Nutrition and Aging: Changes in the Regulation of Energy Metabolism With Aging

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I. Introduction

The human life cycle has undergone dramatic changes in the last century. At the beginning of the 20th century, average life expectancy at birth in the United States for males and females combined was a mere 50 years. Now, 100 years later, average life expectancy is 77 years and is anticipated to increase to an average of 85 years by the year 2125. This change is due primarily to compression in morbidity rather than to an extension of maximum life span. As a result of this, many more individuals are now living longer during the period when they can be classified as “elderly,” and the percentage of the United States population over the age of 65 years has increased from 4% in 1900 to 13% currently (34).

In recognition of the changing world demographics, studies of the effects of aging on physiology and metabolism are increasingly being scrutinized for their ability to...
contribute to better approaches for improving the quality of life in older individuals and preventing late-life disabilities. In this context, understanding changes in energy regulation with aging is particularly important, because prevention of weight loss and fat loss is an important component of maintaining health in old age. The changing demographics now also suggest that weight loss in older persons may not necessarily be manifested by body mass index in underweight ranges; indeed, in National Health and Nutrition Survey (NHANES) II, involuntary weight loss appeared disproportionately in older obese adults and is associated with increased mortality (145).

This review synthesizes data and reviews changes seen in energy regulation with aging and our emerging understanding of underlying mechanisms.

II. CHANGES IN THE REGULATION OF ENERGY INTAKE

A. Comparisons of Young and Elderly Adults

Several disease states common in old age, such as cancer, are well known to be associated with body weight and fat losses. However, there has been no general consensus until recently over whether healthy aging is also associated with weight loss mediated by a decreased ability to regulate energy intake (22, 24, 107, 108, 125, 132, 139).

The first study of this topic was by Roberts et al. (132), who investigated whether older age is associated with weight loss mediated by a decreased ability to regulate energy intake. Since day-to-day variability in energy intake is typically 20–25% (4) while day-to-day variability in energy expenditure is typically only 10% (53), there are necessarily substantial day-to-day fluctuations in energy balance. Overfeeding and underfeeding protocols are usually an attempt to examine experimentally the effects of variability in energy intake and energy balance within magnitudes that may occur during usual life. In the studies of Roberts et al. (132), separate overfeeding and underfeeding studies were conducted, with young and elderly men enrolled in each protocol. There were clear differences between age groups in body weight change (and energy intake) following the intervention, as summarized in Figure 1. Whereas young men responded to overfeeding by decreasing subsequent energy intake and to underfeeding by increasing subsequent energy intake, elderly men had neither of these responses. In consequence, young men tended to lose all the excess weight they gained during overfeeding, and after underfeeding gained back more weight than they had lost during the experimental period, whereas elderly men lost only 29% of the excess weight gained during overfeeding and gained back only 64% of the weight lost during underfeeding.

Thus, in two separate protocols involving opposite, experimentally imposed changes in energy balance, older men had a substantial reduction in their ability to maintain a constant long-term weight and presumably energy balance compared with young men. The fact that the same result was obtained under opposite experimental conditions (overfeeding and underfeeding) suggested a basic difference between age groups rather than an ex-

![FIG. 1.](https://physrev.physiology.org/)

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peripheral artifactual and implies that aging is indeed associated with an impaired ability to accurately regulate energy balance through adjustments in energy intake. However, an unresolved question raised by that study was whether the weight changes persisted over an extended period of time, because the follow-up period was relatively short (~7 wk). In a separate study by the same group (107), body weight change following experimental underfeeding was studied for a 6-mo period. As in the first study, young normal-weight subjects regained essentially all the weight lost during underfeeding, but elderly subjects only gained back 20% of the weight they lost on average. On a shorter time scale, consistent results have also been reported by two other groups. Rolls et al. (139) gave yogurt preloads to young and older men and measured compensation for the additional energy at the subsequent meal. They observed that young men precisely compensated for the preload with the result that net food intake was relatively unaffected, whereas older men did not. Morley (108) also gave preloads to young and older subjects and found less complete compensation in the older subjects than the young ones.

These four studies, together with several animal studies reporting impaired regulation of food intake in old age (11, 27, 56, 65, 70, 76, 108, 187, 194, 196), suggest markedly impaired regulation of energy intake in late life. Moreover, when interpreting the combined results from these investigations, it is important to recognize that, as with most studies of human aging physiology, the subjects were healthy older men and women who would be predicted to be less likely to exhibit age-related decrements in function than the more typical elderly individual with multiple health problems. Thus, although the results observed here should not be extrapolated beyond the types of diets and experimental conditions used in the study, they may nevertheless underestimate the true extent of energy dysregulation in more typical elderly individuals with multiple chronic diseases.

