Journals of Gerontology: SERIES A
2001, Vol. 56A (Special Issue II):81–88

Decreased Food Intake With Aging

John E. Morley

Geriatric Research, Education and Clinical Center, Saint Louis VA Medical Center and Division of Geriatric Medicine, Saint Louis University Health Sciences Center, Saint Louis, Missouri.

There is a physiological decline in food intake with aging. The reasons for the decline in food intake are multifactorial and involve both peripheral and central mechanisms. Altered hedonic qualities of food occur due to alterations in taste and, more particularly, smell with aging. A decline in adaptive relaxation of the fundus of the stomach and an increased rate of antral filling appear to play a role in the early satiation seen in many older persons. Cholecystokinin levels are increased with aging and older persons are more sensitive to the satiating effects of this gut hormone. The decline in testosterone levels in older males leads to increased leptin levels and this may explain the greater decline in food intake with aging in the male. Within the hypothalamus, decreased activity of both the dynorphin (kappa opioid) and neuropeptide Y systems occurs in aging rodents. Cytokines are potent anorectic agents. Many older persons have mild inflammatory disorders that lead to anorexia. Exercise may increase food intake in older persons.

> "I am grateful to old age because it has increased my desire for good conversation and decreased my desire for good food."
>
> —Cicero, DeSenectute, 43 B.C.

As seen from this quotation from Cicero, the concept of a physiological decrease in food intake with aging is certainly not a new one. However, it was not until 1988 that Morley and Silver (1) defined this syndrome as the "anorexia of aging" and began to characterize the mechanisms responsible for this physiological phenomenon. This article reviews what has been an exciting decade in our understanding of the pathogenesis of the "anorexia of aging."

Epidemiology

There are now a number of cross-sectional (1–3) and longitudinal (4–6) population studies demonstrating a decline in food intake with aging. This decline is predominantly due to a decrease in fat intake (7). Both Wurtman and colleagues (8) and Rolls and colleagues (9) have demonstrated that this decline in food intake is also present in healthy elderly persons.

This decline in food intake occurs despite the increase in body fat and the epidemic of obesity that occurs in middle age (3,10). The reasons for this are the decline in physical activity and resting metabolic rate that occurs with aging (11). In addition, the increase in visceral fat with aging increases the efficiency of fat accretion and decreases the ability to oxidize fat (12).

A number of studies have now found that older women have a strong desire to decrease their food intake and lose weight (13–15). In addition, fear of weight gain is seen in a subset of older persons (16), and anorexia nervosa and bulimia have been reported to occur in older persons (17).

Taste, Flavor, and Palatability

Flavor is the sensation that is produced when a substance is placed in the mouth. The sensation of flavor is produced by the interaction of chemoreceptors (olfaction and taste), mechanoreceptors (touch/textures), thermoreceptors (temperature), and nocireceptors (pain). The complex interaction of these different receptors in the nose, mouth, and throat is integrated within the central nervous system to produce an opinion of the flavor of a specific foodstuff. Of all the senses, olfaction appears to be the key to the recognition of taste (18). Palatability is defined as the introspective evaluation of the hedonic (pleasurable) qualities of a food (19). Blundell and Rogers (20) suggested that highly palatable foods enhance food intake through a positive feedback mechanism. Palatability acts as an orosensory reward (21). Pleasantness of food is an important determinant of food choice and in some circumstances food intake (22). Flavor is considered an extremely important component in deciding food choices in older persons (23).

Approximately 1.65% of adults have a chronic chemosensory problem (24). Olfactory problems occur in 1.4% and gustatory problems in 0.6%. Forty percent of persons with chemosensory problems are more than 65 years of age.

Odor perception declines with aging (25). This has been demonstrated to be true for both orthonasal and retronasal stimuli (26). Older women with reduced olfaction had a reduced interest in cooking and consuming a variety of foodstuffs. There is a decline in threshold sensitivity, suprathreshold intensity, and suprathreshold identification of olfaction with aging (18). Schiffman (27) demonstrated a longitudinal decline in odor identification over more than 3 years. This decline was particularly marked in octogenarians. Female subjects have greater smell acuity than males (27). Olfactory thresholds decline to a greater extent in those older persons with dementia (28). Sinusitis is a common disease associated with a marked decline in sense of smell (29,30).

Multiple anatomical changes occur in the normal nose with aging. The olfactory bulbs and tract volumes decline with age after 50 years of age (31). Neither changes in olfactory bulb nor temporal lobe volumes have been directly correlated with the age-related decline in smell.

Absolute taste thresholds increase by two to nine times with aging (32). However, suprathreshold taste thresholds

change little with aging. The decline in taste sensitivity with aging occurs in virtually every old person (33). Stevens and colleagues (34) demonstrated that when older persons have their taste threshold tested on multiple occasions they demonstrate much greater intraindividual variability than do younger persons.

Older persons tend to show a greater decline in bitter taste than in other taste modalities (35). This is true for quinine but not for urea. There are also significant losses in suprathreshold sensitivity to bitter tastes with aging (35). The addition of sweeteners produced a lower elevation of bitter taste thresholds in older persons than in younger persons (35).

The threshold for recognition of monosodium glutamate with 0.5 mM inosine-5′-monophosphate was 2.8 times higher in older persons than younger persons (35). When monosodium glutamate was added to foodstuffs, the optimally preferred concentration was above the detection threshold in water.

Prasad and colleagues (36) have suggested that zinc deficiency may play a role in the elevation of taste threshold with aging. Pathological alterations of decreased taste sensation (hypogeusia) have been associated with iron deficiency, oral candidiasis, xerostomia, and depression (37).

Abnormal taste sensation (dysgeusia) is most commonly associated with psychiatric distress. A variety of medications are associated with abnormal taste (35).

Stevens and colleagues (38) demonstrated that older persons were less capable of detecting salt in a soup recipe. Older persons have lower discrimination scores and higher absolute thresholds for sodium chloride in water. However, thresholds for salt in tomato soup increased approximately 10 times because of the "mixture suppression" effect. In this situation older persons' taste thresholds came closer to approximating those of younger persons but were still at least twice as high.

