pump on adaptive metabolic variance of energy expenditure have not received much research attention, one study showed a two-fold increase in sodium pump activity for both lean and obese mice adapted to a cold environment (Lin, Vander Tuig, Romsos, Aker, & Leveille, 1980). Another study showed that inhibition of the sodium pump eliminates almost all thermogenesis of mice in a cold environment (Stevens & Kido, 1974). If nonshivering thermogenesis and diet-induced thermogenesis are equivalent phenomena, as is suggested by brown adipose tissue research, then diet-induced thermogenesis may also be affected by sodium pump activity. If this is the case, then $\text{Na}^+, \text{K}^+, \text{ATPase}$ may have an important role in the adaptive metabolic component.

Substrate Cycling

Mechanism. Another thermogenic mechanism that has been proposed for the

metabolic component is substrate cycling during glycolysis. Glycolysis is a multistep reaction chain that converts glucose to pyruvate, the latter being a precursor to a molecule that can enter the energy-yielding tricarboxylic acid cycle. Through glycolysis, then, glucose is converted to cellular energy. One of the early reactions in the glycolytic pathway is the conversion of fructose 6-phosphate to fructose 1,6-diphosphate. This reaction is catalyzed by phosphofructokinase.

In addition to glycolysis, the human body can also convert cellular energy back to its original form—glucose—by another pathway called gluconeogenesis. In this pathway, fructose 1,6-diphosphate is converted to fructose 6-phosphate, being catalyzed by an enzyme called fructose di-phosphatase.

As both phosphofructokinase and fructose 6-phosphate are present in the cytosol of the cell, a cycling of fructose 6-phosphate and fructose 1,6-diphosphate is possible. This cycle uses energy because phosphofructokinase utilizes an ATP molecule but produces no work because fructose 1,6-diphosphate is converted immediately back to the beginning substrate (fructose 6-phosphate).

This substrate cycling may provide two functions. First, cycling may provide a regulation of glucose metabolism in the liver (Clark, Bloxham, Holland, & Lardy, 1974). Second, the cycling oxidizes ATP without producing work, so a thermogenic function is implicated (James & Trayhurn, 1976; Newsholme, 1980).

The very limited research on substrate cycling thermogenesis has been done with bumblebees. During rest periods, bumblebees need a source of thermogenesis, because the muscle is producing very little heat. Substrate cycling in the resting bumblebee is inversely related to the environmental temperature (Clark, Bloxham, Holland, & Lardy, 1973). Thus, the greater the need for thermogenesis, the more substrate cycling is observed. The role of substrate cycling in thermogenesis has been further implicated by a study showing nearly equal activities of phosphofructokinase and fructose di-phosphatase in the resting bumblebee (Newsholme, Crabtree, Higgins, Thornton, & Start, 1972).

Dispositional and adaptive metabolic variance. The dispositional metabolic variation in substrate cycling has been intimated (James & Trayhurn, 1976), but so has adaptive variation (Newsholme, 1980). It is reasonable that genetics could predetermine the availability of fructose di-phosphatase which would, in turn, affect the rate of substrate cycling. Also, the biochemical factors that control the activity of both phosphofructokinase and fructose di-phosphatase could be genetically affected. Also, it is very reasonable to postulate that substrate cycling would be reduced if the initial substrate (glucose) is reduced, as is the case with metabolic adaptation. Moreover, the high levels of adenosine monophosphate present in a state of dietary restriction would activate phosphofructokinase and inhibit fructose diphosphatase and so decrease substrate cycling.

So it is theoretically feasible for substrate cycling to affect either the dispositional metabolic variance or the adaptive metabolic variance, or both. No research has been reported that delineates the role of substrate cycling in either component.

Finally, the amount of heat produced by substrate cycling may be insufficient to account for the wide variations observed in thermogenesis. James and Trayhurn (1976) were formerly supportive of the substrate cycling model but recently endorsed brown adipose tissue as being the site of most thermogenesis, at least in animals (James et al., 1981).

Lipoprotein Lipase

Of recent interest in the nature of the metabolic component has been the activity of the enzyme lipoprotein lipase. Adipose tissue lipoprotein lipase resides on the surface of fat cells in order to break down circulating triglycerides for storage in the cells. In other words, adipose tissue lipoprotein lipase acts to store fat.

Dispositional metabolic variance. Animal studies have demonstrated a genetic connection between obesity and adipose tissue lipoprotein lipase. Elevated levels of adipose tissue lipoprotein lipase activity have been reported both in the fatty (*fa/fa*) rat (de Gasquet, Pequignot, Lemon-

nier, & Alexiu, 1973; Gruen & Greenwood, 1981; Gruen et al., 1978) and in the obese (*ob/ob*) mouse (Rath, Hems, & Beloff-Chain, 1974). Gruen et al. (1978) reported an elevated level of lipoprotein lipase activity in preobese rats at 2 weeks of age. This was suggestive of a causal role of lipoprotein lipase elevation in obesity rather than vice versa.