B. Reduced Hunger and Increased Satiation as Mediators of Impaired Defense Against Energy Imbalance

The causes of apparent dysregulation of food intake in old age are not well understood, in large part because the mechanisms underlying successful energy regulation at any age are not fully understood. In young adults, it is generally accepted that multiple overlapping mechanisms exist to regulate energy balance within fairly narrow limits, with hunger and satiety being monitored both peripherally and centrally by several systems. These mechanisms have not proven to be resistant to environmental pressures to overeat, as seen in secular trends of weight gain worldwide during the past 30 years (46). However, there is general agreement that bodily mechanisms for energy regulation do typically protect children and young adults from weight loss if not weight gain. Thus there are multiple candidates for age-related changes that could contribute to the anorexia of aging, as outlined in several recent reviews (8, 10, 62, 108, 111, 126, 134). It is important to recognize that redundancy in energy regulation mechanisms is likely, because of the essentiality of maintaining energy balance within limits that do not prejudice reproduction during young adult life and species survival generally, and this implies that multiple pathways need to fail in old age before a measurable impairment in energy regulation is seen. Thus quite a large number of candidate mechanisms may potentially be impaired in old age for impaired regulation of energy intake to be seen, and work is needed to identify which mechanisms are quantitatively important. The strongest candidates based on current knowledge are summarized below and are combined in a suggested model in Figure 2.

Concerning evidence that the presumed intermediate end points of energy deregulation, hunger and satiety (the latter being defined as the sensation of fullness resulting from eating that leads to cessation of eating), are altered in old age, several studies have documented abnormally low hunger following fasting or experimental induction of negative energy balance in elderly subjects (22, 24, 58, 107, 139, 173, 194, 198). Moriguti et al. (107) reported older subjects in an experimental underfeeding study experienced significantly less frequent symptoms of hunger (assessed using visual analog scales) than young subjects, despite the fact that the older subjects lost significantly more weight and would therefore be expected to experience more frequent hunger. In addition, Clarkston et al. (22) reported that carefully screened older persons tended to be less hungry than younger persons after a standardized overnight fast, and after a standard meal they reported a greater degree of satiation than did younger persons. Intraduodenal nutrient infusion has also been reported to reduce hunger in young but not elderly adults (24), while a low perception of hunger during daily life assessed by the eating inventory questionnaire (173) predicted a 0.5-kg weight loss per year in a group of women with an average age of 61 at baseline (58). Sturm and co-workers (175, 176) further suggested that both decreased premeal hunger and increased postmeal satiation are independent contributors of impaired energy regulation in old age and that the increased satiation is associated with increased antral area (and presumably distension) after consumption of meals. This latter suggestion is also consistent with the animal literature suggesting that low energy intake leading to weight loss in elderly rats is caused by consumption of smaller meals of shorter duration, rather than normal-sized meals at reduced frequency (9). Combined, these results suggest that a reduced perception of hunger and/or increased satiation...
precede and are contributing factors to weight loss in old age.

C. Glucose and Insulin as Potential Mediators of Impaired Regulation of Food Intake

Alterations in glucose homeostasis in old age may contribute to altered hunger and satiety. Blood glucose has long been postulated to be a trigger for hunger signals in both rodents and humans (2, 10, 17, 19, 90, 98), and recent studies in young adults and animal models linking transient small decreases in blood glucose to initiation of food consumption have provided tentative data in support of this speculation (20, 170). Also consistent are the multiple studies of the effect of dietary glycemic index on hunger and energy intake (reviewed in Ref. 127), suggesting that foods with a high glycemic index, such as white bread, breakfast cereals, and other refined carbohydrates (which typically have a glycemic index of 100–120 when white bread is used as the reference with a value set at 100 and which induce relative hypoglycemia 90–120 min after food consumption) promote a more rapid return of hunger and an increase in subsequent energy intake.

Most young adults maintain circulating glucose within the range of 80–140 mg/dl throughout cycles of feeding and fasting, through balanced alterations in secretions of insulin and counterregulatory hormones that serve to facilitate uptake and synthesis and release of glucose under different metabolic conditions. However, when hypoglycemia occurs, it powerfully elicits sensations of hunger in young adults. In contrast, even healthy older adults have a broader range over which circulating glucose is maintained and in addition have attenuated counterregulatory responses and delayed recovery from hypoglycemia (85, 99, 100). Melanson et al. (95) recently reported persistently elevated postprandial glucose and insulin in the older women following consumption of 2,092- and 4,184-kJ test meals compared with younger women. Provided that central mechanisms for converting a signal of low blood glucose into a sensation of hunger are intact in older individuals, as one study (16) but not some others (85, 99, 100) indicated, the elevated postprandial blood glucose (mean values of ~120 mg/dl compared with ~100 mg/dl in young adults) observed by Melanson et al. (95) could potentially lead to an attenuated return of hunger in the postprandial period. The elevated circulating insulin levels (~8% higher than in young adults) that are typical of the reduced insulin sensitivity occurring in old age and which accompanied high postprandial glucose levels in that study (95) may also contribute to a delayed return of hunger, perhaps through a central satiety effect of high insulin levels (196) or by altering central sensitivity to other components in the cascade of me-

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1 Glycemic index is a property of food which is defined as the area under the glucose curve after consumption of the food in an amount containing 50 g carbohydrate, divided by the area under the plasma glucose concentration curve versus time over 2 h after consumption of white bread or glucose (these are two different standards) also containing 50 g carbohydrate.
D. Other Hormonal Mediators of Impaired Regulation of Food Intake

Aging is associated with impairments in numerous hormonal systems within the body (101, 143), which may additionally influence energy regulation and are reviewed in detail elsewhere [for example, Blanton et al. (8) and Horwitz et al. (62)]. Although it is not possible to discern which of the many impairments noted below are quantitatively significant in the dysregulation of energy balance in old age, future studies in humans and animals may help to dissect out the key systems and individual factors.

