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PHYSIOLOGIC DETERMINANTS OF THE ANOREXIA OF AGING: Insights from Animal Studies*

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■ **Abstract** The anorexia of aging is a syndrome characterized by unexplained losses in food intake and body weight that occur near the end of life. Proposed etiologies cover a wide range of biological and psychological conditions. The observation of this phenomenon in older laboratory animals suggests that physiological changes play a significant causal role. Research on the neurochemical control of energy balance has received much attention in recent years, and age-related alterations in the neuropeptidergic effectors of food intake have been implicated in the anorexia of aging. This review provides an update on putative mechanisms underlying this dysregulation of feeding during advanced age.

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INTRODUCTION: THE NATURE OF THE PROBLEM

Throughout most of life, mammals attempt to maintain energy homeostasis via a tightly regulated system controlling food intake and energy expenditure. Failure to preserve steady state levels of body weight/energy stores, as occurs in the anorexia of aging, signals a profound alteration in physiology that has piqued the investigative interests of scientists and clinicians. Advances have been made in describing the events preceding and sequelae following onset of age-related anorexia, yet consensus among investigators about underlying mechanisms has not been reached. A goal of this review is to summarize current knowledge about potential etiological factors.

Definitions of the anorexia of aging may vary, but the syndrome involves the unintentional decline in food intake (and as a result, body weight) that begins near the end of life. Because this syndrome occurs without an obvious cause in otherwise healthy individuals, it has been suggested to constitute a prelude to "natural death" (91). The absence of obvious pathology associated with age-related anorexia distinguishes this form of energy imbalance from anorexia nervosa, a psychological disorder displayed predominantly by young females, and cachexia, a phenomenon characterized by increased resting metabolic rate, elevated cytokines, and muscle and fat wasting related to disease (76). Longitudinal investigations, including the third National Health and Nutrition Examination Survey (NHANES III), the Baltimore Longitudinal Study of Aging, and the New Mexico Aging Study show a progressive decrease in caloric intake in older adults (2, 56, 74); short-term dietary intake observations indicate inadequate caloric intake in the elderly population (95, 107, 114). Furthermore, unexplained weight loss has been described in up to 35% of aged community dwellers (82) and 70% of nursing home residents (139).

Clinical research supports the existence of imbalance in homeostatic mechanisms governing hunger and satiety beginning in the sixth to seventh decades of human life. Beckoff et al. (7) evaluated the effect of dietary glucose supplementation on gastric emptying and food intake in older (age 65–84 years) men and women and showed that subjects did not modify their diets to compensate for additional energy consumed. Using a preloading method, Rolls et al. (122) demonstrated that elderly men (60–84 years old) did not compensate as precisely for changes in caloric intake as did younger men (18–35 years old). In agreement with these data, Roberts (121) found that older men (mean age 68 years) were less successful than were younger men (mean age 22.7 years) in adjusting energy intakes after their diet was altered (i.e., elderly subjects did not self-regulate food intake and resume their "normal" body weights after periods of under- or overfeeding as did the younger men). In addition, less hunger and greater fullness were reported by the older subjects in this study. Clarkston et al. (26) similarly found that the desire to eat after a test meal was attenuated more in aged (70–84 years old) than in younger (23–50 years old) men and women.

Although this age-related anorexia may be a normal part of aging, it commonly results in undernutrition and secondary pathologies such as sarcopenia (39), impaired immunity (146), and physical frailty (43), all of which can substantially compromise quality of life. In an effort to prevent or at least mitigate these problems, investigators have employed a variety of approaches to identify causal agents. Whereas this review includes some data from humans, it emphasizes the biologic and nutritional determinants of age-related anorexia, and thus draws heavily from studies of rodents. The influence of psychosocial disturbances (e.g., depression, senile dementia) is not addressed, and readers are referred to other publications for this information (37, 41, 106). The term senescence is used to describe the terminal stage of aging, when the rate of functional deterioration increases and death occurs shortly thereafter. Rodents, as well as humans, entering this state show significant hypophagia and loss of body weight (11). Mean or median life spans are indicated for those rat strains for which sufficient longevity data exist. We begin with a summary of the short- and long-term control of food intake in young animals and then proceed to address how advanced aging affects both of these levels of control. Conclusions are drawn that suggest likely factor(s) underlying the mechanisms of age-related anorexia.

