

PHYSIOLOGICAL MECHANISMS IN THE ADAPTIVE RESPONSE OF METABOLIC RATES TO ENERGY RESTRICTION

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CONTENTS

INTRODUCTION	49
MECHANISMS OF ADAPTATION OF METABOLIC RATE DURING ACUTE ENERGY RESTRICTION	52
SYMPATHETIC NERVOUS SYSTEM ACTIVITY AND CATECHOLAMINES	52
THYROID HORMONES	55
IODOTHYRONINE–CATECHOLAMINE INTERACTIONS.	57
INSULIN	58
CATECHOLAMINES, IODOTHYRONINES AND INSULIN: THEIR INTEGRATED ROLE IN ALTERING METABOLIC RATE	59
OTHER CALORIGENIC HORMONES	60
<i>Glucagon</i>	60
<i>Growth hormone</i>	60
<i>Glucocorticoids</i>	61
<i>Progesterone</i>	61
SUBSTRATES AND FUELS	62
<i>Free fatty acids</i>	62
<i>Triacylglycerols and fatty acid cycling</i>	63
<i>Protein catabolism and protein turnover</i>	63
RESPONSES OF METABOLIC RATES TO ACUTE ENERGY RESTRICTION: TIME RELATIONS AND HORMONE–SUBSTRATE INTERACTIONS	64
MECHANISMS INVOLVED IN THE METABOLIC RATE CHANGES DURING CHRONIC ENERGY DEFICIENCY	65
SUMMARY	68
REFERENCES	69

INTRODUCTION

When individuals subsist on energy-restricted diets adaptive changes to the limitation in energy intake must occur in order to permit the prolongation of the life of the individual (Mitchell, 1944). The monumental studies on human semi-starvation by Keys *et al.* (1950) have amply demonstrated that following a period of restricted energy intake it is possible to attain energy balance at the new, low level. This new plane of energy balance is attained in part by a reduction in energy output, but is also a consequence of changes in body

composition. Reductions in energy expenditure either by physiological (Keys *et al.* 1950) and/or behavioural responses (Brozek, 1955) are active processes in contrast to the decrease in body tissue which appears to be almost entirely passive and an automatic consequence of the use of body tissues as fuel (Taylor & Keys, 1950). Since these changes, actively or passively induced, permit the prolongation of the life of the individual, they must be considered as beneficial, adaptive responses.

Dietary energy is needed by an individual merely to offset his total daily energy expenditure when he is in energy balance. There are traditionally three physiological components of total daily energy expenditure: (1) basal (BMR) or resting metabolic rate (RMR), (2) thermogenesis, and (3) physical activity. RMR is the minimal rate of energy expenditure at rest compatible with life. BMR refers to the RMR measured under defined conditions of rest after a night's sleep. The RMR, because it includes the small, additional energy expended by postural muscles or movements is usually slightly higher than BMR. The terms BMR and RMR will be used interchangeably in the present review since the differences between the two measurements are negligible. RMR accounts for between 60 and 75% of daily energy expenditure. Thermogenesis is defined as the energy expenditure above BMR or RMR; this includes the effects of food intake, thermogenic agents, cold exposure and psychological influences such as stress. The contribution of physical activity to total daily energy expenditure will depend on the duration and intensity of the physical activity.

Reduction in RMR is one of the more constant findings in experimentally induced semi-starvation or during therapeutic energy restriction. Apfelbaum (1978) has summarized the studies since the beginning of the 20th century which have demonstrated a decrease in BMR as an effect of restricted intake either spontaneously, experimentally or therapeutically. This summary provides data on a number of subjects studied, duration of restricted diet, the percentage weight loss and the decrease in percentage oxygen consumption. Sims (1986) in a comprehensive review has also provided a tabular summary of the more recent studies of the response of obese subjects to a reduction of energy intake, most studies showing a significant reduction in RMR expressed per unit lean body mass, except two which show no change.

The consistent finding of a reduced RMR in the experimental semi-starvation studies on human volunteers undertaken in this century by Benedict *et al.* (1919), Keys *et al.* (1950) and subsequently by Grande *et al.* (1958) resulted in two alternative, but not mutually exclusive, explanations being put forward to explain the decrease in RMR (Grande *et al.* 1958): (1) a decrease *per se* in the metabolic rate or activity of the metabolically active tissues and (2) a decrease in RMR as a consequence of loss of metabolically active tissue mass due to a loss of body-weight. The former response was considered to be an indication of an increased 'metabolic efficiency' of the residual active tissue mass.

Early investigations favoured a reduction in metabolic activity of the body cells and an enhanced metabolic efficiency as being more important since the decline in RMR was relatively greater than that accounted for by body-weight loss. Taylor & Keys (1950), however, considered the decrease in the mass of metabolically active tissue as the main factor responsible for the reduced RMR. From an analysis of their Minnesota semi-starvation data, they concluded that about 65% of the reduction in RMR could be attributed to the shrinkage of the metabolizing mass of body cells and only about 35% to an actual decrease in cellular metabolic rate. Grande *et al.* (1958) applied identical methods of computation to data from another series of experimental human semi-starvation studies. They found quite the reverse distribution with the actual decrease in metabolic activity of the cells contributing to a greater percentage (i.e. 65–73) of the reduction in RMR. These differences in the two series of experimental semi-starvation studies were attributed to the

Table 1. Reduction in basal metabolic rate (BMR) and active tissue mass (ATM) during experimental semi-starvation

	Experimental semi-starvation studies					
	A (n 12)		B (n 12)		C (n 12)	
Day of study	0	168	0	14	0	19/20
Body-wt (kg)	67.5	51.7	71.6	65.4	69.1	62.4
ATM (kg)	38.8	28.7	44.9	42.2	43.4	40.8
BMR (MJ/d)	6.59	4.20	7.29	5.73	6.62	5.49
Decrease in BMR:						
MJ/d	2.39 (-36.3%)		1.56 (-21.4%)		1.13 (-17.1%)	
KJ/kg ATM per d	23.4 (-13.8%)		26.4 (-16.3%)		18.0 (-11.8%)	

A, Keys *et al.* (1950); B and C, Expts 1 and 2 respectively of Grande *et al.* (1958).

obvious differences in the durations of the experiments. In comparison with the long-term Minnesota semi-starvation study of 24 weeks, the experiments of Grande *et al.* (1958) did not exceed 3 weeks of energy restriction. Nevertheless, the decrease in metabolic rate per unit weight of active tissue in the study by Grande *et al.* (1958) was of the same order of magnitude as had been observed in the Minnesota studies after 24 weeks of energy restriction (Keys *et al.* 1950).

Comparison of more recent studies on therapeutically-restricted diets in obese patients also shows the same response over the first few weeks of energy restriction. RMR per kg fat-free mass (FFM) or lean body mass (LBM) decreased by 9.4% at d 35 (Welle *et al.* 1984), 10.1% at d 14 (Shetty, 1980), 12% at d 42 (Webb & Abrams, 1983) and 15% at d 28 (Bray, 1969*b*). The degree of reduction varied largely with the severity of the dietary restriction and the composition of the diet. These values are comparable to the decrease in RMR per kg LBM reported by Grande (1964), i.e. 16.6 and 11.8%, in two separate experiments at the end of 2 and 3 weeks of restriction respectively. Recalculating the data from the two earlier separate experimental semi-starvation studies by Keys *et al.* (1950) and Grande *et al.* (1958), James & Shetty (1982) were able to show that the early fall in RMR is mainly accounted for by metabolic adaptation, i.e. enhanced metabolic efficiency (Table 1). This small reduction in RMR per unit active tissue (16.3%) seen in the first 2 weeks of energy restriction remained essentially unchanged over the subsequent 22 weeks of semi-starvation. However, the greatest contribution to the fall in RMR in the long-term adaptation was the slow decrease in the total mass of active tissues.

It seems reasonable, therefore, to assume that the reduction in RMR during energy restriction (experimental or therapeutic) occurs in two different phases. In the initial phase (the first 2 or 3 weeks) there is a marked decrease in the RMR which is not attributable to the changes in body-weight or body composition. This decrease in RMR per unit active tissue is a measure of the increase in metabolic efficiency of the active tissue mass. With continued energy restriction, the cellular metabolic rate remains nearly constant and the further decrease in RMR is accounted for by a loss of active cellular tissue. Thus, the longer the duration of energy restriction, the more important becomes the contribution of decreased FFM or LBM to the reduction in RMR. This reduction in lean body tissue with prolonged energy restriction is apparently a passive process and a consequence of body tissues being used as metabolic fuel (Taylor & Keys, 1950). The physiological mechanisms concerned with the metabolic adaptation aimed at reducing cellular metabolic rate are not well understood. The present review proposes to examine several factors, such as hormonal

and substrate alterations, that may operate and interact to alter this adaptive component of the RMR. Since reduction in this component is manifest in the early phase of semi-starvation, the related physiological mechanisms must be apparent and, hence, critically evaluated during the first 2–3 weeks of energy restriction.