A 3-week exposure of retirement home residents to a flavor-enhanced diet resulted in an increased intake of some foods but not in total macronutrient or energy intake (39). Flavor-enhanced foods were preferred by older persons. Those on the flavor-enhanced diet also had an enhancement of immune function and an increased grip strength.

In contrast, Drewnowski and colleagues (40) reported that older persons prefer less salty chicken broth to younger persons. They found that older and younger persons were equally capable of detecting the salty taste. Sodium intakes did not relate to salt preferences. Drewnowski (41) has therefore argued that attitudes and social and economic factors are more important than taste thresholds for making food choices.

Sensory-specific satiety is defined as the decline in the pleasurable response to a food as a function of eating. Rolls and McDermott (42) reported that older persons were less likely to develop sensory-specific satiety than younger persons. Studies examining the variety of diet consumed by older persons have been conflicting, finding that older persons consume both a more monotonous (43) or a more varied diet (44) and that older persons have fewer food cravings than younger persons (45).

Alterations in taste, texture, oral feel, and odor of foods with aging are integrated through inputs of the gustatory and olfactory afferents in the brain stem. This can result in altered food preferences and reduce the quality of nutrients ingested. These sensations are modulated by cortical inputs that are derived from psychological factors—for example, perceptions and beliefs about the sensory attributes of food and attitudes including beliefs concerning the health and nutrition properties of foodstuffs, cultural beliefs, and the price and/or value of the food. One way to gain more insight into the interaction of different factors in discriminating between the palatability of foodstuffs for young and older persons would be to utilize consumer research techniques such as preference mapping (46).

Gastrointestinal Tract and Satiation

Numerous animal studies have demonstrated that both the stomach and the small intestine play a role in the regulation of food intake (47). Overall, the intestine acts as a brake on food intake by inducing satiation that results in the termination of a meal. It achieves this by utilizing both ascending nerve fibers in the autonomic nervous system and hormonal signals. These signals are integrated in the nucleus tractus solitarius and the hypothalamus.

As food passes down the esophagus, neuronal messages are sent through the autonomic nervous system to the fundus of the stomach, resulting in dilation of the fundus in preparation to receive food—that is, receptive relaxation (48). When food reaches the stomach it releases nitric oxide (NO), locally causing further fundal smooth muscle relaxation—that is, adaptive relaxation. Food particles are mixed in the fundus and then passed on to the antrum. Antral stretch is directly related to the signaling of satiation (49). The effect of antral stretch on satiation is enhanced by the hormone cholecystokinin (CCK). CCK is released from the duodenum in response to the ingestion of fat and/or protein. A number of gastrointestinal hormones, for example, glucagon-like peptide (50) and pancreatic hormones such as amylin (51), have also been shown to be involved in the satiation cascade.

A number of changes in the gastrointestinal satiation process occur with aging. Overall, these changes tend to result in early satiation in older persons. This has been demonstrated experimentally by Clarkston and colleagues (52). They showed that when older individuals received the same amount of food as younger persons they reported greater satiation. This early satiation was related to the rate of gastric emptying. Older persons have delayed gastric emptying for large (>500-kcal meals), but not small, meals.

There are no data on receptive relaxation and aging. Preliminary data from N. Chien and J. Morley (unpublished data, 1998) suggested that older persons have more rapid fundal emptying, suggesting decreased fundal capacity. Our baroreceptor studies have suggested that older persons have reduced fundal compliance. Despite the reduced fundal compliance, older persons were less aware of fundal distension, possibly because of autonomic dysfunction. This suggests that the fundus *per se* is not directly involved in the increased satiating signals present in older persons. Rodent studies have suggested that the reduced fundic compliance in older persons is due to reduced NO synthase production (53). The smaller capacity of the fundus suggests that there is more rapid antral filling with aging. Increased antral sig-

nals, therefore, appear to be the most likely cause of the early satiation that occurs in older persons (Figure 1).

CCK levels increase with aging (54). CCK slows gastric emptying and therefore will increase antral stretch. Animal studies demonstrated that there is an increased satiating effect of CCK with aging (55). Our preliminary data suggest that this is also true in humans (I. Chapman, M. Horowitz, and J. E. Morley, unpublished observations).

When an intraduodenal tube is used to bypass the stomach, infusion of nutrients directly into the small intestine results in less decrease in hunger in older than in younger persons (56). Wilson and colleagues (57) demonstrated that when a liquid caloric supplement was administered 60 minutes before a meal, older persons ate more than when the same supplement was administered immediately before the meal. These studies support the concept that the antrum is the area involved in signaling the increased satiation to the brain in older persons.

Roberts and colleagues (58) found that when older individuals had their food intake reduced, unlike younger persons, they did not increase their food intake sufficiently to return their weight to its basal level. Similarly, when overfed, older persons failed to subsequently reduce their food intake sufficiently to return their weight to its basal level. The discrepancy between antral and duodenal effects in old, compared to young, persons provides a mechanistic explanation for the findings of Roberts and colleagues.

Pancreatic hormones have been implicated in the regulation of appetite. While much of the literature has suggested that insulin may directly affect appetite, infusions of insulin in humans have failed to demonstrate an effect on appetite or food intake (59). Glucagon and somatostatin both alter food intake, but no studies have been undertaken in older individuals or animals. Amylin, a peptide hormone coreleased with insulin from the Islets of Langerhaus, is a potent anorectic agent when administered peripherally (60). There is no difference in the efficaciousness of amylin when administered to young or older rodents (61). Amylin produces its effect on appetite, in part, by decreasing the rate of gastric emptying (62). This is through a mechanism independent of nitric oxide (63). In humans, amylin levels decrease in middle age and then increase in older age (64). This increase in amylin levels in older age suggests that amylin may play a role in the anorexia of aging and the delayed gastric emptying seen with aging.