Glucagon is currently suggested to be one of the signals of satiation (50, 168, 174), with its action mediated at least in part through vagal afferent signals from the liver and perhaps also by increasing blood glucose (which is another postulated signal, see above). Melanson et al. (95) reported that elderly women have significantly elevated levels of glucagon by up to 25% in response to consumption of meals of 2,002 kJ (500 kcal) or greater, identifying a potential role for glucagon in the apparently enhanced satiation associated with old age.

There is also evidence of both altered synthesis and/or secretion and impaired central responsiveness to gut hormones in late life. For example, fasting levels of the postulated satiety hormone CCK are typically five times higher in elderly individuals than in young adults (83, 87, 170, 175), rise more in response to an intraduodenal fat infusion than in young adults (83), but appear to have a weaker effect in suppressing satiety than expected in relation to circulating levels (84, 175). Concerning evidence for impaired detection of gut hormone signals, the rise in CCK, glucagon-like peptide 1 (GLP-1), and polypeptide YY associated with intraduodenal lipid infusion were significantly correlated with a decrease in hunger in young but not older individuals in one study (84). Consistent data were also obtained in animal models, with administration of exogenous CCK, bombesin, and calcitonin having a greater suppressing effect on food intake in young compared with elderly mice (169). Strum et al. (175) recently suggested that in fact higher CCK in late life is unrelated to the anorexia of aging, based on the finding that abnormal circulating levels exist in both underweight elders (presumably exhibiting the anorexia of aging) and well-nourished elders (presumably without an anorexia of aging). However, if energy dysregulation in old age requires both underlying biological impairments and lifestyle factors that (see below) promote expression of the biological impairments, well-nourished elders could exhibit the same biological factors while differing only in more favorable life-style conditions. Further work is needed to elucidate the role of different metabolic parameters including CCK in the anorexia of aging.

Leptin (57, 199) has also been proposed as a candidate hormone for the anorexia of aging, but emerging data now suggest this is unlikely. In young adults, leptin is secreted by fat cells and acts centrally to reduce feeding and to increase energy expenditure through pathways thought to involve inhibition of synthesis of NPY, which itself stimulates feeding (see below) (8). There is a significant correlation between circulating leptin and body fat

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in young adults (23, 103, 136), but in elderly adults circulating leptin may be lower than expected for body fat levels (8, 136). Furthermore (8, 88, 103, 136, 171, 195), central leptin administration has relatively little effect on food intake and thermogenesis in old, obese rats compared with substantial effects in young, lean ones (for example, 42% reduction in food intake following central leptin administration) (150) due to decreased leptin responsiveness in old age (149, 150, 167).

The fact that a variety of peripheral satiety signals, including CCK, leptin, blood glucose, and the sympathetic nervous system (70), and perhaps ghrelin (52) all appear to be imperfectly detected in old age may be related to impairments in one or more central mechanisms responsible for coordination of energy regulation signals. One important potential candidate is NPY, one of the most abundant peptides in the brain that is an integrator of metabolic endocrine and behavioral systems (73, 74) and acts through various hypothalamic nuclei to stimulate feeding behavior and affect release of hormones that modulate energy metabolism such as insulin (73, 74). The finding of high levels of NPY in both plasma and cerebrospinal fluid of elderly anorectics provides some circumstantial evidence that NPY expression does not relate to the anorexia of aging, since high NPY is predicted to increase feeding in the young (87). However, the fasting-induced increases in both food intake and NPY gene expression normally seen in young rats are consistently attenuated in aging rats (55, 56, 76, 194), indicating that responsiveness to NPY is impaired in old age. Consistent with this suggestion, the feeding and drinking responses to NPY injection in the paraventricular hypothalamic nucleus are markedly attenuated in aged rats (7, 118), with only one-quarter to one-third of the response seen in younger animals (7).

E. Changes in Taste and Smell as Potential Contributors to Impaired Regulation of Food Intake

There are well-documented age-associated declines in taste and smell sensitivity (36, 42, 151–155, 191) that may play a more important role in the energy dysregulation of old age than currently recognized. In particular, most studies (36, 42, 151–156, 191) suggest that detection and recognition thresholds for salt and other specific tastes increase with age, in part because of the use of medications that impact taste (see below) but also because of a loss of functional taste bud number and structure (1) and impaired olfaction.