MECHANISMS OF ADAPTATION OF METABOLIC RATE DURING ACUTE ENERGY RESTRICTION

The obvious choice for the regulatory mechanisms that contribute to an adaptive response which results in a decrease in the rate of cellular metabolism and thereby enhances the metabolic efficiency of the active cellular mass ought to be endocrine in nature. Several hormones are now known to be sensitive to changes in the level of energy intake, the dietary composition and the status of energy balance of the individual (Danforth & Landsberg, 1983). Changes in sympathetic nervous system (SNS) activity and catecholamines, alterations in thyroid hormone metabolism and changes in pancreatic peptide hormones such as insulin and glucagon play an important role in the metabolic response to energy restriction. These changes are not only aimed at lowering the metabolic activity of the active cell mass, but are also essential for the orderly mobilization of endogenous substrates and fuels during a period of restricted availability of exogenous energy.

There are several factors that have to be kept in mind while attributing a regulatory role to hormones in the metabolic adaptation to energy restriction (Danforth, 1989). These include (a) hormonal interactions, synergic or additive, (b) the possibility that substrates and/or products may produce effects (direct and indirect) independently of the hormones themselves, (c) hormones produce their effects by first binding to membrane-bound receptors or nuclear receptors, which are also altered by the change in nutrition; this is particularly true in the case of peptide or thyroid hormones since their receptor sensitivity and receptor responsiveness may be altered by the nutritional status, and (d) post-receptor events may also be influenced by the altered state of nutrition, thus modulating the final outcome. Simple quantitative approaches to alterations in plasma hormone concentrations or plasma appearance rates may be neither meaningful nor conclusive. While trying to understand the mechanisms that may be responsible for modulating O_2 consumption of tissues during energy restriction, and when attributing regulatory roles to the hormones involved, the previously-mentioned factors have to be constantly considered.

SYMPATHETIC NERVOUS SYSTEM ACTIVITY AND CATECHOLAMINES

The thermogenic effects of catecholamines like noradrenaline (NA) when administered intravenously to human subjects are well documented (Steinberg *et al.* 1964; Jung *et al.* 1979*b*; Katzeff *et al.* 1986; Kurpad *et al.* 1989*a, b*). Infusions of adrenaline have also been shown to be thermogenic in human subjects (Sjöström *et al.* 1983; Sjöström, 1985). The calorogenic actions of catecholamines are mediated by two major mechanisms: (a) by increasing the rate of cellular thermogenesis (Himms-Hagen, 1976) and (b) by stimulating the conversion of complex fuels into readily usable substrates (Young & Landsberg, 1977*a*). The increased rate of cellular metabolism induced by catecholamines manifests itself in an elevation in heat production, fuel utilization and O_2 consumption, while its stimulatory effect on the breakdown of complex fuels supplies the energy required for the increased cellular metabolism. Since catecholamines stimulate metabolism, it is conceivable that changes in SNS activity may at least in part explain the reduction in metabolic rate that

occurs with energy restriction. The alteration in sympatho-adrenal activity may become manifest as changes in the circulating levels of catecholamines and their turnover rates, and also result in changes in the responsiveness at the hormone receptor and post-receptor levels. A number of recent reviews have demonstrated this close relationship between energy intake and SNS activity (Landsberg & Young, 1978, 1983*a*; Jung *et al.* 1980*a*; Shetty & Kurpad, 1990).

The most important evidence linking energy intake with SNS activity has been provided by animal experiments. Young & Landsberg (1977*b*) reported a significant decrease in the NA turnover of cardiac tissues in 48 h-fasted rats on adequate intakes of fluid and electrolytes. Their studies suggested that the NA turnover of pancreatic and liver tissues was also sensitive to changes in energy intake (Young & Landsberg, 1979) and demonstrated that overfeeding normal and previously fasted rats by providing them free access to sucrose solutions increased the NA turnover of cardiac tissue. This series of studies linked changes in catecholamine turnover with alterations in energy intake, more specifically carbohydrate intake. This concept of a reduced catecholaminergic drive during energy restriction, developed by Landsberg & Young (1978), was counter to many of the accepted ideas on the control of substrate mobilization during starvation. Traditionally, the increase in lipolysis, maintenance of glucose homeostasis and the increase in glucagon output on fasting have been considered as being indicative of an enhanced sympathetic drive. Emerging evidence shows that these responses are not dependent on an increased catecholamine activity. Adrenalectomy or adrenergic blockade does not prevent an increase in free fatty acid (FFA) output on fasting (Levy & Ramey, 1958; Goodman & Knobil, 1959). Several studies summarized by Jung *et al.* (1980*a*) suggest that the adrenergic component of lipolysis rapidly declines, while the lipolytic activity of energy restriction is under the dominant control of declining plasma insulin levels.

Investigations in obese human subjects have also shown that energy restriction is associated with a lowering in the circulating levels of NA (Shetty *et al.* 1979) along with a decrease in the urinary excretion of hydroxy-3-methoxymandelic acid (HMMA), a metabolite of catecholamines (Jung *et al.* 1979*a*). An earlier report by Kolanowski *et al.* (1975) had already shown that semi-starvation results in a decrease in daily urinary excretion of NA. Bessard *et al.* (1983) have recently shown a decrease in NA in the urine along with a decrease in RMR per kg LBM during energy restriction in obese subjects. Refeeding of previously energy-restricted individuals produced a dramatic rise in urinary HMMA excretion and plasma NA levels within 72 h (Jung *et al.* 1980*b*). These studies confirm that the activity of the human SNS is responsive to alterations in energy intake and is responsible for many of the beneficial effects of energy restriction such as reduced blood pressure (Jung *et al.* 1979*a*; Landsberg & Young, 1984). Like animals, these responses in humans have also been shown to be specific to the carbohydrate content of the diet (DeHaven *et al.* 1980). Thus, there appears to be a similarity in the responses of SNS activity and insulin secretion in that they are most sensitive to the carbohydrate content of the diet both during underfeeding and overfeeding.

Plasma appearance and clearance rates may be better physiological indices of the functional status of SNS activity rather than plasma levels, which are an insensitive index. O'Dea *et al.* (1982), using a constant infusion of tracer NA, were the first to report a diminished clearance and appearance rate of NA in the plasma compartment during energy restriction. The interpretation of these tracer studies may be complicated by errors due to recirculation of the tracer NA and the possibility of additional unknown pools. These studies also tell us nothing about the organs responsible for these changes and yet they are crucial studies that strengthen the interaction between the diet, its composition and SNS activity.

Table 2. Modulation of changes in resting metabolic rate (RMR) during short-term partial energy restriction (PER)

Experimental manipulation		Absolute RMR		RMR (per kg fat-free mass (FFM))*		Reference
		MJ/d	% change	KJ/kg FFM	% change	
PER	Baseline	7.05		130.4		Jung <i>et al.</i> (1979b)
	Day 7	6.62	-6.1	123.8	-5.1	
	Day 14	6.25	-11.4	117.3	-10.1	
L-Dopa + PER	Baseline	6.51		123.6		Shetty <i>et al.</i> (1979)
	Day 7	6.33	-2.8	121.6	-1.6	
	Day 14	6.35	-2.5	122.6	-0.8	
β -Blockade	Baseline	6.89		134.0		Jung <i>et al.</i> (1980b)
	Day 7	6.33	-8.1	124.6	-7.0	
T ₃ + PER	Baseline	7.16		113.3		Shetty (1980)
	Day 14	7.79	+8.8	126.9	+12.0	

L-Dopa, L-dihydroxyphenylalanine; T₃, triiodothyronine.

* FFM estimated by whole-body potassium estimations before and after PER in some cases and calculated from sum of four skinfolds using Durnin & Womersley's (1974) equations and corrected for FFM changes from nitrogen balances in the rest.

Supersensitivity or up-regulation as well as down-regulation of adrenergic receptors has been known to occur in response to altered agonist levels (Lefkowitz *et al.* 1984). A diminished SNS drive manifested by a reduced turnover, diminished appearance and clearance rates and reduced circulating levels of catecholamines is expected to be associated with the development of supersensitivity to agonist stimulation or up-regulation of adrenoceptor numbers (Motulsky & Insel, 1982). Although an increase in adrenergic receptor sensitivity has been reported in individuals with chronic energy deficiency (Shetty & Kurpad, 1990) there are only few studies reporting an enhancement of some of the physiological responses to infused adrenaline during underfeeding of normal individuals (Mansell & Macdonald, 1989).