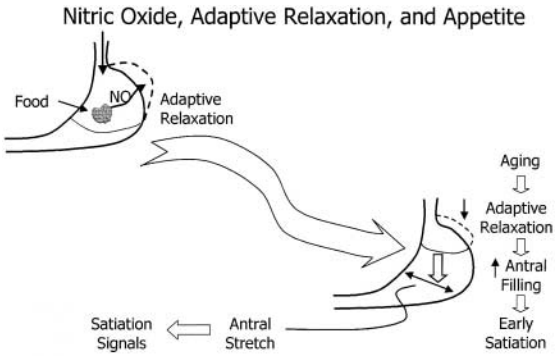

Figure 1. Early satiation of aging: nitric oxide, adaptive relaxation, and appetite. Decreased adaptive relaxation of the fundus of the stomach leads to more rapid antral filling and early satiation.

Leptin and Testosterone

Leptin is a cytokine-like peptide hormone that is secreted from adipose cells (65). Leptin deficiency is responsible for the hyperphagia and obesity of the genetically obese (ob/ob) mouse (66). Leptin deficiency has also been reported as a rare cause of obesity in humans (67). Leptin not only decreases food intake but also increases resting metabolic rate (65). There is also evidence for leptin playing a role in the regulation of the hypothalamic-pituitary-gonadal axis (65).

Studies in aging rodents have reported that both fat mass and leptin levels increase with aging (68,69). Li and colleagues (70) found in aging male rats an increase in leptin gene expression that was out of proportion to the increased adiposity seen with aging. Wolden-Hanson and colleagues (68) reported that the increase in leptin was more closely associated with subcutaneous rather than visceral fat. Leptin administration to young rats results in a selective decrease in visceral adiposity (71). Old Brown-Norway rats have a decrease in visceral adiposity (68) and it is possible that this is due to the increased circulating leptin levels.

With aging in human females there is an increase in leptin levels at middle age and a decrease in older age (10). The decrease in serum leptin levels in women over the age of 60 was reproduced in the New Mexico Aging Process Study and was showen to be more closely related to subcutaneous rather than visceral fat (72). Resting metabolic rate is correlated with leptin levels in females but not in males (73). Exogenous and endogenous estrogens are unrelated to leptin levels in females (74,75).

Males have lower leptin levels than females even when leptin levels are correlated for total adiposity (65,72). In males, in contrast to females, leptin levels increase with aging in both cross-sectional (74,76) and longitudinal (72) studies.

Testosterone levels decline with aging in both cross-sectional (77) and longitudinal (78) studies. This decline in testosterone with aging is correlated with the age-related decline in body mass and strength (79,80). Testosterone replacement in older males increased strength (81). Testosterone in animals has been demonstrated to increase food intake (82).

In both cross-sectional and longitudinal studies multivariant analysis has demonstrated a role of the declining testosterone in the increasing leptin levels (72,73). Testosterone administration to older hypogonadal men suppressed the elevated leptin levels (81). Leptin gene expression is lower in abdominal adipose tissue in men compared to women (83). Wabitsch and colleagues (84) reported that dihydrotestosterone suppressed leptin mRNA in adipocytes and the leptin secretion from these cells in vitro. However, the exact mechanism by which testosterone modulates leptin secretion remains to be determined. It is possible that it involves stimulation of nitric oxide synthase in adipocytes.

Both the absolute and the proportional decline in food intake with aging are greater in males than females (4). Leptin decreases food intake by inhibiting neuropeptide Y and NO

synthase in the hypothalamus (85). It is tempting to speculate that the decline in testosterone in the aging male leads to an increase in leptin and a decline in food intake (Figure 2).

Cytokines

Cytokines are released in response to chronic inflammation, infections, injuries, and neoplasms. These immunoregulatory peptides have a variety of effects that can lead to severe malnutrition (Figure 3). Besides being anorectic, cytokines decrease serum albumin, induce lipolysis, produce muscle protein breakdown, and induce nitrogen loss (86). The decrease in serum albumin occurs not only because of decreased hepatic synthesis and increased catabolism but also because of extravasation of albumin from the intravascular space.

Both interleukin-1 (IL-1) and tumor neurosis factor α (TNFα) produce anorexia. Both of these cytokines directly stimulate leptin mRNA expression and increase serum leptin (87) and induce interleukin-6 production (88). Besides their effects on leptin, cytokines also stimulate hypothalamic corticotrophin releasing factor, which is markedly anorectic (89).

The ciliary neurotrophic factor (CNTF) receptor is one of the members of the IL-6/leptin receptor super family. CNTF is a potent anorectic agent in rodents and humans (90). CNTF reduces hypothalamic neuropeptide Y (NPY) mRNA expression (91). The role of CNTF in the physiological or pathological anorexia of aging is yet to be determined.

There is evidence that TNF is increased in the cerebrospinal fluid of older rodents (92). There is some evidence supporting the concept that TNFα, IL-1 beta, and IL-6 increase in the serum of healthy elderly persons (86). A pathological condition—idiopathic "senile" anorexia—has been associated with increased levels of IL-6 and TNF (93).

The Central Feeding Drive

Within the central nervous system, multiple neurotransmitters are involved in the regulation of food intake (94). While much of the neurotransmitter interactions that regulate food intake and integrate energy balance take place within the hypothalamus, numerous other areas within the central nervous system, such as the amygdala and the nucleus tractus solitarius, are also involved. An oversimplification of the central feeding system is that within the hypothalamus, NPY and norepinephrine are predominantly responsible for driving intake of carbohydrates (47) and the endogenous kappa opioid receptor, dynorphin, is responsible for the intake of fat and highly palatable foodstuffs (95). Numerous other neurotransmitters, for example, orexin A, can also increase food intake (96). Emerging evidence suggests that these neurotransmitters may produce their effects on food intake by activating nitric oxide synthase in anatomically specific sites (97; Figure 4).