OVERVIEW OF THE CONTROL OF FOOD INTAKE IN YOUNG MAMMALS

The control of food intake is the purview of a system comprising neural and chemical signals that act cooperatively, synergistically, or antagonistically to modulate short- and long-term feeding behavior and nutrient disposition. The signals eliciting short-term effects on feeding originate from the oral cavity, gastrointestinal tract, and liver; they travel via the vagus nerve to the brain to modulate meal size. These satiety signals include oronasal stimuli (32), stretch receptor signals transmitted by the stomach and proximal intestine (140), nutrients [e.g., glucose (15, 90) and amino acids (16)], metabolites [e.g., lactate (108), pyruvate (108), and ketones (42)], gastrointestinal hormones [e.g., cholecystokinin (CCK) (49, 104)], and neurotransmitters released in the brain in response to vagal afferent fiber transmissions (96). Short-term signals are integral to the maintenance of energy homeostasis. However, they are not primary determinants of body weight/body adiposity because they can be overridden by long-term control signals. Rather, short-term effectors act in concert with long-term signals (e.g., leptin and insulin) to maintain energy balance over time. Both of these hormones circulate in proportion to recent food intake and body adiposity and enter the brain, where they affect the expression of genes encoding hypothalamic neurochemicals influential in controlling food intake and energy expenditure [e.g., neuropeptide Y (NPY)]. Bidirectional communication between long-term signals and cytokines also occurs to modulate feeding behavior (80). The extensive list of factors involved in control of food intake reflects the complexity of this physiological system and implies that disturbances in maintenance of energy balance may involve dysfunction in a variety of steps or factors. Thus, although evidence presented here may implicate

one determinant of age-related anorexia over another, the interconnectivity among signaling pathways cannot be overlooked.

FUNCTION OF SHORT-TERM REGULATORS OF FOOD INTAKE DURING AGING

Oronasal and Gastrointestinal Signals

Oronasal and gastrointestinal stimuli play an important role in short-term regulation of food intake, and therefore they have been studied extensively in relation to negative energy balance associated with advanced age. Research has tended to concentrate on age-related alterations in olfaction, taste, and gastrointestinal function. A majority of early reports showing significant declines in sensory and gastric function with age-used tissue from persons with unknown medical histories or patients with diagnosed pathologies (3, 102, 150, 160). However, more recent investigations have taken measures to exclude diseased subjects from study. Despite this, methodologies employed in evaluating taste and smell include a substantial subjective component that could complicate direct comparisons of perceived sensations among different age groups.

Analyses indicate that the density and basic structure of taste buds and papillae are maintained in healthy old humans and animals (14, 97, 99). Although evidence supports the conclusion that taste and smell thresholds are elevated with age (29, 31, 156), the impact of these changes on food intake is uncertain. Altered thresholds do not reliably predict changes in recognition of more concentrated stimuli, such as those encountered in an average diet (5, 30). Furthermore, we are unaware of any data that demonstrate a causal relationship between diminished sensory function, reduced hedonic response, and changes in feeding in older individuals (32, 123). Studies on independently living elderly have yielded contradictory results: Griep et al. (53) found that lower energy intake was correlated with poor odor perception, whereas Duffy and colleagues (34) observed no impairment in appetite or food enjoyment as a result of significant olfactory losses. Schiffman & Warwick (132) showed that flavor enhancement of foods prepared for elderly subjects (mean age 85 years) with deficits in taste and smell does not improve food intake enough to affect body weight or body mass index. Until longitudinal data characterizing sensory changes and their relationship to food intake across the life span become available, there is insufficient evidence to conclude that smell or taste deficits contribute significantly to anorexia at advanced ages.