Studies manipulating the sympathetic neurotransmitter status during energy restriction support the important role of SNS activity in the RMR changes seen during semi-starvation (see Table 2). Administration of L-3,4-dihydroxyphenylalanine (L-dopa) leads to its intra-neuronal conversion to dopamine which acts as a sympathomimetic agent to displace NA from its storage site within nerve endings (Landsberg & Bruno, 1973). L-Dopa given to obese subjects, at the onset of energy restriction, results in increases in the circulating venous NA concentrations and also prevents any significant reduction in the RMR despite the severe energy restriction (Shetty *et al.* 1979). The RMR is maintained by L-dopa administration, although the changes in thyroid hormones follow the expected pattern seen during negative energy balance. The administration of L-dopa after a 2-week interval of semi-starvation did not affect the RMR despite inducing a rise in levels of both plasma NA and adrenaline (Shetty *et al.* 1979). The effect of L-dopa is largely peripheral while carbidopa has a predominantly central effect. Carbidopa, since it is not converted in the periphery, does not influence either the RMR changes or circulating NA levels during energy restriction (Jung *et al.* 1981).

The important role of the SNS drive in the adaptive component of RMR is supported by studies using β -adrenergic blockade. On weight maintenance diets, the RMR of obese subjects diminished by 8.7% following the administration of propranolol (Jung *et al.*

1980c). This reduction in RMR was comparable to the RMR reduction seen following energy restriction alone for 3 weeks (9.1%). Similar doses of propranolol produced only a < 2% drop in RMR after 1 week on an energy-restricted diet. β -Adrenergic blockade produced changes in thyroid hormone metabolism both on maintenance diets and energy-restricted diets, similar to those seen during energy restriction. Although β -adrenergic blockade affects peripheral thyroid metabolism, the major action of the blocking agent on RMR was by direct inhibition of SNS-mediated stimulation of metabolism rather than indirectly by its effects on peripheral thyroid metabolism (Jung *et al.* 1980c). A recent study has confirmed the effects of β -adrenergic blockade on resting metabolism; it does not, however, seem to prevent the increase in RMR seen consequent to overfeeding (Welle *et al.* 1989).

The adrenal medulla, unlike the SNS, is stimulated by energy restriction (Young *et al.* 1984). This small increase in adrenaline helps substrate mobilization with the lipolytic activity in man being sensitive to variations in adrenaline within the physiological range (Galster *et al.* 1981). The increase in adrenaline has no effect on thermogenesis since the levels needed to stimulate RMR are considerably higher. Thus, the SNS shut down associated with adrenal medullary stimulation will aid substrate mobilization with no effect on the RMR.

THYROID HORMONES

The thermogenic effects of thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), in man are undisputed. Hollingsworth *et al.* (1970) gave T_3 to hospitalized obese patients and observed an increase in O_2 consumption. T_3 in doses of 100 μg or more consistently increases metabolic rates and, although the effect is small, it is readily measurable (Bray *et al.* 1971, 1973). Administration of 80 μg T_3/d even while on an energy-restricted diet raised the metabolic rates of obese subjects by 9–10% over a period of 2 weeks (Shetty, 1980).

The stimulation of thermogenesis by thyroid hormones can be demonstrated both in vivo and in vitro in isolated tissues such as muscle, liver, kidney and intestine (Guernsey & Edelman, 1983). This action is mediated primarily through nuclear T_3 receptors in most tissues and is the result of increased membrane-bound $\text{Na}^+\text{-K}^+$ ATPase (EC 3.6.1.37) activity. There is also evidence that T_3 has direct mitochondrial effects which could mediate its thermogenic actions (Sterling, 1979). Clausen & Chinet (1986) have shown, however, that the contribution of the Na pump to total cellular energy turnover was insufficient to account for changes in whole-body thermogenesis. Shulman *et al.* (1985) recently demonstrated an increase in futile cycling of glucose to glucose-6-phosphate and fructose-1-phosphate to fructose-1,6-phosphate in muscle by thyroid hormones.

Thyroid hormones are important components of the metabolic adaptations associated with energy restriction and overfeeding and they influence both carbohydrate and lipid metabolism (Minderop *et al.* 1987; Oppenheimer *et al.* 1987). The thyroid hormone changes seen in response to restricted intakes of energy have been well reviewed in recent years (Jung *et al.* 1980a; Danforth & Burger, 1989) and are summarized here.

Energy restriction does not seem to affect the circulating levels of total T_4 (free and bound) which usually remain unchanged since there is no evidence of a change in the production rates of T_4 . When T_4 levels show a tendency to fall they return to prefasting levels as the fast continues. Free T_4 may show a rise transiently during starvation and this is secondary to the inhibitory effects of a high plasma FFA concentration on plasma protein binding of T_4 (Spencer *et al.* 1983). There is a rapid decline in serum T_3 during fasting or partial energy restriction (Shetty *et al.* 1979). The response of T_3 to energy restriction seems to be most specific to restriction of carbohydrate (O'Brian *et al.* 1980;

Insulin:	(IU L)	22.4	7.0
Glucagon:	(pg ml)	226	287
Catecholamines:	NA (ng ml)	0.17	0.07
	ADR (ng ml)	0.04	0.03

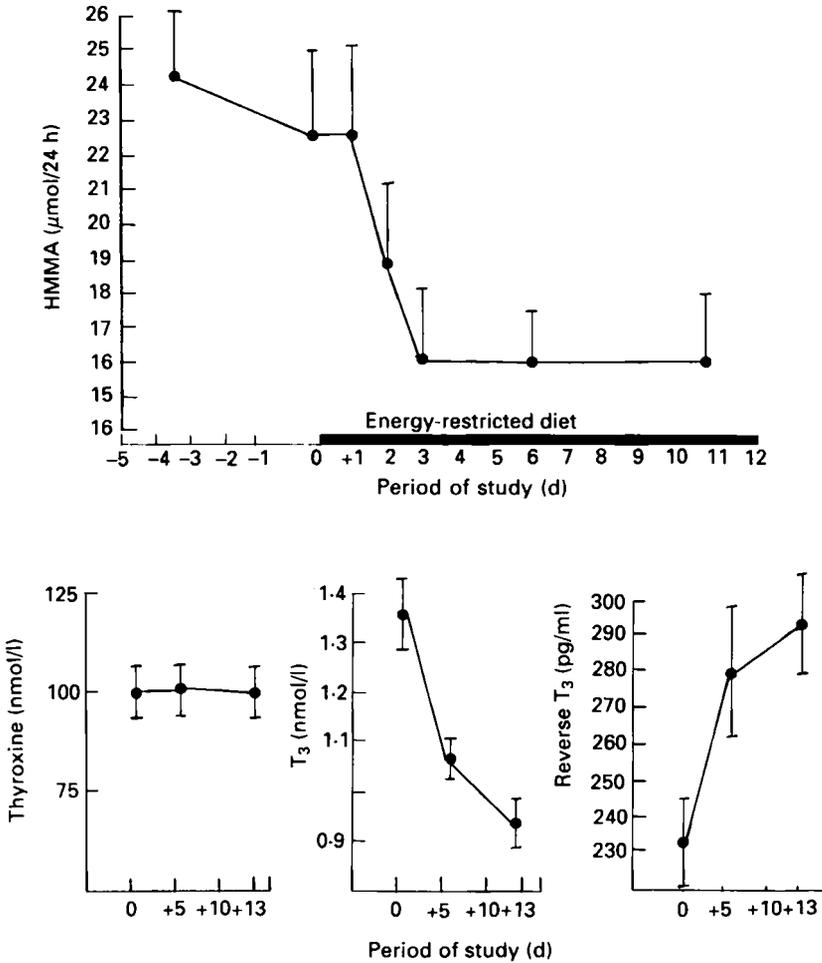


Fig. 1. Changes in plasma levels of insulin, glucagon and catecholamines, 24 h urinary excretion of hydroxy-3-methoxymandelic acid (HMMA) and thyroid hormones during acute semi-starvation in obese subjects (compiled from Jung *et al.* 1978, 1979a; Shetty *et al.* 1979). T₃, triiodothyronine; NA, noradrenaline; ADR, adrenaline. Points are means with their standard errors represented by vertical bars.

Danforth, 1986). The decrease in T₃ is rapid (within 24 h) and usually reaches levels 40–50 % below normal within 3–4 d (Fig. 1). The drop in T₃ is not due to changes in T₃ clearance rates. It is attributed to a reduction in the synthesis of T₃ by the peripheral conversion of T₄ to T₃. The primary effect of energy restriction appears to be on the type I outer ring deiodinase and not on the inner ring deiodination (Danforth & Burger, 1989).