Intact senses of taste and smell appear to be necessary for the cephalic phase of digestion, which includes the initial increases in salivary, gastric, pancreatic, and intestinal secretions that initiate digestion (148, 153). The cephalic phase of postprandial metabolism is initiated by olfactory, gustatory, and cognitive stimulation by food and includes activation of both the sympathetic and parasympathetic nervous systems, which in turn initiate and augment multiple digestion-related processes that serve to prepare the body to absorb nutrients (15). Cognitive, visual, and olfactory stimulation can elicit a release of saliva that averages between one-fourth and two-thirds of that noted following masticating, but not swallowing, food. Because saliva contains digestive enzymes that initiate the breakdown of starch, the increased production of saliva following consumption of most foods (21, 197) may actually accelerate carbohydrate digestion and absorption. Tasteless stimuli have minimal effect on gastric acid release and pancreatic secretions, whereas palatable foods have long been known to result in marked stimulation of secretions that may promote digestion (64, 117).

Related to this observation, there is preliminary evidence suggesting that palatability may influence the rate of nutrient absorption and/or initiate gluconeogenesis (147, 172). Sawaya et al. (147) observed that consumption of bland foods decreases the glycemic response to test meals compared with palatable meals of identical macronutrient composition, which suggests there may be a reduced rate of gastric emptying and hence slower digestion of bland foods. Consistent results were reported by LeBlanc and Brondel (72), and although Warwick et al. (189) reported no differential effect of palatable versus bland liquids on circulating glucose, liquid test meals were used in that study. Liquids appear to have very different effects on satiety from solids (89), which may possibly explain the different results obtained. Teff and Engelman (179) also found no difference in postprandial blood glucose responses to palatable versus unpalatable test foods, but the foods used in that study were only chewed and not swallowed, which would be predicted to attenuate the cephalic response.

If the losses in taste and smell associated with aging have an equivalent effect (i.e., making food seem more bland, as commonly reported), the anticipated decrease in gastric emptying and likely delayed absorption of nutrients could help explain the reported increase in satiation and decrease in hunger in old age. Consistent with this suggestion, elderly individuals eat more of individual foods if they are flavor-enhanced (157), and in another study smell was significantly correlated with hunger and appetite (31). It should be noted that, in this latter study, there was no association between smell and reported energy intake; however, documented inaccuracies in the measurement of reported energy intake (160) make the validity of such correlations uncertain. Additionally reported by Schiffman et al. (152), elderly individuals have a reduced ability to identify individual foods in blinded tests. If foods taste more similar, the pleasure of a diverse diet will presumably be reduced, thus tending to decrease...
dietary variety in the absence of environmental and social factors working in the opposite direction.

F. Reduced Dietary Variety as a Mediator of Impaired Regulation of Food Intake

Studies in laboratory rats, cats, and hamsters have shown that energy intake is greater when a variety of foods is provided compared with when only a single food is provided (92, 93). Numerous single-meal studies in humans also show this phenomenon (93, 141). While two longer-term studies have shown that laboratory rats have greater body fat and body fat gain when fed a variety of foods compared with when only a single food is fed (81, 142), long-term studies in humans have been lacking until recently. McCrory et al. (92) recently reported on the long-term association between dietary variety and body fatness in healthy adult men and women (92). In multiple regression analyses controlled for age and sex, dietary variety from a combined group of sweets, snacks, condiments, entrees, and carbohydrates was positively associated with body fatness, and in the same model dietary variety from vegetables was negatively associated with body fatness. In other words, individuals who consumed a wide variety of higher energy foods coupled with a low variety of vegetables were relatively fatter.

Self-reported records of dietary intake indicate that dietary variety is reduced in old age (17, 39), and a recent study also demonstrated particularly low dietary variety among elderly adults with low body mass index (BMI) (133). The reasons why dietary variety decreases in old age and is particularly low in elders suffering from low BMI are not fully understood but may potentially provide an additional explanation for weight loss in old age. Concerning potential mechanisms, a study by Rolls and McDermott (140) observed that older adults have reduced “sensory specific satiety,” a term used to describe the phenomenon of declining pleasantness of food as it is consumed. The adolescent and young adult subjects of Rolls and McDermott (140) responded in the expected manner to a yogurt preload (i.e., decreased desire to eat yogurt but not other offered foods), but older subjects did not respond and in fact reported an equivalent desire to eat yogurt and other test foods after the preload. Although necessarily short-term and requiring confirmation in a larger study, these data suggest that older adults lack normal patterns of sensory specific satiety that encourage wide dietary variety. The underlying reason for decreased sensory specific satiety in old age may potentially be traced back to the declines in taste and smell sensitivity associated with aging documented above (36, 42, 151–156, 191), with their predicted impact on the extent of digestion and availability of incoming substrates into the circulation.

G. Medical and Social Factors

Many social and medical changes associated with aging have been suggested to cause weight loss, such as poverty, bereavement, social isolation, poor dentition, chronic disease, and the use of multiple prescription medications (36, 54, 108–111, 157). In addition, depression has been suggested as an important cause of weight loss among the elderly, a finding that has been confirmed in an analysis of cohort data (35). However, it is interesting to note that the study of DiPietro et al. (35) showed that depression was associated with weight loss only in individuals aged 55 years or older and was actually associated with weight gain in younger adults. One potential explanation for this finding (132) is that psychosocial factors are potential catalysts for weight loss only when there is an underlying impairment in the regulation of food intake that allows impediments to eating to be expressed.