The integrity of gastrointestinal function at advanced ages has been difficult to establish owing to the confounding influence of atrophic gastritis, an acquired disease that is prevalent in the elderly (20, 45, 126). Many studies showing reduced gastric secretion and/or emptying at older ages did not exclude the presence of atrophic gastritis or its causative bacterium, *Helicobacter pylori* (51, 65, 87, 109, 150, 160); and at least two investigations using human subjects in whom gastric disease was strictly excluded demonstrated no decrease in gastric acid secretion with age (50, 71). However, whereas Feldman et al. found that infection with *H. pylori* could

explain the higher incidence of reduced gastric acid secretion in elderly subjects, controlling for its presence did not remove an independent negative effect of age on pepsin output (39a). Further, Oneta et al. (109a) reported that the enhanced alcohol metabolism they observed in elderly subjects with normal gastric morphology was caused by slower gastric emptying. These findings notwithstanding, Horowitz et al. (65) concluded that changes in gastric emptying observed in older humans were small, within the normal range found in younger controls, and unlikely to be of clinical significance. A subsequent study of ~100 elderly persons who were placed on a 100-g fat diet while in a metabolic unit for 6 days showed that fecal fat concentrations did not increase between the age range of 20–95 years, thus arguing against the notion that malabsorption is characteristic of old age (4).

Studies on aging rats have also produced contradictory results. Smits & Lefebvre (141) compared gastrointestinal transit time in 3-, 12-, and 24-month-old male Wistar rats and demonstrated delayed gastric emptying in the oldest group. Others, however, observed no significant effects of age on rates of gastric emptying (94, 151).

In general, the available data do not support the occurrence of reduced gastric secretion in healthy aged individuals. Without such an association, it is premature to implicate stomach dysfunction as a primary contributor to the anorexia of aging. Although a causal relationship has been suggested between age-related anorexia and *H. pylori* infection (113), this represents a correlation of decreased food intake with age-associated disease rather than with normal aging processes.

Endogenous Opioids

The sensory pleasure response to food, particularly fats and sweets, is mediated, in part, by endogenous opioids, including dynorphin, β-endorphin, and the enkephalins (32, 52). Injection of opioids into the cerebral ventricles of animals results in increased food intake, and blocking opioid receptors inhibits feeding in animals and humans (145, 147, 162). Opioids may stimulate feeding by acting independently or by enhancing the effects of other neuropeptides (e.g., NPY) and neurotransmitters (e.g., dopamine) involved in the regulation of food intake (48, 81, 124).

It has been proposed that impaired opioid action contributes to the anorexia of aging. Evidence for age-related declines in hypothalamic opioid concentrations is provided by Forman et al. (44), who reported decreased β-endorphin content in 19–23-month-old versus 3–5-month-old male Sprague-Dawley rats (median life span 28 months), and by Dupont et al. (35), who showed lower levels of enkephalins in 24–26-month-old than in 4–5-month-old male Sprague-Dawley rats. Plasma and cerebrospinal fluid β-endorphin concentrations are lower in humans with idiopathic senile anorexia (aged 70–84 years) than in normal-weight controls (88). However, following treatment of the anorectic individuals with megestrol acetate (an appetite stimulant), significant increases in cerebrospinal fluid β-endorphin levels were observed without improvements in food intake or body weight.

Other studies dispute the postulate that decreased sensitivity to opioids or reduced opioid concentrations are causal factors in age-related anorexia. Gosnell