Associated with the reduction in T_3 there is an increase in reverse T_3 (rT_3) during fasting (Chopra, 1977). The increase in rT_3 is progressive, beginning much later than the fall in serum T_3 seen during energy restriction. After 2–3 weeks of fasting or semi-starvation the rT_3 returns to normal levels (Carlson *et al.* 1977) at a time when the concentrations of T_3 are being maintained at a low level. The peripheral kinetics of T_3 and rT_3 are dissociated. T_3 production rates decrease during starvation while the transient changes in rT_3 depend not on changes in production but on decreased clearance of rT_3 . This is partly due to reduced hepatic deiodinase which catabolizes rT_3 (Danforth & Burger, 1989). However, the catabolic rate of rT_3 is much higher (Chopra, 1977) than the rate of T_3 breakdown, thus accounting for the smaller changes in the circulating concentrations of rT_3 as compared with the plasma changes in T_3 .

Normally fed subjects are expected to show an increase in pituitary thyroid-stimulating hormone (TSH) concentrations and an augmented TSH response to thyrotrophin-releasing hormone (TRH) following a reduction in circulating concentrations of T_3 or T_4 . This, however, does not appear to be the case when either fasting, semi-starvation or low carbohydrate intakes decrease T_3 concentrations. During starvation or energy restriction TSH concentrations seem to either increase (Burger *et al.* 1980) or remain unaltered (Carlson *et al.* 1977). The TSH response to TRH is also either unaltered (Gardner *et al.* 1979) or appears to be blunted (Burger *et al.* 1980). These observations are indicative of an alteration in the sensitivity of the hypothalamo-hypophyseal feedback systems during energy restriction.

The reciprocal changes in T_3 and rT_3 concentrations during energy restriction are bound to contribute to the reduction in metabolic rate. The tissue responsiveness to T_3 may not be altered since exogenous administration of T_3 increases the metabolic rate and reverses the RMR fall during energy restriction and weight loss (Hollingsworth *et al.* 1970; Bray *et al.* 1971; Shetty, 1980; Welle & Campbell, 1986). There is evidence, however, which suggests that prolonged energy restriction can decrease the nuclear T_3 receptors (Schussler & Orlando, 1978); this reduction in receptor numbers is not necessarily a direct consequence of the fall in T_3 levels (Bernal *et al.* 1978). There is also a reduction in the binding capacity of nuclear T_3 receptors which seems to be an independent but synergic adaptation to energy restriction (Burman *et al.* 1977).

IODOTHYRONINE–CATECHOLAMINE INTERACTIONS

Thyroid hormones, i.e. the iodothyronines, and catecholamines demonstrate synergic potentiation of each others' activities, at the periphery. This synergic interaction may be important when nutritionally modulated changes are induced in either or both hormone systems. Iodothyronine–catecholamine interactions can occur at several levels: (1) the effects of one on the synthesis and secretion of the other, (2) the effect of catecholamines on the peripheral conversion of T_4 to T_3 and (3) the effect of thyroid hormones on the sensitivity of the effector tissues to catecholamines.

Thyroid follicles are innervated by sympathetic nerve fibres which may influence and regulate thyroid hormone secretion (Young & Landsberg, 1983). Thyroid status affects the functional state of the SNS, the relationship contrary to common belief being an inverse one. Thyroid hormone deficiency is associated with an enhanced SNS activity since both NA turnover rate and plasma NA appearance rate are markedly increased when thyroid hormone is deficient (Landsberg & Axelrod, 1968).

Catecholamines have an effect on the peripheral thyroid hormone metabolism. Adrenaline is known to enhance the peripheral conversion of T_4 to T_3 (Galton, 1965). β -Adrenergic blockers such as propranolol decrease the production of T_3 (Jung *et al.* 1980c);

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this suppression of the peripheral T_4 to T_3 conversion was seen in obese subjects both during a weight maintenance diet and an energy-restricted diet. Kinetic tracer studies have also demonstrated a suppression of peripheral conversion of thyroid hormones (Lumholtz *et al.* 1978). Administration of L-dopa, a precursor of catecholamines, failed to influence the T_3 changes associated with energy restriction, although the expected rise in rT_3 with semi-starvation was prevented (Shetty *et al.* 1979).

Thyroid hormones have an effect on the peripheral tissue sensitivity to catecholamines and this is possibly mediated via the β -adrenergic receptor as well as the receptor-linked adenylate cyclase (EC 4.6.1.1) – cyclic AMP system. Thyroid hormones increase the number of β -adrenergic receptors in several tissues such as myocardium, skeletal muscle, adipose tissue and lymphocytes and also affect the adenylate cyclase – cyclic AMP system (Bilezikian & Loeb, 1983). They may enhance the coupling of β -receptor and cyclic AMP generation. These changes are expected to result in increased tissue sensitivity to catecholamines. The thermogenic effects of thyroid hormone are mediated by Na^+K^+ ATPase; this enzyme is also a target for catecholamines through stimulation of β -adrenergic receptors (Swann, 1984).

The interactions between thyroid hormones and catecholamines may influence their mutual roles in regulation of thermogenesis. Thyroid hormones are the principal regulators of basal metabolic rates (Himms-Hagen, 1983), while the regulation of adaptive thermogenesis is mediated largely by catecholamines (Landsberg & Young, 1983*b*). However, thyroid hormones do have a permissive and synergic role in the adaptive component. While administration of T_3 even in low doses can prevent the drop in metabolic rate seen during energy restriction (Welle & Campbell, 1986), administration of catecholamines fails to stimulate metabolic heat production in hypothyroid rats (Rothwell *et al.* 1982). SNS-mediated thermogenesis in response to carbohydrate intake also requires thyroid hormones (Rothwell *et al.* 1982) and adrenaline-mediated thermogenesis in the newborn pig is enhanced by thyroid hormone administration in a dose-dependent manner (Kaciuba-Uscilko, 1973).

INSULIN

Insulin is another pre-eminent hormone that regulates energy balance. Insulin is needed to permit glucose uptake into the cells for oxidation as well as for storage. Insulin can increase energy expenditure in several ways. It has a direct stimulating effect on Na^+K^+ pumping across the cell membrane (Moore, 1981). Increased Na pump activity in skeletal muscle has been demonstrated following insulin administration (Clausen & Kohn, 1977; Landsberg & Young, 1985). Insulin also stimulates the SNS; during the euglycaemic-hyperinsulinaemic clamp, variations in the insulin concentrations resulted in a dose-dependent change in the concentrations of plasma NA without alterations in plasma glucose (Rowe *et al.* 1981). The enhancement by insulin of the sympathetic tone has been confirmed by subsequent studies using the hyperinsulinaemic clamps (Acheson *et al.* 1984; Christin *et al.* 1986). These studies have also confirmed the thermogenic role of insulin. In a series of clamp studies utilizing somatostatin to block endogenous insulin secretion, the group in Lausanne showed that step-wise increase in glucose uptake alone, with insulin concentrations kept constant, caused an increase in thermogenesis comparable to that found when plasma insulin was allowed to rise. When insulin alone was increased without changes in glucose uptake, plasma NA levels increased and this increase correlated with the thermogenic response. Insulin is thus said to mediate cellular thermogenesis by either of two mechanisms, the former obligatory by increasing glucose uptake, and the latter facultative by increasing catecholamine activity (Sims, 1986).

Starvation or partial energy restriction brings about a significant lowering in circulating

insulin levels. This is the primary hormonal signal that allows for an orderly transition from the fed to the fasted state without the development of hypoglycaemia. As the fasted state extends beyond 12–14 h the decline in circulating insulin levels results in the stimulation of amino acid mobilization, gluconeogenesis, lipolysis and ketogenesis all of which are aimed at the mobilization of endogenous fuels as substrates (Sherwin & Felig 1987). This reduction in plasma insulin levels is also bound to influence the metabolic rate at rest.