Concerning social isolation, de Castro and de Castro (30) reported that less energy is eaten at meals taken alone compared with meals eaten in company, with the difference in energy intake between the two situations being a substantial 30%. Although such data are generally used to suggest that social eating is disadvantageous because it promotes overeating and obesity, the opposite (namely, that eating alone leads to undereating and weight loss) may be an equally valid interpretation. This is especially true when it is considered that humans are a gregarious animal species and naturally eat in social groups (102). This is directly relevant to the issue of low energy intake in the older population, because bereavement and functional disabilities can limit social contact (86). Thus an increased frequency of eating alone may be one of the factors contributing to low energy intake in older adults. Furthermore, there is a positive association between the frequency of eating restaurant food and body fatness (91) and for reasons of social isolation and functional disabilities, older adults may eat out less frequently. In support of this suggestion, in the recently reported NHANES 1999–2000 survey, adults younger than 45 years of age reported meals out approximately twice as often as those over the age of 65 years (66). The combination of these different observations and findings suggests a potentially important role for reductions in social meals and eating out in the low energy intake and body weight loss of older adults, which is independent of any biological impairments associated with aging.

III. CHANGES IN ENERGY EXPENDITURE WITH AGING

A. Basal Metabolic Rate

Basal metabolic rate (BMR) is the energy expenditure of an individual after a 12- to 14-h overnight fast
during a period of mental and physical rest in a thermodeutral environment and reflects energy use of the body for such basic functions as maintenance of electrochemical gradients, transporting of molecules around the body, and biosynthetic processes. Frequently, a “resting energy expenditure” is measured in preference to a BMR. Resting energy expenditure is quantitatively similar to the BMR, but it is not subject to all the exacting requirements of a BMR. In this review, measurements of resting energy expenditure are taken to be equivalent to BMR.

Typically, BMR is the largest component of energy expenditure and comprises 50–70% of total expenditure in most adults. A decline in BMR with aging is well recognized (68, 119) and is implicit in standard equations for predicting BMR in healthy men and women of different ages (40). A longitudinal study by Keys et al. (68) documented a decline in BMR with age of 1–2% per decade; based on this assessment, a reduction in BMR of ~400 kJ/day can be predicted between 20 and 70 years of age.

The question of whether the decline in BMR with aging can be accounted for by concomitant alterations in body composition, or whether there is also a decline in BMR per unit of tissue, has been studied by several research groups. Many (48, 69, 116, 120, 128, 188) though not all (26, 144, 183) cross-sectional studies reported that BMR is lower in old age even after adjustment for lower fat-free mass in older individuals, with adjusted BMR values being ~5% lower for elderly adults than for young adults. However, loss of fat-free mass is not the only body composition change that occurs during the adult human life cycle, and in particular, there is usually a substantial increase in fat mass from young adulthood to middle age that often quantitatively exceeds the concomitant loss of fat-free mass (resulting in net weight gain). Two investigations also analyzed changes in BMR with aging in relation to individual variability in both fat-free mass and fat mass (27, 186). In both of these studies, there was a significantly lower BMR in elderly adults compared with young ones. Because adipose tissue is metabolically active, albeit less metabolically active than muscle and other components of fat-free mass (40), failure to account for the increase in fat mass through middle age in analyses of BMR could theoretically underestimate BMR adjusted for fat-free mass and help explain the conflicting results of the earlier studies.

More recently, three additional studies have further examined BMR in relation to compartmentalized body composition. Roubenoff et al. (144) examined BMR in relation to total body potassium (an indicator of metabolically active tissue independent of such compartments as extracellular water) and found no effect of age on the relationship between total body potassium and BMR. Consistent with this suggestion, Kutsuzawa et al. (71) found no effect of age on muscle energy metabolism of the forearm assessed by $^{31}$P-magnetic resonance spectroscopy, and Bosy-Westphal et al. (13) found no effect of age on BMR when organ sizes within the free-fat mass (assessed by magnetic resonance imaging) were taken into account (different organs are known to have tissue-specific rates of energy expenditure). These reports, suggesting no effect of age on BMR beyond that due to the loss of different body tissues is taken into account, would appear to conflict with the further finding of Willis et al. (193) that there is a significant age-associated decline in cerebral glucose metabolism (indicating energy expenditure since glucose is the primary metabolic fuel of the brain). However, Willis et al. (193) also quantified the change in cerebral glucose metabolism with age, and the estimated 5 g/day decrease in glucose use between 20 and 70 years for an adult with normal brain size would result in an estimated decrease in BMR of only 125 kJ/day, which is <2% BMR for most adults and would not be detected significantly except in extremely large studies. Taken together, these observations indicate that BMR is indeed lower in the elderly compared with young adults even after taking body composition changes associated with aging into account, but the difference is so small (<2% based on changes in brain glucose metabolism) that it can be considered insignificant.

B. The Thermic Effect of Feeding

The thermic effect of feeding, previously known as specific dynamic action, is the increase in energy expenditure above basal that is associated with consuming, digesting, and assimilating food. Some of the increase in energy expenditure can be directly attributed to the metabolic costs of digestion, resynthesis of macronutrient polymers, and related processes (termed “obligatory thermogenesis”), while the other component of the increase appears to be due to concomitant activation of the sympathetic nervous system (termed “facultative thermogenesis”) (28).