These feeding drive neurotransmitters are held in check by a complex cascade of inhibitory neurotransmitters (94). The best delineation of these systems is the serotonin-corticotrophin releasing factor (CRF) system (98). CRF levels are elevated in the cerebrospinal fluid of patients with an-

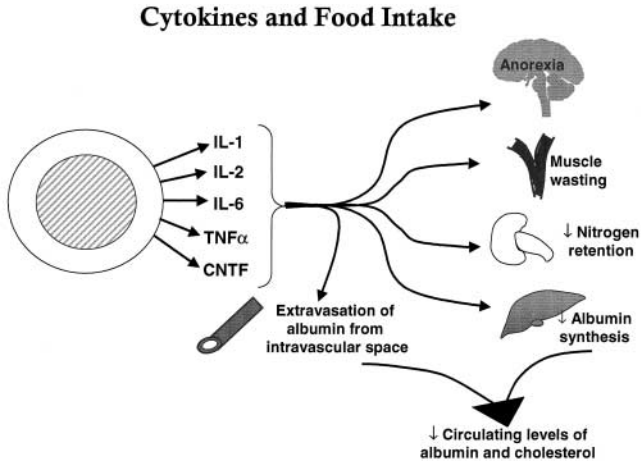

Figure 3. Cytokines and food intake: mechanisms by which cytokines produce anorexia, weight loss, and malnutrition. CNTF = ciliary neurotrophic factor; IL-1 = interleukin-1; IL-6 = interleukin-6; TNFα = tumor necrosis factor.

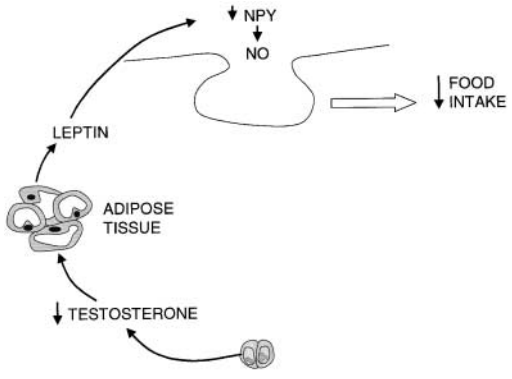

Figure 2. Mechanism by which declining testosterone levels lead to a decreased food intake with aging (NO = nitric oxide).

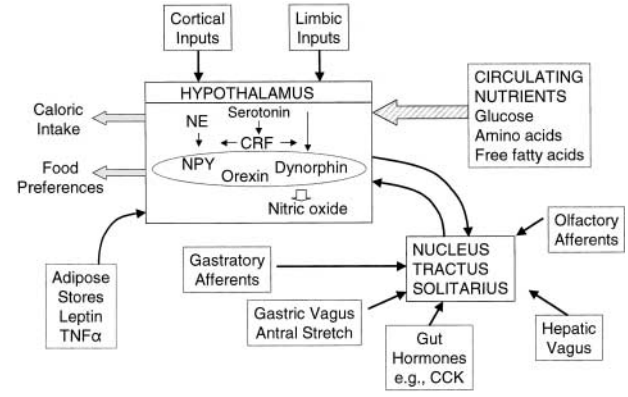

Figure 4. Diagram of the multiple inputs that regulate food intake into the central nervous system and the transducer system in the hypothalamus. Norepinephrine (NE), neuropeptide Y (NPY), orexin, and dynorphin drive food intake by activating nitric oxide (NO). The serotonin-corticotrophin releasing factor (CRF) system attempts to decrease feeding.

orexia nervosa and in approximately two thirds of patients with depression (99). It has been suggested that CRF may play a central role in the pathophysiology of anorexia in these conditions (47). A full description of the neurotransmitters implicated in the regulation of the central feeding drive is beyond the scope of this review.

Studies on the central feeding drive and the anorexia of aging to date have been confined to rodents. There is clear evidence of a decline in the opioid feeding drive system with aging in both rats (100) and mice (101). This appears to be due predominantly to a decline in opioid receptor activity with aging (102). The decline in the opioid feeding drive is compatible with the decrease in total fat intake that occurs in aging humans (4).

Recent studies have suggested that NO may play a coordinating role in appetite regulation. Evidence that NO plays a key role in increasing food intake includes:

1. NO synthase antagonists decrease food intake and body weight (103).
2. NO synthase levels in the hypothalamus are altered by modulating nutrient intake (104).
3. NO synthase levels are increased in the hypothalamus of the genetically obese (ob/ob) mouse (105) and NO synthase inhibitors produce a marked decrease in food intake and body mass in these mice (106).
4. NO donors increase food intake (107).
5. Leptin decreases and NPY increases NO synthase (97).

In old mice NO synthase inhibitors are more potent in reducing food intake than in young mice (108). Aging is associated with a decline in mRNA for NO synthase. Thus, preliminary evidence supports the possibility that the decline in food intake with aging is due to a decline in brain NO synthase. This may explain the greater decline in caloric ingestion with aging in males, as this age-related decline in testosterone results in increased leptin levels, decreased NPY, and decreased NO synthase (Figure 2).

Exercise and Food Intake

In young persons exercise increases food intake. Exercise is thought to increase the preference for carbohydrates and thus result in a decrease in fat content in a diet (109). However, the effects of exercise on food intake are not obvious over the short term, although some evidence suggests acute exercise does not result in a depletion of glycogen stores on food intake (110). King and colleagues (111) failed to show an effect of a substantial increase in energy expenditure due to intense exercise on hunger or food intake within 48 hours. Thus, there is little evidence for a strong coupling between short-term energy expenditure and energy intake. In addition, physical exercise over a 3-day period failed to alter leptin levels (112). Even an 18-week weight training exercise program that increased average daily metabolic rate failed to increase energy intake (110).

With aging there is a decline in physical activity and resting metabolic rate (11). Poehlman and Danforth (113) found that an 8-week endurance training program (cycling exercise) in older persons increased total energy expenditure by both increasing the direct energy cost of physical activity and by elevating resting metabolic rate. This increase was partially due to an increase in norepinephrine appearance rate. In addition, energy intake was increased by 12%.