CATECHOLAMINES, IODOTHYRONINES AND INSULIN: THEIR INTEGRATED ROLE IN ALTERING METABOLIC RATE

An interesting model inter-relating the contributions of the three most important thermogenic hormones, i.e. catecholamines, iodothyronines and insulin in regulating the metabolic rate has been outlined by Danforth (1989). Changes in energy intake influence SNS activity, thyroid hormone metabolism, and insulin secretion. The nutritional signal is not the same for these three key energy-regulating hormones. Energy balance can be attained at many levels of intake and expenditure. When intakes are lowered (or increased), energy balance is attainable with a proportionate reduction (or increase) in energy expenditure. Alterations in peripheral thyroid metabolism are seen only when there is an energy imbalance, i.e. energy deficit or surfeit. In one study two groups of obese subjects were given the same restricted diet while one of the groups was also exercised to enhance the energy deficit (Phinney *et al.* 1988). T_3 concentrations decreased in both groups but the decrease was more marked as was the decline in RMR in the group which had a greater negative energy deficit, i.e. the energy-restricted and exercised group. In an earlier study by Danforth's group (Woo *et al.* 1985), no change was observed in T_3 concentrations when overfeeding was associated with a compensatory increase in physical activity. However, T_3 concentrations increased when overfeeding was not accompanied by an increase in physical activity, i.e. a state of positive energy balance. In both groups of overfed subjects (with and without compensatory increase in physical activity) the RMR increased. Whether energy deficit was induced by energy restriction or by increase in physical exercise the decline in T_3 levels was similar. This suggests that peripheral thyroid metabolism is altered in conditions of energy imbalance irrespective of the levels of intake or expenditure. When energy imbalance is incurred, the changes in peripheral thyroid hormone metabolism vary in the direction of the energy imbalance, i.e. negative energy balance will lead to decreased T_3 levels and vice versa. Peptide hormones like insulin also behave in the same manner as do thyroid hormones. In the case of nutrition-induced alterations in SNS activity, the SNS response is determined by the energy flux irrespective of whether the subject is in energy balance or not. An increase in energy flux can be induced by increase in energy intake. When this increase is accompanied by a compensatory increase in energy expenditure energy balance will be maintained. This state will, however, be associated with an increase in SNS activity and an increase in RMR but with no alterations in T_3 and insulin levels. Catecholamines may, thus, play the more important role in modulating the adaptive component of RMR as a metabolic response to energy restriction.

Danforth's (1989) hypothesis attempts to uncouple the nutrition-induced alterations in thyroid hormones and insulin from the changes in SNS activity and RMR. SNS activity is mainly responsible for the RMR changes associated with alterations in energy balance. The level of energy intake or expenditure determines the SNS activity while the energy balance status determines the peripheral thyroid metabolism and peptide hormone secretion. According to this model, the definitive reduction in RMR seen during energy restriction can only be associated with a decrease in T_3 and insulin as well as NA levels. This inter-relationship is of considerable importance in unravelling the mechanisms associated with the reduction in metabolic rate seen during starvation or partial energy restriction.

OTHER CALORIGENIC HORMONES

Hormones with potential metabolic and calorogenic activity, such as glucagon and growth hormone, also change rapidly during the early phase of semi-starvation or total fast. These hormones, though of secondary importance in terms of their thermogenic role, are capable of influencing the metabolic rate during energy restriction and, hence, need to be considered.

Glucagon

Glucagon infusions have been shown to be calorogenic in man (Trisotto *et al.* 1970). We have been unable to demonstrate any change in RMR in obese euthyroid women during a slow intravenous infusion of 40 μg glucagon at 0.81 $\mu\text{g}/\text{min}$ over a period of 45 min despite a doubling of plasma glucagon levels (Shetty, 1980). In a recent study, Nair (1987) has reported a 15% increase in RMR during a combined administration of somatostatin and glucagon compared with the RMR observed during the infusion of somatostatin alone which induces an insulin deficiency. In this study, there was a 3.5-fold increase in plasma glucagon levels which increased the O_2 consumption by 15% and the protein oxidation rates by 29%. The mechanism by which glucagon exerts its calorogenic effect is not clear.

Plasma glucagon concentrations increase early in starvation (Kolanowski *et al.* 1975; Cahill, 1976) and this rise is associated with a drop in plasma insulin levels. These reciprocal changes in pancreatic peptide hormones are generally considered to be an essential adaptive mechanism aimed at maintaining adequate glucose production during the first days of starvation. Similar changes in glucagon levels have also been reported during semi-starvation on hypo-energetic protein diets in normal subjects, a peak rise in levels being reached by day 5 of energy restriction (Weisswange *et al.* 1975). There are no specific studies showing the effect of the composition of the diet on glucagon concentrations during energy restriction, although it is generally believed that like other counter-regulatory hormones, glucagon also responds to the carbohydrate content of the diet which may be the primary substrate signal of the fed *v.* the fasted state (Danforth, 1989).

The hyperglucagonaemia seen during early starvation or energy restriction results primarily from decreased glucagon removal rather than secretion. With prolongation of the fast, plasma glucagon levels return towards basal values because of a reduction in secretion and a progressive decline in metabolic clearance (Danforth, 1985, 1989). The increased glucagon secretion associated with the insulin deficiency in the early phase of energy restriction may contribute a little to increase the metabolic rates.

Growth hormone

GH is also thermogenic and is known to produce a small but significant effect on the RMR in human subjects (Henneman *et al.* 1960). In obese subjects, administration of 5 mg human GH/d, produced a significant increase in basal O_2 consumption after only 3 d of administration (Bray, 1969a). The mechanism by which GH induces thermogenesis is not yet clearly understood; it does not, however, depend on the secretion or presence of thyroid hormones. It is likely that this calorogenic effect of GH is mediated by the release of FFA (Bray, 1976). GH increases the mobilization of FFA from adipose tissue as a result of increased triacylglycerol lipolysis; it also increases the sensitivity of catecholamine-mediated lipolytic activity (Isaksson *et al.* 1985).

Starvation is known to stimulate GH secretion and an increase in the levels of GH during fasting is well documented (Cahill *et al.* 1966). There is considerable variation in human GH levels during fasting, some subjects showing no increase while others show a marked increase during the fast. The inconsistent response of GH to energy restriction has been

confirmed by subsequent studies (Kolanowski *et al.* 1975) which would considerably undermine the role of GH as a thermogenic agent during fasting.

There are no systematic studies on GH levels during any period of semi-starvation and the effects of partial energy restriction on GH secretion were only recently investigated. GH increases transiently with energy restriction and its secretion appears to be sensitive both to the level of carbohydrate which suppresses secretion and to protein which stimulates secretion (Danforth, 1989). Arginine-stimulated GH secretion is markedly reduced by the high carbohydrate content of the diet. The suppression in GH secretion is present even if the total energy intake is reduced but the carbohydrate content is kept constant. The importance of the composition of the diet on GH secretion was best demonstrated when healthy subjects were fed on a weight-maintenance diet completely devoid of carbohydrate for 10 d. They showed a decline in blood glucose and insulin levels mimicking the fasted state, but without the transient increase in GH normally seen in a briefly fasted subject (Danforth, 1985). The lack of a rise in GH supports the idea that the normal relationship between glucose and insulin during starvation is not dependent on GH. The increase in GH seen during energy restriction may have a role to play in the conservation of the active tissue mass since short-term GH administration is known to conserve LBM during dietary restriction in obese subjects (Clemmons *et al.* 1987). A recent report indicates that this effect too is sensitive to carbohydrate intake (Snyder *et al.* 1989).

Glucocorticoids

Glucocorticoids are not known to be thermogenic, although recent suggestions indicate that, along with catecholamines and glucagon, adrenal corticoids may stimulate futile cycling of substrates in muscle (Newsholme, 1980). Adrenal glucocorticoids will influence the metabolic pathways concerned with the ready availability of substrate fuels including the mobilization of muscle protein as gluconeogenic precursors. Glucocorticoids may have little to do with the metabolic adaptation to a fast; they may, however, exert a permissive role on other important hormonal signals that accompany restricted intakes of energy. For instance, basal levels of cortisol and GH contribute to the gluconeogenic response initiated by the decline in plasma insulin levels and the rise in plasma glucagon levels that occur during a short-term fast. Glucocorticoids are also now known to modulate the sensitivity of tissues to T_3 by increasing the affinity of the nuclear receptors to the hormone (De Nayer *et al.* 1987).

A small rise in plasma cortisol has been noticed during fasting (Galvao-Teles *et al.* 1976), while Schultz *et al.* (1964) have reported no change in cortisol secretion rate in fasted obese subjects. Most recent reports indicate that cortisol secretion does not alter during a total fast (Sabeh *et al.* 1969; Kolanowski *et al.* 1975) and that no change occurs either in the diurnal pattern of plasma cortisol or in the daily excretion of 17-hydroxy-corticosteroids or urinary cortisol (Croxon *et al.* 1977). A decline in the urinary excretion of cortisol metabolites like 17-keto-steroids is also known to occur with fasting (Schachner *et al.* 1965; Cahill *et al.* 1966) and has been attributed to a decrease in cortisol removal from plasma due to an increase in transcortin capacity (Kolanowski *et al.* 1975).