et al. (52) evaluated feeding responses to naloxone (an opioid antagonist) in Fischer 344 (F344) rats aged 2, 12, 22, and 28 months (median life span of F344 rats is ~25.5 months). They found that low doses of naloxone resulted in decreased food intake in 2- and 12-month-old rats but not in 22- and 28-month-old animals. The two older groups responded similarly to all antagonist treatments, and the 28-month-old treated rats ate significantly more compared with baseline than did the 22-month-old group. A study from our laboratory provides indirect evidence for a functional feeding reward system during advanced aging. When offered a choice of a basal semipurified diet and a high-fat, high-sucrose diet, older (25–29^{+}-month-old) male F344 rats maintained a preference for the palatable diet comparable to that seen in younger rats (11). Similarly, when male F344 rats were given a choice between lemon- and vanilla-flavored low-fat diet, we found no difference in the percent of each selected by old rats that had entered senescence (i.e., hypophagic and losing weight) versus those that were presenescent (body weight–stable). In male Sprague-Dawley rats, Lau & Tang (81) noted no differences in levels of hypothalamic methionine (met)-enkephalin and β-endorphin among 3-, 8-, and 23-month-old animals; and Wang et al. (155) found no effect of age on levels of hypothalamic β-endorphin or enkephalins in male Sprague-Dawley rats aged 3, 12, and 22 months, with the exception of lower daytime concentrations of met-enkephalin in the oldest animals. Additional reports indicate an absence of an age effect on hypothalamic β-endorphin and met-enkephalin levels in male Sprague-Dawley rats beyond the age of sexual maturity (47, 98, 144). Taken together, these data do not support a causal link between opioid system dysfunction and the anorexia of aging.

Cholecystokinin

Cholecystokinin (CCK) is a hormonal mediator of gastrointestinal short-term satiety signals that is thought to act centrally on brain feeding systems and peripherally by slowing gastric emptying and activating visceral sensory nerves (120). Investigation of CCK as an effecter of age-related anorexia stems from the premise that CCK signaling becomes progressively stronger with age, ultimately suppressing food intake to the point of weight loss. A number of studies have tested this hypothesis, but their results are not in agreement.

MacIntosh et al. (86) observed higher plasma CCK concentrations in older (65–80 years) than younger (20–34 years) men during both fasting and intraduodenal lipid infusion. In contrast to younger men, the older men did not report any change in hunger sensation after nutrient infusion. Thus, it was concluded that there was no clear evidence that increased CCK secretion caused the reduced appetite and food intake accompanying normal aging. MacIntosh et al. further proposed that aging may be associated with resistance to the appetite-suppressant effects of CCK even in the context of possible hypersensitivity to the gastric-emptying effects of this peptide (85). Voigt et al. (153) tested the effects of intraperitoneal administration of CCK on food intake under two different feeding conditions in younger (2-month-old) and older (23-month-old) male Wistar rats. In food-deprived animals, CCK reduced feeding similarly in both age groups, whereas under fixed (meal) feeding

conditions, the highest dose of CCK significantly reduced food intake only in the oldest rats. Silver et al. (138) demonstrated greater sensitivity to CCK in 25-month-old than 8-month-old male C57BL/6Nnia mice (median life span 27 months). In response to intraperitoneal injection of an antagonist to peripheral CCK receptors, young but not old mice ate significantly more than baseline levels. Old (3 years) guinea pigs had higher intestinal CCK concentrations than did 1-year-old animals, but these levels were accompanied by decreased pancreatic and gallbladder CCK receptor sensitivity (115).

Other investigators have observed either no change or decreased CCK concentrations/potency with age. Basal and postprandial plasma CCK levels were found to be similar in young (mean age 29 years) and old (mean age 80 years) human subjects (9). Miyasaka et al. (100) also showed no significant effect of age on basal and stimulated CCK release in older (25–29-month-old) and younger (5–8-month-old) male and female Wistar rats. Khalil and colleagues (73) observed that comparable gallbladder contractions in response to fat ingestion in younger (22–42-year-old) and older (60–84-year-old) men and women were associated with significantly higher plasma CCK levels in the aged group, suggesting attenuated responsiveness to CCK. A comparable study by Masclee et al. (89) yielded similar results. Sandstrom & El-Salhy (129) quantified duodenal endocrine cell types in four age groups of NMRI mice (1, 3, 12, and 24 months old) and found no difference in the number of CCK-immunoreactive cells among the groups.