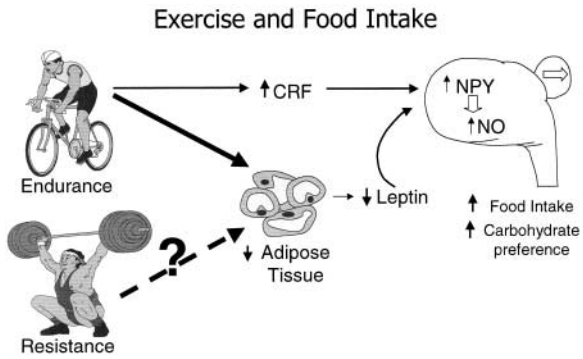

Figure 5. Exercise and food intake: acute exercise results in an increase in corticotrophin releasing factor (CRF) and a decrease in food intake. Exercise over many weeks leads to a decline in leptin levels, resulting in an increase in neuropeptide Y (NPY) and nitric oxide (NO) in the hypothalamus and in food intake.

Fiatarone and colleagues (114) studied the effects of resistance exercise in older nursing home residents. In those doing resistance exercises there was a nonsignificant tendency to increase intake of the caloric supplement.

Thus, there is some evidence that exercise (especially endurance exercise) may increase food intake in older persons. The mechanism(s) by which this may occur are totally unknown. Decreased body fat with exercise may eventually lead to a decline in leptin levels and, therefore, increased food intake secondary to an increase in NPY and NO. Over the short term the stress of exercise will increase corticotrophin releasing factor (115), which provides an explanation for the uncoupling between energy expenditure and energy intake when exercise is first started (Figure 5).

Conclusion

There is a physiological decline in food intake with aging. The reasons are multifactorial and may include alterations in the hedonic qualities of food (decreased odor and taste), increased gastrointestinal satiation signals, increased leptin levels (predominantly in males secondary to the age-related decline in testosterone), and a decline in the central feeding drive. This physiological anorexia places the older persons at major risk for developing severe anorexia in cases of disease (116,117). Disease is often associated with cytokine release that not only produces anorexia but also decreases muscle protein synthesis and causes extravasation of albumin out of the intravascular space. Physical activity declines with aging and endurance exercise can increase energy intake and carbohydrate preference. The mechanism(s) coupling altered muscle mass with the decline in food intake during the aging process are deserving of intensive study.

Acknowledgments

Address correspondence to John E. Morley, MB, BCh, Division of Geriatric Medicine, Saint Louis University Health Sciences Center, 1402 S.