Progesterone

Progesterone has been shown to be thermogenic when administered either to normal or ovariectomized women (Barton & Wiesner, 1945; Kappas & Palmer 1965). Increased progesterone secretion during the luteal phase of the menstrual cycle has been implicated in the rise in sleeping metabolic rate expressed per kg FFM seen when energy expenditure measurements were made serially during a menstrual cycle (Bisdee *et al.* 1989). Little is known about the changes in ovarian hormones during semi-starvation. However, SNS

activity is known to influence progesterone production by the ovary. During the menstrual cycle, elevated catecholamines have been reported in the luteal phase (Davidson, 1985). β -Adrenergic activation stimulates ovarian progesterone production (Jordan *et al.* 1978) while β -adrenergic blockade abolishes the rise in the plasma progesterone associated with cervical dilatation in the first trimester of pregnancy (Fylling, 1971). The reduction in SNS activity and the drop in catecholamines during energy restriction may indirectly influence progesterone production and its likely thermogenic contribution.

SUBSTRATES AND FUELS

The metabolic response to acute energy restriction (partial or complete) represents an integration of hormonal changes, substrate mobilization and fuel use designated to (a) maintain glucose production by glycogenolysis and gluconeogenesis to meet the needs of the obligate glucose-consuming tissues, in particular the brain, (b) maximize the selective utilization of major storage fuel in adipose tissue and (c) minimize the dissipation of tissue protein and, thus, spare the breakdown of vitally needed body protein (Cahill, 1976). After a few days of fasting, glucose production by the liver is mainly by gluconeogenesis since liver glycogen would have been rapidly depleted. There is a marked increase in FFA released from adipose tissue and muscle preferentially uses FFA as a substrate rather than glucose. Keto-acid production increases progressively and plateaus by the end of the second week. As the ketone level rises in plasma, the brain reduces its dependence on glucose and begins to utilize keto acids as fuel.

During an experimental fast in six normal male subjects, the blood glucose dropped below prefast levels by day 3, while FFA levels rose and peaked about the same time; glycerol levels also rose to a peak by day 3 (Cahill *et al.* 1966). Keto-acids (acetoacetate and β -hydroxybutyrate) rose by the second day and reached peak plateau levels between days 6 and 8 of the fast. Similar changes in circulating levels of substrates were also seen during semi-starvation (Weisswange *et al.* 1975): circulating levels of glucose dropped, FFA and glycerol levels rose to reach a peak by the 5th day. Blood lactate rose, pyruvate dropped and ketone bodies increased. A recent study also demonstrated a rise in FFA and glycerol with a slight reduction in glucose levels and a drop in plasma triglyceride levels by day 5 of semi-starvation (Shetty, 1980).

Free fatty acids

The only substrates whose alterations may be of some relevance to the regulation of metabolic rates during energy restriction are likely to be FFA. FFA are thermogenic; *in vitro* studies have demonstrated that FFA stimulate the metabolism of liver slices (Krebs, 1972) and also slices of kidney cortex (Lee *et al.* 1962). Infusion of heparin with or without triglycerides (Intralipid) increased circulating levels of FFA and the rise in FFA consequently increased O_2 consumption in lean and obese subjects without any associated change in circulating catecholamines (Jung *et al.* 1980*b*). The relationship between the rise in FFA and the increase in O_2 consumption appeared to be physiological, showing a tendency to a linear relationship when the plasma FFA rise exceeded $1000 \mu\text{mol/l}$. Isotopic work by Issekutz *et al.* (1968) had demonstrated that a linear relationship existed between the rate of FFA oxidation and the circulating FFA levels when the rise was greater than $1000 \mu\text{mol/l}$. They had also demonstrated a similar response in O_2 uptake following the rise in FFA. The increased circulating FFA levels of over $1000 \mu\text{mol/l}$ observed during the first week of energy restriction in human subjects may contribute to the RMR by approximately 18 KJ/h.

Triacylglycerols and fatty acid cycling

Some evidence has recently been presented to show that the energy cost of triacylglycerol–fatty acid cycling which accounts only for a small proportion of the resting energy expenditure (< 0.5%) in overnight fasted individuals increases sixfold following a 4 d starvation (Elia *et al.* 1987). Starvation produced a threefold increase in glycerol turnover and a sixfold increase in the calculated rate of esterification or recycling of energy into the triacylglycerol stores. The calculated energy cost of triacylglycerol–fatty acid cycle also increased sixfold. Factors that are responsible for the stimulation of re-esterification during starvation are not clear and may be dependent on neurohormonal factors or may possibly result from the elevated FFA levels. This may contribute in some small measure to the total energy expenditure during an energy-restricted state.

Protein catabolism and protein turnover

Apart from FFA, tissue protein mobilization will liberate amino acids as an energy source during energy restriction. The maintenance of substantial nitrogen excretion during the first week of a partial or complete starvation is well documented indicating the extent to which tissue protein provides the metabolic substrates for gluconeogenesis (Cahill, 1976). It has been estimated from the 24 h N excretion that in a normal man fasting for 3–4 d approximately 75 g amino acids are released from muscle (Cahill *et al.* 1966; Cahill, 1976). Cahill (1976) has proposed that the rate of protein catabolism in starvation is determined by the gluconeogenic demands and with prolonged starvation there is a decline in tissue protein catabolism due to a fall in the glucose needs of nervous tissue and increased dependence on ketones. Henry *et al.* (1988) have a different perspective. They argue that in normal adults the reduction in N excretion seen with fasting is part of an overall reduction in fuel use as a consequence of the reduced BMR and not due to any specific sparing of body protein. They argue that the relative importance of tissue protein as a fuel during fasting is dictated by the adiposity of the subject, the fall in N excretion and RMR occurring in parallel in the normal fasting adult, in contrast to the selective reduction in the use of protein as a fuel in the obese.

It is well recognized that protein synthesis makes a significant contribution to energy expenditure and whilst there is less certainty about the cost of protein breakdown it is generally believed that it will not represent a significant cost (Waterlow & Millward, 1989). Waterlow & Jackson (1981) have shown a constant relationship between whole-body protein turnover and the 0.75 power of body-weight, a relationship that holds for BMR over a wide range of species. They have also shown how these relationships hold good for an infant and an adult. Approximate estimates suggest that protein synthesis accounts for 10% of the BMR (Millward *et al.* 1976; Waterlow & Millward, 1989). Obese subjects receiving a low energy intake showed no effect on either their protein synthetic or breakdown rate unless there was an additional deficiency of dietary protein intake (Garlick *et al.* 1980). On a protein-free diet, the alterations in protein turnover were mainly due to a reduction in protein breakdown rate. Whole-body protein synthesis and degradation changes rapidly during a fast. There is a 40% reduction in whole-body protein synthetic rate and a 50% reduction specifically in muscle protein synthesis (Waterlow, 1984). The decrease in T_3 levels that occur during energy restriction can help mediate by reducing protein degradation (Millward, 1985). Obese adults on a low-protein low-energy diet reduced N loss and achieved near balance during the first few weeks of energy restriction. This was reversed by the administration of T_3 and the N excretion doubled (Koppeschaar *et al.* 1983). It can, hence, be concluded that some amount of energy saving may occur as

a result of the T_3 fall although the processes of protein turnover may be only marginally affected during partial energy and protein restriction.

RESPONSES OF METABOLIC RATES TO ACUTE ENERGY RESTRICTION: TIME RELATIONS AND HORMONE-SUBSTRATE INTERACTIONS

From the literature on the effects of a complete fast (Benedict, 1915; Takahira, 1925) or of semi-starvation in obese subjects (Bray, 1969*a, b*; Shetty 1980) it is seen that the RMR responds slowly with the onset of energy deprivation. The time lag is usually of the order of 48 h; by day 4 the RMR begins to fall and by day 6 or 7 there is a significant reduction as compared with prerestricted baselines. There may be several factors operating to maintain the RMR at basal levels during the first 2–4 d of restricted intake.

The time lag in the RMR response to partial or complete energy restriction may be attributed to the time for the transition from the fed to the fasted or restricted state. The hormonal signals would respond to these changes and a coordinated outcome would initiate a reduction in cellular metabolic rate (see Fig. 2). This reduction in the rate of metabolism of the active tissue mass would be affected by three major hormonal signals acting in a concerted manner. SNS activity would respond fairly rapidly to the reduced energy flux, while the sustained negative energy balance from energy restriction would signal the reduction in insulin secretion and induce more slowly the changes in peripheral thyroid metabolism. When the level and activity of all three key thermogenic hormones decreases, this would reduce cellular metabolism and cause a measurable decrease in the RMR. Recent studies in humans (Danforth & Burger, 1989) support our earlier surmise that the nutritionally induced changes in SNS activity appear to be critical to the adaptive decrease in RMR. The reduced peripheral T_3 production, which is also influenced by the changes in catecholamines, will in synergy with the rapid reduction in catecholamines contribute to this. Thyroid hormones, however, seem to play a slower, more prolonged and permissive role. Intermittent periods of refeeding carried out during the classical semi-starvation studies of this century also reveal how the RMR responds to refeeding are also not immediate. The refeeding studies confirm the contribution from reduced cellular metabolism to the decrease in RMR during dietary restriction. In Benedict's (1919) study the metabolic rate measurements were made after 4 d of refeeding (during Thanksgiving, 1917) and after 18 d (during Christmas recess, 1917–18) and were found to return to near normal levels even without the restoration of body-weight to control levels. In the Minnesota studies of Keys *et al.* (1950), the earliest measurements of metabolic rate were made 10 d after rehabilitation and the increase in metabolic rate was related to the energy intake of the rehabilitation diet. Even during refeeding of semi-starved obese subjects (Jung *et al.* 1980*b*) the changes in SNS activity (as measured by plasma levels of NA and 24 h urinary excretion of HMA) show a dramatic rise within 1 d of the increased intake. The changes in peripheral thyroid metabolism take longer.