Studies with human subjects have further implicated the role of adipose tissue lipoprotein lipase in obesity. Several studies have demonstrated more lipoprotein lipase activity per adipose cell among the obese than among normal human subjects (Campbell, Faibisoff, & Brodows, 1974; Pykalisto, Smith, & Brunzell, 1975; Taskinen & Nikkila, 1977). Similarly, Schwartz, Brunzell, and Bierman (1979) reported elevated levels of adipose tissue lipoprotein lipase activity in subjects with Prader-Willi syndrome—a genetic disease characterized by massive obesity. Among control subjects, there was also a positive correlation between adipose tissue lipoprotein lipase activity and percentage of ideal bodyweight. Also, Schwartz and Brunzell (1981b) reported an .87 correlation between lipoprotein lipase activity and percentage of ideal body weight in men.

Adaptive metabolic variance. Of course, these static measurements of adipose tissue lipoprotein lipase and weight do not allow one to infer causation. Studies have been reported, however, that measured changes in lipoprotein lipase activity with changes in dietary intake both retrospectively and prospectively (Schwartz & Brunzell, 1981a).

In a preliminary retrospective study, Schwartz and Brunzell (1978) measured adipose tissue lipoprotein lipase activity in men who had lost between 10% and 29% of their body weight and had maintained the loss for 4–28 months. Unlike most metabolic abnormalities in obesity, adipose tissue lipoprotein lipase had not returned to normal levels in these subjects. In fact, adipose tissue lipoprotein lipase activities in the experimental group were, on the average, 3 times greater than in the control group. The investigators suggested that there may be a genetically determined “set point” for body weight that is homeostati-

cally controlled by lipoprotein lipase activity.

Consistent with this hypothesis are the results of studies by Taskinen & Nikkila in which they found a 78% reduction of adipose tissue lipoprotein lipase activity in human nonobese subjects with the onset of a severe caloric restriction (1979) but only a 50% reduction for obese subjects (1981). Such a difference would make weight loss more difficult for the obese than for the nonobese because fat storage would remain more active in the obese.

Taskinen and Nikkila (1981) as well as other investigators (Guy-Grand & Bigorie, 1975; Persson, Hood, & Angervall, 1970) reported a decrease in adipose tissue lipoprotein lipase activity which accompanies dietary restriction. Only one prospective study has been reported, however, in which the investigators consider adipose tissue lipoprotein lipase activity after the dietary restriction was discontinued (Schwartz & Brunzell, 1981b). Obese males lost an average of 16 kg on a 600 kcal/day diet. After the diet, the average adipose tissue lipoprotein lipase activity was more than 4 times the pre-diet adipose tissue lipoprotein lipase activity (the variance in activity was quite high after weight loss). Of the 8 subjects, 7 had significantly higher activity levels of lipoprotein lipase after the weight loss than before. Four subjects were followed for 8–14 months. Three of these subjects had regained their weight losses and had adipose tissue lipoprotein lipase activities that were near their pre-diet levels. The remaining subject had kept off most of the weight lost during the program but continued to have a marked elevation in adipose tissue lipoprotein lipase activity.

Thus, there is evidence from both animal and human studies that points to a causal role of adipose tissue lipoprotein lipase in obesity. Schwarz and Brunzell (1981a) noted that if lipoprotein lipase elevation is caused by obesity, then it should be lowered with weight loss, as other metabolic consequences of obesity are. Instead, they demonstrated a dramatic homeostatic reaction of lipoprotein lipase activity in response to weight loss. Gruen et al. (1978) also implicated a causal role of lipoprotein lipase

when they reported elevated levels in the adipose tissue of 2-week-old preobese rats.

It is hoped that these results will be replicated and that appropriate longitudinal studies will be forthcoming in order to provide a greater understanding of the role of adipose tissue lipoprotein lipase in human obesity. The potential relevance of this area of research to obesity is promising.

Discussion

Although the involvement of thermogenesis is central to some of the mechanisms reviewed, it is of secondary importance in fat storage mechanisms. Three thermogenic mechanisms, related to brown adipose tissue, $\text{Na}^+, \text{K}^+, \text{-ATPase}$, and substrate cycling, have been considered for their role in the metabolic component. The first two have received strong support in animal research, and substrate cycling has not been researched extensively. However, none of the three thermogenic mechanisms has received substantial support from research with human subjects. Hence, it is difficult to fully evaluate the role of thermogenic mechanisms on human obesity.

One mechanism—lipoprotein lipase activity—has been reviewed that postulates fat storage variation in obesity. The lipoprotein lipase postulation has received significant empirical support. In fact, unlike any other mechanism proposed for the metabolic component, the lipoprotein lipase postulation has received substantial support from both animal and human research.

The glycerol phosphate shuttle mechanism is both a thermogenic and a fat storage postulation. NADH oxidation is more efficient, and thus thermogenesis decreases with dietary restriction. Also, obese subjects tend to have increased glycerol 3-phosphate levels which may lead to enhanced fat storage. Research on the glycerol phosphate shuttle, however, is quite limited despite the time span since the first studies were reported. Yet the existing research is particularly noteworthy because human subjects were used in the investigations.