Grand Blvd., Room M238, Saint Louis, MO 63104. E-mail: morley @slu.edu

References

1. Morley JE, Silver AJ. Anorexia in the elderly. *Neurobiol Aging.* 1988;9:9–16.
2. Aloia JF, Vaswani A, Ma R, Flaster E. Aging in women—the four-compartment model of body composition. *Metabolism.* 1996;45:43–48.
3. Silver AJ, Guillen CP, Kahl MJ, Morley JE. Effects of aging on body fat. *J Am Geriatr Soc.* 1993;41:211–213.
4. Steen B, Isaksson B, Svanborg A. Body composition at 70 and 75 years of age: a longitudinal population study. *J Clin Exp Gerontol.* 1979;1:185–192.
5. Chumlea WC, Garry PJ, Hunt WC, Rhyne RL. Distribution of serial changes in stature and weight in a healthy elderly population. *Hum Biol.* 1988;60:917–925.
6. Vellas BJ, Hunt WC, Romero LJ, Koehler KM, Baumgartner RN, Garry PJ. Changes in nutritional status and patterns of morbidity among free-living elderly persons: a 10-year longitudinal study. *Nutrition.* 1997;13:515–519.
7. Daily dietary fat and total food energy intake. Third National Health and Nutrition Examination Survey, phase I, 1988–1991. *MMWR Morb Mortal Wkly Rep.* 1994;43:116–125.
8. Wurtman JJ, Lieberman H, Tsay R, Nader T, Chew B. Calorie and nutrient intakes of elderly young subjects measured under identical conditions. *J Gerontol Biol Sci.* 1988;43:B174–B180.
9. Rolls BJ, Dimeo KA, Shide DJ. Age-related impairments in the regulation of food intake. *Am J Clin Nutr.* 1995;62:923–931.
10. Perry HM III, Morley JE, Horowitz M, Kaiser FE, Miller DK, Wittert G. Body composition and age in African American and Caucasian women: relationship to plasma leptin levels and gonadal steroids. *Metabolism.* 1997;46:1399–1405.
11. Morley JE. Nutrition and the older female: a review. *J Am Coll Nutr.* 1993;12:337–343.
12. Melanson KJ, Saltzman E, Russell RR, Roberts SB. Fat oxidation in response to four graded challenges in younger and older women. *Am J Clin Nutr.* 1997;66:860–866.
13. Hetherington MM, Burnett L. Ageing and the pursuit of slimness: dietary restraint and weight satisfaction in elderly women. *Br J Clin Psychol.* 1994;33:391–400.
14. Donkin AJ, Johnson AE, Morgan K, Neale RJ, Page RM, Silburn RL. Gender and living alone as determinants of fruit and vegetable consumption among elderly living at home in urban Nottingham. *Appetite.* 1998;30:39–51.
15. Pliner P, Chaiken S, Flett GL. Gender differences in concern with body weight and physical appearance across the life span. *Pers Soc Psychol Bull.* 1990;16:263–273.
16. Miller DK, Morley JE, Rubenstein LZ, Pietruszka FM. Abnormal eating attitudes and body image in older undernourished individuals. *J Am Geriatr Soc.* 1991;39:462–466.
17. Morley JE, Flood JF, Silver AJ. Opioid peptides and aging. *Ann NY Acad Sci.* 1990;579:123–132.
18. Murphy C, Gilmore MM, Seery CS, Salmon DP, Lasker BR. Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. *Neurobiol Aging.* 1990;11:465–469.
19. Yeomans MR. Taste, palatability and the control of appetite. *Proc Nutr Soc.* 1998;57:609–615.
20. Blundell JE, Rogers PJ. Hunger, hedonics, and the control of satiation and satiety. In: Friedman MI, Tordoff MG, Kare MR, eds. *Chemical Senses: Appetite and Nutrition*. Vol. 4. New York: Dekker; 1991:127–148.
21. Berridge KC, Pecina S. Benzodiazepines, appetite and taste palatability. *Neurosci Biobehav Rev.* 1995;19:121–131.
22. Hetherington MM. Taste and appetite regulation in the elderly. *Proc Nutr Soc.* 1998;57:625–631.
23. Schiffman SS, Gaitlin CA. Clinical physiology of taste and smell. *Annu Rev Nutr.* 1993;13:405–436.
24. Hoffman HJ, Ishii EK, MacTurk RH. Age-related changes in the prevalence of smell/taste problems among the United States adult population. Results of the 1994 disability supplement to the National Health Interview Survey (NHIS). *Ann NY Acad Sci.* 1998;855:716–722.
25. Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. *Science.* 1984;226:1441–1443.
26. Pierce J, Halpern BP. Orthonasal and retronasal odorant identification based upon vapor phase input from common substances. *Chem Senses.* 1996;21:529–543.
27. Schiffman SS. Taste and smell losses in normal aging and disease. *JAMA.* 1997;278:1357–1362.
28. Murphy C, Cain WS. Taste and olfaction: independence vs interaction. *Physiol Behav.* 1980;24:601–605.
29. Downey LL, Jacobs JB, Lebowitz RA. Anosmia and chronic sinus disease. *Otolaryngol Head Neck Surg.* 1996;115:24–28.
30. Apter AJ, Mott AE, Frank ME, Clive JM. Allergic rhinitis and olfactory loss. *Ann Allergy Asthma Immunol.* 1995;75:311–316.
31. Yousem DM, Geckle RJ, Bilker WB, Doty RL. Olfactory bulb and tract and temporal lobe volumes. Normative data across decades. *Ann NY Acad Sci.* 1998;855:546–555.
32. Stevens JC, Cain WS. Changes in taste and flavor in aging. *Crit Rev Food Sci Nutr.* 1993;33:27–37.
33. Stevens JC, Cruz LA, Marks LE, Lakatos S. A multimodal assessment of sensory thresholds in aging. *J Gerontol Psych Sci.* 1998;53B: P263–P272.
34. Stevens JC, Cruz LA, Hoffman JM, Patterson MQ. Taste sensitivity and aging: high incidence of decline revealed by repeated threshold measures. *Chem Senses.* 1995;20:451–459.
35. Cowart BJ, Yokomukai Y, Beauchamp GK. Bitter taste in aging: compound-specific decline in sensitivity. *Physiol Behav.* 1994;56: 1237–1241.
36. Prasad AS, Fitzgerald JT, Hess JW, Kaplan J, Pelen F, Dardenne M. Zinc deficiency in elderly patients. *Nutrition.* 1993;9:218–224.
37. Osaki T, Ohshima M, Tomita Y, Matsugi N, Nomura Y. Clinical and physiological investigations in patients with taste abnormality. *J Oral Pathol Med.* 1996;25:38–43.
38. Stevens JC, Cain WS, Demarque A, Ruthruff AM. On the discrimination of missing ingredients: aging and salt flavor. *Appetite.* 1991; 16:129–140.
39. Schiffman SS, Warawick ZS. Effect of flavor enhancement of foods for the elderly on nutritional status: food intake, biochemical indices, and anthropometric measures. *Physiol Behav.* 1993;53:395–402.
40. Drewnowski A, Henderson SA, Driscoll A, Rolls BJ. Salt taste perceptions and preferences are unrelated to sodium consumption in healthy older adults. *J Am Diet Assoc.* 1996;96:471–474.
41. Drewnowski A. Taste preferences and food intake. *Annu Rev Nutr.* 1997;17:237–253.
42. Rolls BJ, McDermott TM. Effects of age on sensory-specific satiety. *Am J Clin Nutr.* 1991;54:988–996.
43. Fanelli MT, Stevenhagen KJ. Characterizing consumption patterns by food frequency methods: core foods and variety of foods in diets of older Americans. *J Am Diet Assoc.* 1985;85:1570–1576.
44. Drewnowski A, Henderson SA, Driscoll A, Rolls BJ. The Dietary Variety Score—assessing diet quality in healthy young and older adults. *J Am Diet Assoc.* 1997;97:266–271.
45. Pelchat ML. Food cravings in young and elderly adults. *Appetite.* 1997;28:103–113.
46. Clark JE. Taste and flavour: their importance in food choice and acceptance. *Proc Nutr Soc.* 1998;57:639–643.
47. Morley JE. Neuropeptide regulation of appetite and weight. *Endocr Rev.* 1987;8:256–287.
48. Morley JE. Anorexia of aging: physiologic and pathologic. *Am J Clin Nutr.* 1997;66:760–773.
49. Jones KL, Doran SM, Hveem K, et al. Relation between postprandial satiation and antral area in normal subjects. *Am J Clin Nutr.* 1997;66: 127–132.
50. Gutzwiller JP, Goke B, Drewe J, et al. Glucagon-like peptide-1: a potent regulator of food intake in humans. *Gut.* 1999;44:81–86.
51. Morley JE, Flood JF, Farr SA, Perry HM III, Kaiser FE, Morley PM. Effects of amylin on appetite regulation and memory. *Can J Physiol Pharmacol.* 1995;73:1042–1046.
52. Clarkston WK, Pantano MM, Morley JE, Horowitz M, Littlefield JM, Burton FR. Evidence for the anorexia of aging: gastrointestinal transit and hunger in healthy elderly vs. young adults. *Am J Physiol.* 1997;272:R243–R248.
53. Sun WM, Doran S, Jones KL, et al. Effects of nitroglycerin on liquid