The thermic effect of feeding is equivalent to 8–15% of ingested metabolizable energy. Some studies report a decrease in the thermic effect of feeding in old age (51, 106, 161, 164, 180, 185), while other studies report no change (27, 49, 96, 121, 182, 188). To avoid the potential concern that meal size might influence differences in TEF between young and older individuals, Melanson et al. (96) measured the thermic effect of feeding at three levels of energy intake. There was no significant difference in the thermic effect of feeding between the age groups, and mean postprandial values for energy expenditure above initial fasting values were actually slightly higher in the older group than the young group. Although no conclusive explanation can currently be given for the different results between some of the studies, a suggested explana-
tion (96) is that the thermic effect of feeding does not decline with aging per se, but that some studies may have confounded age with factors that decrease thermic effect of feeding independent of aging, such as obesity and/or digestive problems that limit nutrient absorption. Alternatively, one recent study documented decreased β-adrenergically stimulated thermogenesis in aging, seen as an 18% greater infusion of isoprenaline needed to increase metabolic rate by 15% (67); the same group further reported diminished fat oxidation in response to isoprenaline (3). It is therefore possible that there is a small decrease in the sympathetic nervous system component of TEF with age but that quantitatively it is hard to detect and has given rise to inconsistent results between studies.

C. Total Energy Expenditure and Physical Activity Level

The third major component of energy expenditure is the energy expenditure for physical activity and arousal (these individual components are usually grouped together due to the difficulty of separating them experimentally). Energy expenditure for physical activity and arousal, together with the BMR and the thermic effect of feeding, comprise an individual’s total energy expenditure, which is equivalent to dietary energy requirements during weight maintenance. In theory, energy expenditure for physical activity and arousal, and hence total energy expenditure, can be determined by recording the amounts of time devoted to different activities and the energy costs of those activities (measured in a laboratory by respiratory gas exchange) and summing the individual components in what has been called the “factorial” method. However, in practice it is difficult to avoid underestimation of energy expenditure by this method because it is impossible to record every type of activity, and there are nonaccountable activities such as fidgeting that tend to get under-recorded (37, 135).

To avoid the pitfalls of the factorial method, substantial effort has been directed towards developing the doubly labeled water method as an alternative, longer term, and more accurate technique for measurement of total energy expenditure. This method was originally developed for use in small animals (77, 78), based on the principle that if two isotopes of water (H2 18O and 2H2O) are administered and their disappearance rates from a body fluid such as urine monitored, the disappearance rate of 2H2O reflects water flux and the disappearance rate of H2 18O reflects water flux plus carbon dioxide production rate (79). The difference between the two disappearance rates can therefore be used to calculate carbon dioxide production rate over a period of 1–3 wk, from which total energy expenditure can be calculated if information is available on respiratory quotient (177). Validation studies of the doubly labeled water method have been conducted in human infants and adults of different ages using respiratory gas exchange or dietary energy intake as the reference method (129, 159). All these studies showed a close agreement between total energy expenditure determined by doubly labeled water and total energy expenditure determined by a reference method, with a coefficient of variation for the new method of 2–6%. In consequence, the doubly labeled water method is now widely recognized as an accurate and precise method for assessment of total energy expenditure in human subjects. Delayed isotopic equilibration is recognized in elderly subjects, presumably due to the incomplete bladder emptying that frequently occurs in old age (6, 114, 158), but this effect has been demonstrated only for short equilibration periods after dosing (such as 4 h); in practice, this limitation can be eliminated by employing longer equilibration periods as recommended by Blanc et al. (6). Because the doubly labeled water method calculates the rate of carbon dioxide production, rather than the rate of energy expenditure, and because the heat equivalent of carbon dioxide varies with the substrates being oxidized (129, 159), it is necessary to have an estimate of the respiratory quotient (RQ) of the subject during the measurement period. Usually, RQ is estimated from information on the subjects’ dietary intake, either their reported macronutrient intakes or normative data from population surveys, and errors from necessary assumptions and errors in dietary records are recognized to be small and usually <2% (177).