These data do not clearly demonstrate that advanced age is associated with increased levels of and/or heightened sensitivity to CCK. Under experimental conditions of chronic CCK administration, food intake and body weight are not significantly changed (28), apparently because the resulting reduction in meal size is compensated for by increased meal frequency (157). Although satiety factors such as CCK are powerful effectors of individual meal size, they are purported to have limited independent influence on long-term energy balance (61, 159).

FUNCTION OF LONG-TERM REGULATORS OF FOOD INTAKE DURING AGING

Leptin

Leptin has a major role in the long-term regulation of energy balance via its central effects on food intake and energy expenditure. Secreted by white and brown adipocytes, leptin passes the blood-brain barrier to bind receptors within the arcuate (ARC) nucleus, paraventricular nucleus (PVN), and ventromedial hypothalamus (18). One mechanism whereby leptin inhibits food intake and stimulates energy expenditure involves altered transcription of hypothalamic neuropeptides. Among these are the orexigenic peptides NPY (77), agouti-related peptide (101), and melanin-concentrating hormone (148), whose expression leptin decreases; and the anorexic peptides proopiomelanocortin (24) and cocaine- and amphetamine-related transcript (79), whose mRNA levels are increased by leptin. Because circulating leptin levels are positively correlated with adiposity (62, 84) and the

percentage of body fat tends to increase through middle age (38, 85, 111), an independent effect of age on serum leptin concentration has been investigated. At least two studies in humans have demonstrated that after adjustment for body fat, a significant inverse relationship between serum leptin and age exists (110, 127). Experiments in humans and rodents have shown that serum leptin concentrations increase with age in parallel with body fat and fall with the decline in adiposity during advanced age (1, 11, 12, 111). The fact that the lower concentrations of serum leptin seen in senescent F344 rats do not prevent their decreased food intake suggests the possibility of dysfunctional leptin signaling and/or the involvement of other pathways.

Whereas the integrity of leptin signal transduction has yet to be investigated in animals displaying age-related anorexia, decreases in both the density of hypothalamic leptin receptors and leptin-induced STAT3 activation are seen in old, obese rats (130, 131). Leptin resistance in overweight, aged (24-month-old) male F344/Brown Norway rats is manifested, in part, by reduced suppression of NPY mRNA expression (137). These data leave open the possibility that disrupted leptin signaling (as opposed to increased leptin levels) occurs in other forms of age-related energy imbalance such as anorexia.

Insulin

Substantial evidence supports the role of insulin as a long-term modulator of food intake and energy expenditure (136, 159). Insulin is secreted by endocrine cells of the pancreas in response to carbohydrate and protein ingestion, and both fasting and postprandial insulin levels are correlated with body adiposity (62). Circulating insulin is transported across the blood-brain barrier over a period of hours, which is consistent with insulin's role as a long-term regulator of energy balance rather than as a short-term satiety factor. There are insulin receptors within the ARC of the hypothalamus (6), and central insulin administration affects expression of neuropeptides such as NPY (133, 135). Central insulin infusion also potentiates the satiety effect of peripherally administered CCK (40). In addition, insulin administration increases adipose expression of leptin [reviewed in (60)]. Thus, in theory, increased insulin could contribute to the anorexia of aging via several mechanisms.

However, our studies of rodents indicate that insulin levels are not elevated during chronological aging (27). In one study comparing endocrine function in whole perfused pancreas and islets of Langerhans isolated from male F344 rats 6, 12, and 26 months old, we showed that glucose-stimulated insulin secretion was not significantly altered with age. In fact, we found that although islets isolated from 26-month-old presenescent rats secreted significantly less insulin than did islets from 6-month-old animals, more β-cells in older than younger rats were responsive to glucose (133). Thus, the levels of insulin seen in these old presenescent rats suggest that they are maintaining normal insulin secretion through compensatory mechanisms. Several additional investigations support these results (57, 92, 93, 143).