Finally, two cautionary notes are in order. First, there may be a tendency to as-

sume that if one applicable mechanism of the metabolic component of human obesity can be found, then other proposed mechanisms are insignificant or unsubstantiated. It may be more realistic to assume that several mechanisms are involved in metabolic variation but that some mechanisms may contribute more to obesity than others. Also, different mechanisms may operate in different individuals. Some may involve thermogenic action; others may involve fat storage action. It is unlikely that the comprehensive search for genetic variation in human obesity will be completed in the near future.

Second, most of the five mechanisms reviewed have been researched only in the case of negative energy balance due to caloric restriction. It is not clear whether the mechanisms respond similarly in the case of negative energy balance due to increased physical activity. One mechanism that has received attention for its response to exercise is the substrate cycling mechanism. This is of negligible significance, however, because the research was not related to obesity in any way and because bumblebees (nonmammals) were used as experimental animals. Also, the effects of physical training on lipoprotein lipase have been studied (Marniemi, Peltonen, Vuori, & Hietanen, 1980). Increases in adipose tissue lipoprotein lipase with high physical activity were noted. However, subjects in the investigation were nonobese males, and the physical activity did not lead to a negative caloric balance, so it is difficult to assess the effects of exercise as a weight-reduction tool on lipoprotein lipase activity. The differential responses of adaptive biochemical mechanisms to diet and exercise may be an important issue for future research.

Intervention for Metabolic Components

As research interest in the metabolic bases of obesity continues, intervention strategies for dealing with the adaptive and dispositional metabolic components of obesity will be forthcoming. One strategy for maintaining weight-loss rates once the metabolism begins to adapt is to increase physical activity at increments similar to

the decreasing thermogenesis (Stuart et al., 1979). This "natural" intervention is nearly ideal. Exercise not only leads to weight loss but also promotes beneficial physiological changes which enhance good health. Moreover, exercise can be enjoyable and psychologically beneficial (Franklin & Rubenfire, 1980; Katahn, 1982).

Yet there is one serious drawback to the widespread implementation of exercise in weight management; people do not do it! Dishman (1982) reported a 50% drop-out rate in exercise programs. Even this is perhaps a low estimate in the case of obesity. The 50% recidivism rate applied to organized programs; the rate may be much higher for individual resolutions. Further, Dishman reported an inverse relation between body fat and adherence. Obese subjects have a higher body fat content than the normal population, so an estimate of 50% recidivism may be spuriously low.

Pharmacological intervention may become a possibility as research on the nature of the adaptive and dispositional metabolic components continues. Already, it is intriguing to consider the possible effects of an oxidative phosphorylation uncoupling agent or a sodium pump activating agent or the effect of a lipoprotein lipase inhibitor on the metabolic component.

Future Research

Three lines of research can be suggested. First, the effectiveness of exercise recommendations as generally incorporated within behavioral weight-management attempts is equivocal (Thompson, Jarvie, Lahey, & Cureton, 1982). In studies in which frequency and longevity of exercise reach certain minimal standards, the effectiveness of exercise in weight loss has been more clearly established (Franklin & Rubenfire, 1980; Gwinup, 1975; Leon, Conrad, Hunninghake, & Serfass, 1979; O'Hara, Allen, & Shephard, 1977). More research is needed to investigate the effects of vigorous exercise in conjunction with behavioral programs. It may be of particular interest to compare the rapidity, permanence, and physiological effects of weight loss due to activity alone with the same measures of

weight loss due to dietary restriction alone or with some combination of diet and exercise. Such a research strategy could be preliminarily investigated with animals and then later tested with humans.

Second, the biochemical mechanisms reviewed here are in need of further research verification. Brown adipose tissue has an important role in the metabolic adaptation of overfed rodents. It is not yet clear, however, whether brown adipose tissue has the same role in humans with a restricted dietary intake. For future intervention, it may also be important to determine the mechanism within brown adipose tissue which generates heat. Current possibilities include the uncoupling of oxidative phosphorylation and the activity of the sodium pump. It would be of interest to know whether the increased activity of cafeteria-fed rat brown adipose tissue is ouabain sensitive.

Similarly, the glycerol phosphate shuttle has been implicated for its role in the metabolic component, but there is no current estimate of the degree of thermogenic or fat storage that is due to the shuttle itself. Understanding the relative importance of the glycerol phosphate shuttle activity awaits such research.

Third, after an increased understanding of the etiology and maintenance of obesity is obtained, the development of effective intervention and prevention strategies is the next logical step. It is reasonable to postulate that an educational prevention-oriented program that emphasized individual variation of dietary and exercise needs to parents and children would reduce obesity in future generations. Moreover, research on lipoprotein lipase activity is promising in that it has been applied to both animal and human subjects. If future research is consistent in showing a causal relation between lipoprotein lipase activity and obesity, the advent of pharmacological intervention to reduce tendencies to regain weight previously lost and to counteract genetic predispositions to obesity may be forthcoming.

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