gastric emptying and antropyloroduodenal motility. *Am J Physiol.* 1998;275:G1173–G1178.
54. MacIntosh CG, Andrews JM, Jones KL, et al. Effects of age on concentrations of plasma cholecystokinin, glucagon-like peptide 1 and peptide YY and their relation to appetite and pyloric motility. *Am J Clin Nutr.* 1999;69:999–1006.
55. Silver AJ, Flood JF, Song AM, Morley JE. Evidence for a physiological role for CCK in the regulation of food intake in mice. *Am J Physiol.* 1989;256:R646–R652.
56. Cook CG, Andrews JM, Jones KL, et al. Effects of small intestinal nutrient infusion on appetite and pyloric motility are modified by age. *Am J Physiol.* 1997;273:R755–R761.
57. Wilson MMG, Purushothaman R, Morley JE. Oral preloads and aging. *J Am Geriatr Soc.* 1997;37:108A.
58. Roberts SB, Fuss P, Heymann MB, et al. Control of food intake in older men. *JAMA.* 1994;272:1601–1606.
59. Chapman IM, Goble EA, Wittert GA, Morley JE, Horowitz M. Effect of intravenous glucose and euglycemic insulin infusions on short-term appetite and food intake. *Am J Physiol.* 1998;274:R596–R603.
60. Edwards BJ, Morley JE. Amylin. *Life Sci.* 1992;51:1899–1912.
61. Morley JE, Flood JF, Horowitz M, Morley PM, Walter MJ. Modulation of food intake by peripherally administered amylin. *Am J Physiol.* 1994;267:R178–R184.
62. Kong MF, Stubbs TA, King P, et al. The effect of single doses of pramlintide on gastric emptying of two meals in men with IDDM. *Diabetologia.* 1998;41:577–583.
63. Morley JE, Suarez MD, Mattammal M, Flood JF. Amylin and food intake in mice: effects on motivation to eat and mechanism of action. *Pharmacol Biochem Behav.* 1997;56:123–129.
64. Edwards BJ, Perry HM III, Kaiser FE, et al. Age-related changes in amylin secretion. *Mech Ageing Dev.* 1996;86:39–51.
65. Morley JE, Perry HM III, Baumgartner RP, Garry PJ. Leptin, adipose tissue and aging—is there a role for testosterone? *J Gerontol Biol Sci.* 1999;54A:B108–B109.
66. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature.* 1998;395:763–770.
67. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature.* 1997;387:903–908.
68. Wolden-Hanson T, Marck BT, Smith L, Matsumoto AM. Cross-sectional and longitudinal analysis of age-associated changes in body composition of male Brown Norway rats: association of serum leptin levels with peripheral adiposity. *J Gerontol Biol Sci.* 1999;54A:B99–B107.
69. Mizuno T, Bergen H, Kleopoulos S, Bauman WA, Mobbs CV. Effects of nutritional status and aging on leptin gene expression in mice: importance of glucose. *Horm Metab Res.* 1996;28:679–684.
70. Li H, Matheny M, Nicolson M, Turner N, Scarpace PJ. Leptin gene expression increases with age independent of increasing adiposity in rats. *Diabetes.* 1997;46:2035–2039.
71. Barzilai N, Wang J, Massilon D, Vuguin P, Hawkins M, Rossetti L. Leptin selectively decreases visceral adiposity and enhances insulin action. *J Clin Invest.* 1997;100:3105–3110.
72. Baumgartner RN, Waters DL, Morley JE, Patrick P, Montoya GD, Garry PJ. Age-related changes in sex hormones affect the sex difference in serum leptin independently of changes in body fat. *Metab Clin Exp.* 1999;48:378–384.
73. Nicklas BJ, Toth MJ, Poehlman ET. Daily energy expenditure is related to plasma leptin concentrations in older African American women but not men. *Diabetes.* 1997;46:1389–1392.
74. Kohrt WM, Landt M, Birge SJ Jr. Serum leptin levels are reduced in response to exercise training, but not hormone replacement therapy, in older women. *J Clin Endocrinol Metab.* 1996;81:3980–3985.
75. Baumgartner RN, Ross RR, Waters DL, et al. Serum leptin in elderly people: associations with sex hormones, insulin, and adipose tissue volumes. *Obesity Res.* 1999;7:141–149.
76. Luukkaa V, Pesonen U, Huhtaniemi I, et al. Inverse correlation between serum testosterone and leptin in men. *J Clin Endocrinol Metab.* 1998;83:3243–3246.
77. Korenman SG, Morley JE, Mooradian AD, et al. Secondary hypogonadism in older men: its relation to impotence. *J Clin Endocrinol Metab.* 1990;71:963–969.
78. Morley JE, Perry HM III, Kaiser FE, et al. Longitudinal changes in testosterone, luteinizing hormone and follicle stimulating hormone in healthy older males. *Metabolism.* 1997;46:410–413.
79. Morley JE, Kaiser FE, Raum WJ, et al. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. *Proc Natl Acad Sci USA.* 1997;94:7537–7542.
80. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. *Mech Ageing Dev.* 1999;107:123–136.
81. Sih R, Morley JE, Kaiser FE, Perry HM III, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab.* 1997;82:1661–1667.
82. Mooradian AD, Morley JE, Korenman SG. Biological actions of androgens. *Endocr Rev.* 1987;8:1–28.
83. Lonnqvist F, Arner P, Nordfors L, Shalling M. Overexpression of the obese (ob) gene in adipose tissue of human obese subjects. *Nat Med.* 1995;1:950–953.
84. Wabitsch M, Blum WF, Musch R, et al. Contribution of androgens to the gender difference in leptin production in obese children and adolescents. *J Clin Invest.* 1997;100:808–813.
85. Calapai G, Corica F, Allegra A, et al. Effects of intracerebroventricular leptin administration on food intake, body weight gain and diencephalic nitric oxide synthase activity in the mouse. *Br J Pharmacol.* 1998;125:798–802.
86. Baez-Franceschi D, Morley JE. Physiopathology of the catabolism associated with malnutrition in the elderly. *Zeischrift fur Gerontologie und Geriatrie.* 1999;32:12–19.
87. Grunfeld C, Zhao C, Fuller J, et al. Endotoxin and cytokines induce expression of cytokines, the ob gene product, in hamsters. *J Clin Invest.* 1996;97:2152–2157.
88. Oldenburg HS, Rogy MA, Lazarus DD, et al. Cachexia and the acute-phase protein response in inflammation are related by interleukin-6. *Eur J Immunol.* 1993;23:1889–1894.
89. Uehara A, Sekiya C, Takasugi Y, Namiki M, Arimura A. Anorexia induced by interleukin 1: involvement of corticotrophin-releasing factor. *Am J Physiol.* 1989;257:R613–R617.
90. Xu B, Dube MG, Kalra PS, et al. Anorectic effects of the cytokine, ciliary neurotrophic factor are mediated by hypothalamic neuropeptide Y: comparison with leptin. *Endocrinology.* 1998;139:466–473.
91. Fantuzzi G, Benigni F, Sironi M, et al. Ciliary neurotrophic factor (CNTF) induces serum amyloid A, hypoglycaemia and anorexia, and potentiates IL-1 induced corticosterone and IL-6 production in mice. *Cytokine.* 1995;7:150–156.
92. Siren AL, Liu Y, Feuerstein G, Hallenbeck JM. Increased release of tumor necrosis factor-alpha into the cerebrospinal fluid and peripheral circulation of aged rats. *Stroke.* 1993;24:880–886.
93. Arnalich F, Hernanz A, Vazques JJ, Amores A. Cell-mediated immune response and cytokine production in idiopathic senile anorexia. *Mech Ageing Dev.* 1994;77:67–74.
94. Morley JE. The neuroendocrine control of appetite: the role of the endogenous opiates, cholecystokinin, TRH, gamma-amino-butyric-acid and the diazepam receptor. *Life Sci.* 1980;27:353–368.
95. Morley JE, Levine AS, Yim GK, Lowy MT. Opioid modulation of appetite. *Neurosci Biobehav Rev.* 1983;7:281–305.
96. Sweet DC, Levine AS, Billington CJ, Kotz CM. Feeding response to central orexins. *Brain Res.* 1999;821:535–538.
97. Morley JE, Alshaher MM, Farr SA, Flood JF, Kumar VB. Leptin and neuropeptide Y (NPY) modulate nitric oxide synthase: further evidence for a role of nitric oxide in feeding. *Peptides.* 1999;20:595–600.
98. Rosenthal MJ, Morley JE. Corticotropin releasing factor (CRF) and age-related differences in behavior of mice. *Neurobiol Aging.* 1989;10:167–171.
99. Nemeroff CB. The role of corticotropin-releasing factor in the pathogenesis of major depression. *Pharmacopsychiatry.* 1988;21:76–82.
100. Gosnell BA, Levine AS, Morley JE. The effects of aging on opioid modulation of feeding in rats. *Life Sci.* 1983;32:2793–2799.
101. Kavaliers M, Hirst M. The influence of opiate agonists on day-night feeding rhythms in young and old mice. *Brain Res.* 1985;326:160–167.
102. Morley JE, Flood JF, Silver AJ. Opioid peptides and aging. *Ann NY Acad Sci.* 1990;579:123–132.