However, not all investigators have found that insulin secretion remains unchanged during aging. Researchers using in vitro methods have demonstrated decreased (8, 19, 22, 23, 103, 117, 118, 149) or increased (17, 83) insulin secretion with age. The varied results most likely reflect differences in age groups used as comparison for old rats. For example, Reaven and colleagues (116, 118) suggested an age-related alteration of insulin secretion per β-cell when they reported differences between 2- and 12-month-old Sprague-Dawley rats. Given that the median life span of the Sprague-Dawley rat is $\sim$28 months, 12 months of age would represent young adulthood. Moreover, 2-month-old Sprague-Dawley rats are still growing at an exponential rate, suggesting that differences between the age groups more closely reflect development than aging. When more developmentally mature rats are compared with rats near the end of their median life span, differences in insulin levels are not seen (57, 92, 125, 143).

Studies of humans have also yielded varied results on insulin secretion in old age. Korosi et al. (75) examined insulin response to a 3-hour oral glucose tolerance test in healthy young (23 ± 1 years) and elderly (age 80 ± 2 years) subjects and found no difference between age groups. Bourey et al. (13), utilizing a hyperglycemic clamp technique to investigate insulin secretory responses of young (24 years) and older (65 years) subjects, noted no significant changes in older subjects with normal glucose tolerance. However, Kahn et al. (68) demonstrated a higher and more sustained peak of serum glucose following an oral glucose tolerance test in older than younger subjects. It is unclear if this higher serum glucose reflected decreased insulin secretion, insulin resistance, or some other abnormality in glucose disposal.

Difficulties with interpretation of data from in vivo assessment of insulin secretion in aging subjects may arise if obesity and level of physical activity are not considered (23, 55, 68). Several investigations have demonstrated that insulin secretion during in vivo clamp and tolerance tests does not change in nonobese, healthy, or physically active older humans. Indeed, extensive research by Reaven and co-workers (46, 64, 119, 154) led them to conclude that aging has a relatively minor effect on indices of glucose homeostasis, including insulin secretion. Rather, it is more likely that the age-related alteration of insulin secretion observed in some investigations more closely reflects obesity and/or physical inactivity than biological aging per se. Thus, existing data do not support the hypothesis that enhanced insulin secretion or responsiveness is associated with age-related anorexia.

Hypothalamic Neuropeptides

NEUROPEPTIDE Y AND FEEDING BEHAVIOR Neuropeptide Y has been the subject of substantial interest in elucidating the etiology of age-related anorexia owing to its potent stimulatory effects on feeding. Synthesis of NPY within the ARC nucleus of the hypothalamus and release in the PVN positively correlate with the normal circadian rhythm of feeding in rats, and NPY levels are greatly increased during food restriction (70, 128, 163). Injection of NPY into the PVN and perifornical

areas of the hypothalamus elicits overeating and rapid weight gain (67, 69), whereas immunoneutralization of hypothalamic NPY or blockade of its receptor suppress the hyperphagic response to food deprivation (33, 142).

NPY also influences peripheral metabolic systems so as to favor energy storage. That is, it modulates activity of the sympathetic nervous system and hypothalamic-pituitary axis to stimulate lipogenic enzymes in adipose tissue and the liver and to reduce brown adipose tissue thermogenesis (10, 36, 134). These actions of NPY critical to defending energy stores (i.e., stimulating appetite and reducing caloric expenditure) have led investigators to search for an association between impairments in NPY function and the anorexia of aging. Because of invasive methods required to determine the integrity of the brain's neurochemical system, research in this area has relied primarily on animal models.

In studies of male F344 rats we demonstrated that their initial feeding response to NPY was blunted after they became senescent (12). We injected NPY into a lateral ventricle of young (8-month-old) and old (24–30-month-old) rats and characterized feeding patterns displayed during the subsequent 24-hour period. We found that although old weight-stable (presenescent) and young rats responded similarly to the stimulatory effects of NPY at the first postinjection meal, old weight-losing (senescent) rats had significantly smaller increases in the size and duration of their first post-NPY meal. Interestingly, however, the total amount of food eaten during the 24 hours after NPY injection was not lower in the senescent than presenescent rats, suggesting that compensatory mechanisms may have limited the presenescent rats' feeding or stimulated the senescent rats' food intake. Nonetheless, the fact that the NPY-induced food intake of the presenescent rats was significantly greater than that of the senescent rats during hours 1 and 2 after injection suggests blunted NPY responsiveness in the latter.