Metabolic changes initiated mainly by a reduction in insulin levels which is the key hormonal signal, aided by a rise in plasma glucagon, will help mobilize glucose from liver by glycogenolysis and subsequently increase gluconeogenesis and lipolysis. An increase in amino acid mobilization will take place when the active tissues begin to act as a source of substrate fuels. Euglycaemia will be maintained both by an increase in hepatic glucose production as well as reduced utilization of glucose both in muscle and adipose tissue. A shift in the substrate fuels used by the tissue occurs later with a preference for fatty acids and ketone bodies.

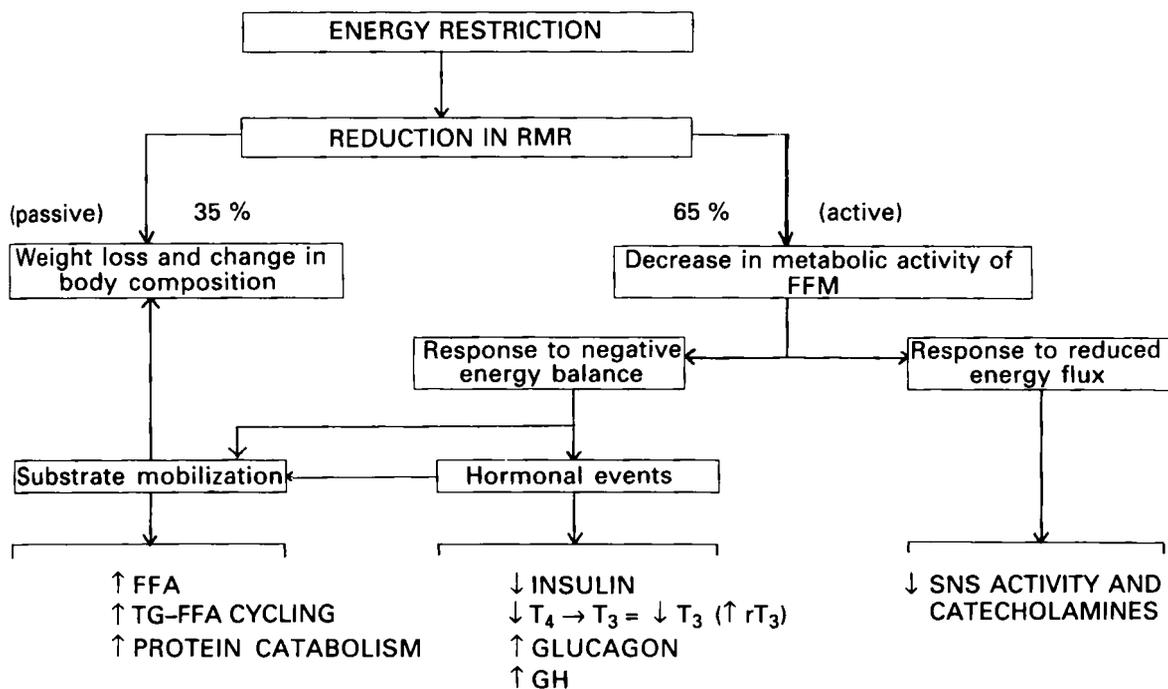


Fig. 2. Possible mechanisms involved in the adaptive reduction in resting metabolic rate (RMR) during short-term energy restriction. FFA, free fatty acids; FFM, fat-free mass; TG, triacylglycerols; T_4 , thyroxine; T_3 , triiodothyronine; rT_3 , reverse T_3 ; GH, growth hormone; SNS, sympathetic nervous system.

It is likely that two separate mechanisms operate to produce the delay in the RMR response to energy restriction: (a) a time lag in the physiological mechanisms that are involved in the actions of the three key thermogenic hormones (NA, insulin and T_3) as they decrease on energy deprivation. This delay varies with each hormone and may operate at several levels including the post-receptor level; (b) the RMR may be maintained in the initial days of energy restriction due to a rise in glucagon levels, an increase in the availability of endogenous substrate fuels such as FFA, and an enhanced tissue protein catabolism all of which may tend to stimulate cellular metabolism. Subsequent reduction in RMR and energy output are inevitable if the energy deficit has to be met.

MECHANISMS INVOLVED IN THE METABOLIC RATE CHANGES DURING CHRONIC ENERGY DEFICIENCY

It seems to be a universal assumption that the physiological and metabolic responses of the human body to chronic energy deficiency are similar to and can be explained on the basis of the changes that occur during experimental or therapeutic energy restriction. This has resulted in considerable interest among nutritionists to look for physiological changes suggestive of an increase in metabolic efficiency of the active tissues even in states of chronic energy deficiency. Demonstration of a reduction in O_2 consumption per unit active tissue (FFM or LBM) has been considered to be indicative of an enhanced metabolic efficiency and as a sign of true metabolic adaptation (Waterlow, 1986). A decrease in BMR per kg

FFM (or LBM) in turn implies that the increase in metabolic efficiency is demonstrable in the other components of energy expenditure, particularly a decrease in the energy cost of physical activity of the individual (Ferro-Luzzi, 1985).

If, in fact, enhanced metabolic efficiency is an accompaniment of long-standing or chronic energy deficiency, one should be able to demonstrate changes in the key hormonal mechanisms that we believe play an important role in this response. The information on malnutrition in children and its relationship to catecholamines is confusing. In a small number of malnourished children the 24 h urinary excretion of metanephrines (expressed in $\mu\text{g}/\text{m}^2$ body surface area (BSA)) was significantly lower than in normal controls or in those children after recuperation (Bourgeois *et al.* 1973). Hoeldtke & Wurtman (1973) observed a reduction in urinary excretion of vanillyl mandelic acid (VMA) and dopamine, an unaltered NA excretion and an elevated adrenaline excretion in acute kwashiorkor. Ramirez *et al.* (1978) reported a high output of HMMA in malnourished children; whether these children were infected or were already under dietary rehabilitation is not clear. Graham & Placko (1975) found elevated catecholamine concentrations in infected malnourished children while uninfected marasmic infants showed a rise in catecholamine excretion during partial recovery. Similar increases during rehabilitation have been reported by others (Parra *et al.* 1973). Adults with protein-energy malnutrition have low levels of T_3 (Rastogi *et al.* 1974). Chopra & Smith (1975) have reported lower T_3 and free T_3 levels in adults with protein-energy malnutrition which responds to refeeding. Similar changes in thyroid status are seen, but are more marked in infants (Ingenbleek & Beckers, 1975) and children (Graham & Blizzard, 1973; Onuora *et al.* 1983) with malnutrition. Impaired glucose tolerance and a blunted insulin secretory response to glucose have been reported in protein-energy malnutrition (James & Coore, 1970; Rao & Raghuramulu, 1972; Milner, 1972). Nutritional rehabilitation results in partial recovery (within weeks) of the glucose tolerance and insulin secretion. Whether the impairment persists in later life is not resolved although recent animal models of protein-energy malnutrition in early life show a persistence of the impairment of insulin secretion (Swenne *et al.* 1987).

A critical analysis of the available information on catecholamines, insulin and thyroid status in chronic undernutrition or energy deficiency irrespective of whether they are in children or adults would confirm a reduction in all three hormones. Measurements made in a large group of healthy, active and non-anaemic but chronically energy-deficient individuals with short stature, low body-weights, low body mass indices on low energy intakes showed low basal levels of NA and low T_3 levels as compared with well-nourished controls; they, however, had comparable levels of T_4 and free T_3 (Shetty *et al.* 1988; Shetty, 1990). Their insulin levels varied. These energy-deficient subjects showed several functional characteristics indicative of changes in their SNS activity (Shetty & Kurpad, 1990) and lowered thermogenic responses to NA infusions (Kurpad *et al.* 1989*b*). These changes in their SNS activity and thyroid status, which are similar to that seen during experimental or therapeutic energy restriction, are on the face of it indications of the existence of a true metabolic adaptation since it has been argued in the present review that such alterations in these key thermogenic hormones have, possibly, an important role to play in the adaptive changes in BMR.