103. Morley JE, Flood JF. Evidence that nitric oxide modulates food intake in mice. *Life Sci.* 1991;49:707–711.
104. O'Shea RD, Gundlach AL. Food or water deprivation modulate nitric oxide synthase (NOS) activity and gene expression in rat hypothalamic neurones: correlation with neurosecretory activity. *J Neuroendocrinol.* 1996;8:417–425.
105. Morley JE, Kumar VB, Mattammal M, Villareal DT. Measurement of nitric oxide synthase and its mRNA in genetically obese (ob/ob) mice. *Life Sci.* 1995;57:1327–1331.
106. Morley JE, Flood JF. Effect of competitive antagonism of NO synthetase on weight and food intake in obese and diabetic mice. *Am J Physiol.* 1994;266:R164–R168.
107. Racotta R, Soto-Mora LM, Pinon-Lopez MJ, Quevedo L. Effect of intraperitoneal nitroprusside and adrenergic agonists on food and water intake. *Physiol Behav.* 1998;63:455–461.
108. Morley JE, Kimar VB, Mattammal M, Farr SA, Morley PM, Flood JF. Inhibition of feeding by a nitric oxide synthase inhibitor: effects of aging. *Eur J Pharmacol.* 1996;311:15–19.
109. Tremblay A, Almeras N. Exercise, macronutrient preferences and food intake. *Int J Obesity.* 1995;19:S97–S101.
110. Snitker S, Larson DE, Tataranni PA, Ravussin E. Ad libitum food intake in humans after manipulation of glycogen stores. *Am J Clin Nutr.* 1997;65:941–946.
111. King NA, Lluch A, Stubbs RJ, Blundell JE. High dose exercise does not increase hunger or energy intake in free living males. *Eur J Clin Nutr.* 1997;51:478–483.
112. Dirlewanger M, DiVetta V, Giusti V, Schneiter P, Jequier E, Tappy L. Effect of moderate physical activity on plasma leptin concentration in humans. *Eur J Appl Physiol.* 1999;79:331–335.
113. Poehlman ET, Danforth E Jr. Endurance training increases metabolic rate and norepinephrine appearance rate in older individuals. *Am J Physiol.* 1991;261:E233–E239.
114. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med.* 1994;330:1769–1775.
115. Richard D. Exercise and the neurobiological control of food intake and energy expenditure. *Int J Obesity.* 1995;19:S73–S79.
116. Wilson MM, Vaswani S, Liu D, Morley JE, Miller DK. Prevalence and causes of undernutrition in medical outpatients. *Am J Med.* 1998; 104:56–63.
117. Morley JE, Kraenzle D. Causes of weight loss in a community nursing home. *J Am Geriatr Soc.* 1994;42:583–585.