An earlier investigation by Pich et al. (112) demonstrated an age-related decline in hypothalamic NPY function that was associated with reduced food intake. Using two groups of male Sprague-Dawley rats (3 and 24 months old) and two feeding states (24-h food-deprived and satiated), they measured the effects of NPY injection into the PVN. The feeding response elicited by NPY at 30, 90, and 240 min postinjection was attenuated in older compared with younger satiated and food-deprived rats, but no age difference was seen at 22 h after injection. Lower levels of NPY immunoreactivity within the PVN were found in older than younger animals. Pich's group concluded that the impaired sensitivity to exogenous NPY and the reduction of NPY in the PVN of aged rats might be partly responsible for age-related anorexia.

LEVELS AND EXPRESSION In addition to assessing NPY potency, brain concentrations of NPY peptide as well as mRNA levels of preproNPY (ppNPY) and other orexigenic and anorexic neuropeptides have been evaluated in rats exhibiting age-related anorexia. We found significantly higher ARC mRNA levels of ppNPY in senescent than comparably aged presenescent male F344 rats but no difference in agouti-related peptide message levels (Horwitz, Gabaldon, Hamilton, Gavel, &

McDonald, unpublished data). This greater NPY expression in the senescent rats is consistent with their decreased body weight and lower adiposity and should have signaled increased food intake. However, food intake was decreased, consistent with the blunted response of senescent rats to injections of NPY (12). Notably, quantification of hypothalamic mRNA levels for proopiomelanocortin (precursor to alpha-MSH, an inhibitor of food intake), the anorexic peptide cocaine- and amphetamine-related transcript, and the orexigenic peptides orexin and melanin-concentrating hormone showed no changes in the senescent rats that could explain their reduced food intake (Horwitz, Gavel, Gabaldon, Hamilton, & McDonald, unpublished data). Although Li et al. (85) found no perturbations in hypothalamic NPY mRNA levels in old (31-month-old) versus young (3-month-old) and middle aged (24-month-old) male F344xBN rats, the two older groups displayed similar levels of food intake, adiposity, leptin mRNA, and body weight, indicating that the 31-month-old rats were not exhibiting age-related anorexia.

In contrast to our results for senescent F344 rats are data on ad libitum–fed and 72-h fasted young (3-month-old), middle-aged (12-month-old) and old (24-month-old) male BN rats (54), showing that expression of hypothalamic ppNPY was greater in the young than older rats, whether fed or fasted. Moreover, whereas ppNPY gene expression increased with fasting in all groups, the response was attenuated in the older rats. It is important to note, however, that the 24-month-old BN rats were significantly younger than the median life span for this rat strain (29 months). Therefore, a majority of these animals may have not have been anorectic. In addition, the fact that the reduction in ppNPY mRNA in the BN rats occurred in the middle-aged animals and did not show significant change thereafter is better explained as part of a transition from youth to adulthood and/or increased adiposity, rather than a transition from presenescence to senescence.

There are other reports of age-related changes in NPY concentrations within the rat brain. Kowalski et al. (78) found that although changes in corticotropin-releasing hormone (an inhibitor of feeding) and the opioids met-enkephalin and β-endorphin varied with age depending on brain area, NPY levels were more consistently decreased throughout the brain (including the hypothalamus) in older male Wistar rats (values for 26-, $<$18-, $<$4-month-old rats). They concluded that the NPY peptidergic system is one of the more susceptible to aging and that physiological functions involving NPY are preferentially impaired during aging. Similarly, Cha and colleagues (21) showed severe loss of cerebral cortex NPY neurons in aged (20–29-month-old) compared with young (4–6-month-old) Sprague-Dawley rats.