BMR expressed either in absolute terms (i.e. MJ/d) or expressed per unit BSA are always low in individuals who are chronically undernourished or energy-deficient. Undernourished German prisoners who had lost more than 25% of their body-weight had BMR per unit BSA 16% below normal values (Beattie & Herbert, 1947). Male adults who were malnourished and semi-starved showed a 20% reduction in their BMR per unit BSA (Venkatachalam *et al.* 1954). Victims of severe malnutrition in the Warsaw ghettos also had markedly lower BMR varying between -10% and -40% depending on the severity of the

malnutrition (Fliedebaum *et al.* 1979). Similar findings were reported in other groups of chronically malnourished individuals during the Second World War. The picture, however, is confusing when attempts were made to express BMR per unit weight of the active tissue mass; some of the previously-described studies on malnourished subjects were in fact interpreted as failing to demonstrate any significant decrease in metabolic rate per unit active tissue mass, although the BMR per unit BSA were lower (Beattie & Herbert, 1947; Venkatachalam *et al.* 1954). Ashworth (1968) while reporting a 12% reduction in BMR in Jamaican subjects on low energy intakes also confirmed her inability to show clear-cut evidence of an adaptive response in the BMR.

In one study a conscious and deliberate attempt was made to demonstrate possible similarities in the metabolic response to prolonged experimental semi-starvation and chronic undernutrition. BMR measurements made in healthy, undernourished labourers in 1972–3 (Shetty, 1984) showed a reduction in the metabolic activity of the active tissue mass which perhaps could be interpreted as indicating an enhanced metabolic efficiency, although the major share of the fall in BMR was attributed to a decrease in the total mass of lean tissues. Recalculation of data from an earlier report by Ramanamurthy *et al.* (1962) also showed that the BMR expressed per unit active tissue was considerably lower in adult, undernourished males. However, a large number of measurements made over the last decade, in chronically energy-deficient subjects who had functional changes in their SNS activity and thyroid hormone status showed no reduction in BMR per unit FFM (Kurpad *et al.* 1989*b*). On the contrary, it now appears that BMR expressed per kg FFM is significantly higher in a large number of chronically energy-deficient subjects as compared to well-nourished controls (M. J. Soares & P. S. Shetty, unpublished results). A comparable and equally large series of BMR measurements reported by Srikantia (1985) also showed the same trend, BMR per unit body-weight increasing as the weight-for-height expressed as a percentage of standard diminished. BMR measurements made in a rural, south Indian village (McNeil *et al.* 1987) were also comparable to ones referred to earlier and provided no evidence of metabolic adaptation in individuals from poor socio-economic groups on lower levels of intake. The changes in BMR measurements made on chronically-undernourished individuals over the last two to three decades in India seem to show a trend over a period of time when food intake surveys have also indicated a remarkable increase in the mean energy intake of individuals and households (Rao *et al.* 1985).

The evidence that mechanisms of improved efficiency of energy utilization are operative in free-living populations on low energy intakes with very similar but compromised anthropometry appears therefore to be tenuous and contradictory. If enhanced metabolic efficiency is indeed present during chronic undernutrition, then a reduction in BMR per kg FFM may not necessarily reflect this phenomenon. If individuals who have anthropometric or functional characteristics suggestive of long-term energy inadequacy manifest a reduction in BMR per kg FFM, either BMR per kg active tissue is not an index of metabolic efficiency as is universally believed (Waterlow, 1986) or metabolic efficiency is not a characteristic and constant feature of chronic energy deficiency. Changes in BMR per unit of active tissue mass are perhaps not a *sine qua non* for metabolic efficiency.

Recent studies examining changes in body composition of adults with naturally occurring chronic undernutrition reveal a gradation of changes related to the severity of the deficiency (Barac-Nieto *et al.* 1978). Body cell mass was reduced even with moderate deficiency and the muscle mass was more affected than other cells. Muscle cell mass seemed to decrease linearly with increasing severity of undernutrition, while the visceral cell mass showed little change. Other recent estimations also indicate a greater reduction in muscle mass with visceral mass apparently being spared (M. J. Soares & P. S. Shetty, unpublished results). Protein turnover using ¹⁵N-labelled glycine in those chronically undernourished

with elevated BMR per kg FFM also revealed the existence of a greater visceral pool and a reduced muscle mass (P. S. Shetty, M. J. Soares, L. S. Piers, S. Robinson, A. A. Jackson & J. C. Waterlow, unpublished results). These findings may help explain the increase in BMR per unit active tissue since the FFM or LBM appears to have a higher proportion of the metabolically active visceral mass as opposed to a relatively less active muscle mass.

Passmore & Draper (1964) attempted to partition the resting O_2 utilization among the principal organs of a healthy man. According to them skeletal muscles, which comprise nearly 50% of body-weight, contribute about 18% of resting metabolism, while visceral organs such as the liver, heart and kidney use up nearly 45% of the total O_2 consumption at rest. A more recent analysis by Keys *et al.* (1973) shows that in normal adults the combined weights of the brain and liver constitute only 3–5% of total body-weight but require about 40% of RMR while skeletal muscle which constitutes between 25 and 50% of body-weight accounts for only 15–25% of RMR. An elegant series of experiments by Koong & Ferrell (1990) has demonstrated how animal models of similar body-weight, produced by different nutritional regimens, show a change in BMR corrected for metabolic body size when the visceral mass:body-weight ratio changes. These experiments prove that metabolically active tissues account for a significant proportion of basal metabolic activity which is far in excess of the proportional weights of these tissues. RMR, thus, seems to be dictated by the heterogeneity of active protoplasmic tissues in the body, and these various aerobic tissues are vastly different per unit mass in different individuals and nutritional states. These disproportionate rates of requirement of O_2 at rest per unit mass of the tissue explains why a variety of body compositional variables do not always predict RMR as well as we should expect them to.

Along with these changes in body composition seen during long-term energy inadequacy, there is also a change in the extra-cellular fluid compartment which will also contribute to influence the BMR expressed per unit active tissue (Barac-Nieto *et al.* 1978; Widdowson, 1985). Chronically undernourished subjects who have to do hard physical labour may be expected to have relatively more dense bones which may also influence this variable and thereby contribute further to demonstrate an apparent increase in metabolic efficiency (Sims, 1986). If the range of body composition changes seen during chronic energy deficiency influence the BMR per unit active tissue, undoubtedly BMR per unit FFM or LBM cannot reflect a true change in the metabolic efficiency of the active tissue mass of the body. Partitioning of the body into FFM or LBM and fat mass is inadequate; simple techniques need to be evolved to further partition FFM or LBM into muscle and visceral masses. Investment in clinical evaluation of body composition is clearly an emerging area demanding further research inputs.

SUMMARY

Energy restriction in humans results in a reduction in the BMR. Over a short period, the decrease in metabolic activity of the tissues contributes most to this reduction: in the long run the loss of body tissue contributes more to the lowered BMR. Several physiological mechanisms, chiefly hormonal, operate to decrease the metabolic activity of the tissue mass to enhance its metabolic efficiency. SNS activity is toned down, signalled by the decrease in energy flux, while the negative energy deficit initiates changes in peripheral thyroid metabolism and lowers insulin secretion. The reduction in the activities of these three key thermogenic hormones possibly acts in a concerted manner to lower cellular metabolic rate. Changes in other hormones such as glucagon, growth hormone and glucocorticoids will influence these changes and at the same time in association with the insulin deficiency will

promote endogenous substrate mobilization which will lead to an increase in circulating FFA and ketone bodies. The elevated FFA levels, alterations in substrate recycling and protein catabolism will also influence the resting energy expenditure. What contribution reductions in $\text{Na}^+\text{-K}^+$ pumping across the cell membrane and futile substrate cycling (now considered possible sensitive metabolic regulators) make to the reduced energy output is not known. These hormonal and metabolic changes that accompany energy restriction aid the survival of the organism and can, hence, be considered as adaptive in nature.

Whether similar adaptive changes occur in individuals who have been chronically energy deficient for long periods is very doubtful. Chronically undernourished subjects may show similar alterations in some of the hormones as well as functional changes in their responses. However, the changes in metabolic rate which have been considered as indicative of an enhanced metabolic efficiency of the tissues may well be attributed to incorrect estimates of FFM and to the body compositional changes that accompany chronic undernutrition. It is, hence, unlikely that the reduction in metabolic rate per unit active tissues, when seen in the undernourished, reflects a true increase in metabolic efficiency which can be considered as a beneficial, adaptive response.

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