A critical mass of doubly labeled water data has accumulated over the past 15 years, making it possible to evaluate typical changes in total energy expenditure and energy expenditure for physical activity (calculated as the difference between total energy expenditure and BMR plus the thermic effect of feeding, or indicated by a physical activity level calculated as the ratio of total energy expenditure to BMR). Several studies have reported lower total energy expenditure in elderly adults compared with young adults (116, 122, 138, 148), and the summary of data from different adult age-groups shown in Figure 3 illustrates a progressive substantial decline in total energy expenditure (and hence physical activity level) with age (5). Additional studies have also investigated differences in 24-h sedentary energy expenditure when adults are confined to a whole body calorimeter. In these studies, sedentary energy expenditure is lower in elderly adults than in young adults when activity in the chamber is flexible (186), but in whole body calorimeter protocols that standardize 24-h activity, there has been no difference in 24-h energy expenditure between age groups (186). Taken together, these data demonstrate declines in both planned exercise and spontaneous physical activity in healthy old age.
The causes of declining total energy expenditure and physical activity with age are not well understood. The declines with age are reported to parallel an increase in body fat mass, suggesting that changes in body composition may be important (130). Regression analyses predicting energy expenditure from body fat and fat-free mass in individuals of different ages show that there is a positive association between fat-free mass and energy expenditure but a negative association of fat mass with energy expenditure (130). Thus it is reasonable to speculate that the increase in body fat mass may help promote a decrease in energy expenditure for physical activity. In NHANES III, in those over 70 years, increased BMI or body fat was associated with limitations in functional living activities such as carrying groceries, suggesting that increasing body fat may influence energy expenditure through impairment of daily activities (29). However, Westerterp and Meijer and co-workers (94, 192) have pointed out that the decline in physical activity energy expenditure with age is most strongly predicted by age itself and not by body composition, indicating an effect of aging on expenditure independent of the quantity of lean tissue and fat mass. It is also noteworthy that maximal oxygen consumption is recognized to decline progressively with age, and very active individuals have declines of ~50% between 20 and 80 years that are of similar magnitude (albeit higher absolute values) to those experienced by sedentary individuals (33). These observations suggest that some parallel changes in fitness, energy expenditure for physical activity, and body composition with age are probably an inevitable consequence of the aging process, probably due to underlying hormonal and biochemical changes in skeletal muscle and the cardiovascular system rather than a cumulative consequence of long-term inactivity. Further studies are needed to determine the extent to which energy expenditure for physical activity can be maintained in old age in the general population, with the expectation based on current research that potential specific effects on energy balance may be small since any increase in energy expenditure associated with training seems to be offset by decreased voluntary energy expenditure at other times of the day (94, 192). However small the effects on energy balance, additional effects of exercise include positive effects on cardiovascular and bone health and prevention of falls and frailty.

D. Energy Expenditure Responsiveness to Energy Imbalance

The concept that energy expenditure plays an important role in the regulation of energy balance has been the subject of numerous investigations since the beginning of the 20th century (113), and it is now widely recognized that energy expenditure increases or decreases only to a limited extent to match energy intake to minimize changes in energy balance resulting from overeating or undereating (14, 59, 137).

Several studies published over the last decade have suggested there may be important changes in energy expenditure responsiveness to changes in energy balance with aging. Roberts and colleagues (107, 131, 146) conducted a series of overfeeding and underfeeding studies to examine the magnitude of changes in total energy expenditure and components of energy expenditure to energy imbalance in young (age 20–30 years) and elderly (age 60–80 years) men. In a combined analysis of the first overfeeding and underfeeding studies, a significantly attenuated resting energy expenditure response to changes in energy balance was observed in the elderly men (Fig. 4). Thus, during positive energy balance, the increase in
resting energy expenditure was lower in elderly men than young men relative to the level of energy imbalance. Similarly, the decrease in resting energy expenditure with negative energy balance was reduced in the elderly subjects. These changes can be predicted to result in greater fluctuations in body weight and fat mass with overeating and undereating in the elderly, due to reduced compensation from adaptive changes in energy expenditure. The differences between the age groups were statistically explained by differences in muscle mass between the groups, suggesting that 1) muscle is an important site of adaptive thermogenesis in humans and 2) the declines in muscle mass with age explain the reduced capacity for changes in energy expenditure with negative energy balance. However, when the results of these studies were separated into those obtained during overfeeding and underfeeding, the age-group difference in change in resting energy expenditure was only significant in the overfeeding group. Thus the question of whether alterations in energy expenditure responsiveness to changes in energy balance are general or specific to negative energy balance was unresolved.

To further examine this issue, the same group conducted a second, longer study to examine changes in the capacity for reducing energy expenditure with negative energy balance in young and elderly subjects. The results of this second study were consistent with the combined overfeeding/underfeeding analysis, showing an attenuated reduction in BMR during negative energy balance in the elderly subjects compared with young subjects (27). One theoretical expectation from these findings is that elderly people should lose more weight for the same decrement in energy intake. Consistent with this prediction, the second, longer underfeeding study in the series documented greater weight loss during underfeeding in elderly subjects than in young subjects despite the fact that compliance with the study diet appeared to be no different between the age groups.

**IV. CHANGES IN FUEL UTILIZATION WITH AGING**

The ability of the body to oxidize dietary fat must be a critical determinant of the success or failure of body energy regulation, because exogenous fat that is not oxidized must be stored (43, 44). Thus, if fat oxidation can adapt on a meal-to-meal or even week-to-week basis to match the fat content of the diet, there will be no net fat deposition or loss over time, and body adipose stores will remain constant. However, body fat stores will increase if fat oxidation is less than fat intake, and conversely, body fat stores will decrease if fat oxidation is greater than fat intake. The potential role of reduced fat oxidation in the development of obesity in adults of all ages is seen in the data from epidemiological studies that link consumption of a high-fat diet to increased body fat (80) and in dietary intervention studies that have showed higher energy intakes on high-fat diets than on low-fat diets matched for palatability (80). More direct evidence is also seen in the prospective studies that have demonstrated a significant association between low fat oxidation, relative to intake, and subsequent weight gain (200), although it is important to note both that positive energy balance is essential for net fat accumulation and that measurements of substrate oxidation have a strong potential to be confounded by uncontrolled dietary intake in the days before scientific study.