The differences in experimental methods employed in the aforementioned NPY studies may reveal important insights into the postulated progression of NPY functional deterioration upon advancing age. Most investigators have used groups of animals of differing chronological ages to show decreasing NPY concentrations with age. In our studies in which we examined responses to intracerebroventricular injections of NPY, rats were followed longitudinally and displayed changes in NPY responsiveness concurrent with the onset of senescence. Thus, the stimulation of feeding via NPY may begin to diminish in the latter third of life and progress beyond

a critical threshold in senescence, resulting in a drive to eat that is insufficient to sustain life.

Dopamine and Norepinephrine

Neurotransmitters such as dopamine and norepinephrine play a critical role in the regulation of food intake. Data support a relationship between the dopaminergic and adrenergic systems in the balance of hunger and satiety, and evidence indicates the existence of interactions among these monoamines and peptides that influence feeding behavior (59, 72). As aging has been associated with decreased dopaminergic (63, 158) and noradrenergic (25, 58) function, it is possible that alterations in monoamine production, signal transduction, or metabolism could contribute to the anorexia of aging. This postulate has not been sufficiently tested, however, and its mention in the literature is often restricted to discussions of how such alterations may be influenced by age-associated decrements in NPY function (21, 66, 78).

Cytokines

The interactions of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6), with neurochemicals such as leptin, CCK, and NPY are important factors in the anorexia that often accompanies chronic infectious, neoplastic, and autoimmune diseases (80). In addition, cytokines may play a role in the control of normal feeding. Food ingestion represents a significant antigen load in the gut, evoking host defense actions of cytokines (164). It has been proposed that increased circulating cytokine levels are common in the elderly, owing to the presence of chronic illness, and thus may contribute to the anorexia of aging (105). A study in which cytokine synthesis and release were pharmacologically downregulated by megestrol acetate in cachectic geriatric nursing home patients showed improved appetite in treated subjects versus controls. However, no changes in body weight or body composition were observed until three months after treatment was discontinued (161).

We have found that senescent male F344 rats do not have higher serum levels of IL-1β than do presenescent rats, but they do have higher TNF-α concentrations (152). While these results suggest that TNF-α may be involved in the anorexia of the senescent rats, until more data are available, support for a significant role of inflammatory agents in the etiology of age-related anorexia will remain speculative.

CONCLUSIONS

Notwithstanding the caveats mentioned throughout this review, there are general conclusions that can be drawn. The fact that the physiological system controlling food intake is complex and redundant emphasizes the likelihood that age-related anorexia has numerous causes. Thus, further understanding of the underlying mechanisms demands investigative approaches that are open to considering

multiple possibilities and utilize various model systems. It is also useful to focus on candidate determinants. In this regard, the available data indicate that short-term regulation of food intake via signals from the gastrointestinal tract (including endogenous opioids and CCK) is not consistently modified by aging. Furthermore, because these short-term signals regulate individual meal size rather than body energy stores, dysfunctional short-term signaling cannot fully explain the progressive decline in food intake and body weight characteristic of anorectic aging animals. Rather, impairments in one or more long-term signals/pathways regulating food intake are implicated. Although insulin and leptin levels are not elevated in healthy elderly humans or in senescent rats, alterations in the effectiveness of NPY signaling are evident in old rats experiencing spontaneous decreases in food intake and body weight, suggesting that altered NPY responsiveness is a strong candidate effecter in the anorexia of aging.

Clearly, there remains much to be revealed about the underlying causes of declining food intake near the end of life. A more thorough understanding of this phenomenon can contribute to optimizing quality of life during its final stages. Clarifying the mechanisms of the anorexia of aging can also offer clues to other aspects of the aging process. However, a challenge to research on aging is verification of an index of biological age that can be used by gerontologists. Such a biomarker would provide a predictor of mortality and therefore facilitate the direct comparison of research results. Because no biomarker has been broadly accepted, most experiments have relied on chronological age as an indicator of the extent of aging. As we have discussed in this review, significant difficulties can be encountered when interpreting data from studies using only chronological age. For age-related anorexia, the senescent rodent (12) appears to be a valuable animal model.

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