Nevertheless, observations to date raise the question of whether there might be age-associated alterations in fat oxidation in the postprandial state that could help explain age-associated changes in body fatness. In a longitudinal 24-h whole body calorimeter study, Rising et al. (124) reported a mean 0.019 RQ increase over time in seven Pima Indian subjects (indicating ~5% greater carbohydrate oxidation and 5% less fat oxidation), and consistent results were more recently reported in a larger population by Levadoux et al. (75). Melanson et al. (96) used postprandial measurements of oxygen consumption and carbon dioxide production to observe that, following meals simulating the size of a snack or a small meal (1,046 and 2,092 kJ), older women had rates of fat oxidation comparable to those in young women (Fig. 5). However, the same elderly women had significantly lower fat oxidation following consumption of a moderately large meal (4,184 kJ). In regression analyses, maximal oxygen consumption, lean body mass, and circulating triglycerides explained individual differences in fat oxidation. However, the number of subjects was rather small for this type of analysis, and there were several similar models with comparable statistical significance, so the separation of age from body composition and fitness was not possible. These statistical findings are consistent with known influences on fat oxidation. For example, skeletal muscle mass is known to be the primary site for fat oxidation, and vigorous activity influences insulin sensitivity and hence the extent to which fat is used as a fuel source instead of carbohydrate (60).

Concerning fat oxidation in the fasting state, there are reports of both increased and decreased fasting fat oxidation in elderly individuals (12, 18). In addition, Melanson et al. (97) observed no significant effects of age per se on fasting fat oxidation measured over 10 h, but there was a significant negative effect of body fat in the best-fitting multiple regression model, which was probably due to the fact that the fatter subjects were in the older group. These latter observations appear consistent with the data of Calles-Escandon et al. (18) and lend weight to the suggestion that aging may also be associated with no increase in fat oxidation, and perhaps even a
decrease in fat oxidation after taking fat mass into account (which is positively correlated with fasting fat oxidation in younger subjects; see Ref. 162).

The fact that the apparent impairments in fat oxidation in old age are associated with reduced muscle mass and fitness suggest that alterations in fuel availability with age may underlie differences in fat oxidation, and therefore that exercise may help reverse or attenuate the age-associated effects through alterations in insulin sensitivity. Consistent with this view, several previous studies, including one in elderly subjects, have reported increased fasting fat oxidation with improved fitness, resulting from increased muscle mass and increased activity of fat oxidative enzymes in muscle (60, 63, 181). Additional evidence comes from another study documenting impaired fat oxidation in association with persistently high levels of circulating glucose for several hours in the postmeal period after consumption of a moderate-large meal size (95). The young women in that study responded to increasing meal size with appropriately increased circulating insulin and minimal changes in circulating glucagon, with the result that circulating levels of glucose increased only slightly with increasing meal size and showed the expected pattern of a small initial increase followed by a rapid return to baseline. Appropriate patterns of insulin, glucagon, and glucose were also seen in the older women during the fasting experiment and after consumption of the 1,046 kJ meal. In contrast, consumption of the 2,092-kJ meal, and to an even greater extent the 4,184-kJ meal, caused a substantial prolonged increase in circulating levels of both insulin and glucagon (but not free fatty acids) in the older group. The trend toward elevation in glucagon with meal consumption is noteworthy because it is in direct contradiction to the expected meal-induced suppression of glucagon secretion in individuals without non-insulin-dependent diabetes (25) and may well be a contributor to the persistent postmeal elevation in circulating glucose. The net effect of these changes, coupled with the expected underlying modest degree of insulin resistance in older individuals (41), was a substantial increase in the peak circulating glucose during the postmeal period and a persistent elevation of circulating glucose throughout the 5-h postprandial study period. Thus, although classified as normally glucose tolerant in an oral glucose tolerance test performed during the screening examination, these older women did in fact exhibit abnormal glucose profiles when challenged with mixed meals of 2,092 kJ or greater. Since fat oxidation is suppressed by high levels of circulating glucose (45), these high levels of glucose help explain why fat oxidation was suppressed.

V. SUMMARY, CONCLUSIONS, AND FUTURE DIRECTIONS

Several lines of evidence demonstrate that dysregulation of energy intake occurs in old age even in apparently healthy individuals and increase the risk of energy imbalance. There is also emerging data suggesting equivalent dysregulation of body energy expenditure and substrate oxidation in old age. The extent to which body weight and fat increases or decreases in response to age-related energy dysregulation will depend on the prevailing environmental circumstances and health of the
individual. Since body weight change is associated with such undesirable consequences as micronutrient deficiencies, frailty, increased hospital admission, an increased risk of disability from falls, delayed recovery from injury, and premature death (32, 112, 115, 178), further research is clearly needed to identify the specific underlying causes of aging-associated energy dysregulation. Current research also points to the potential for manipulation of dietary factors such as variety, taste, and meal size for preventing weight loss or weight gain through compensatory changes in energy intake.

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