Anorexia, Sarcopenia, and Aging

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Food intake declines throughout the life span. This physiologic anorexia of aging is caused in part by alterations of stomach-fundus compliance and release and activity of cholecystokinin. In addition, the decline in testosterone in males results in elevated leptin levels that increase the anorexia. There is also evidence that cytokines play a role in the pathogenesis of anorexia and sarcopenia, thus accelerating the development of frailty in older persons. Numerous treatable causes of anorexia and weight loss exist. Depression is the most commonly diagnosed cause of pathologic weight loss in older persons. Nutrition 2001;17:660–663. ©Elsevier Science Inc. 2001

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INTRODUCTION

With aging there is a decline in food intake.1 This occurs to a greater extent in men than women. This decline in food intake also is seen when the food intake of very healthy older persons is examined.2 We have termed this physiologic decline in food intake the anorexia of aging.3 This decline in food intake with aging has multiple causes including an increase in the activity of the peripheral satiation system and a decline in the activity of the central feeding system.

The decrease in food intake coupled with a decrease in exercise leads to a decline in muscle mass (sarcopenia). This physiologic anorexia of aging also makes older persons more vulnerable to developing severe anorexia and muscle wasting when they develop disease. This condition is known as cachexia, from the Greek kakos ‘bad’ and hexis ‘condition.’ However, the pattern of weight loss seen with cachexia differs from that seen with pure nutrient deficiency, suggesting that other factors also are involved in producing protein catabolism and muscle wasting.

PERIPHERAL SATIATING SYSTEMS

Taste thresholds increase with aging and olfaction declines. These changes can be particularly dramatic when the older person takes medications. In addition, zinc deficiency, which can occur with a variety of diseases such as diabetes, can further elevate the taste threshold.3 However, despite these changes, altered hedonic values appear to play a minor role in the anorexia of aging.4

The stomach is a major player in producing the early satiation often seen in older persons. With aging there is a decline in compliance of the fundus of the stomach,5 which leads to more rapid filling of the antrum. Antral distention is the signal that is sent to the central nervous system to terminate the meal.6 Clarkston et al.7 found that large meals are associated with delayed gastric emptying and increase satiation.

When glucose is placed directly into the duodenum, it actually enhances appetite in older persons but suppresses it in younger persons.8 In contrast, fat produces the release of the satiating hormone, cholecystokinin, from the duodenum. Compared with younger persons, older persons have an increase in basal cholecystokinin levels and a marked increase in cholecystokinin in response to intraduodenal fat.9 In addition, cholecystokinin in older animals and humans is a more potent satiating agent.10 There is no evidence that other peripheral, satiating, gut peptides play a role in the anorexia of aging.11 Insulin, which is often elevated in older persons,12 has been shown not to produce satiation in humans.13

GROWTH HORMONE

Growth hormone and insulin growth factor-1 decline in older persons.13 Insulin growth factor-1 has been shown to have more dramatic decreases in malnourished persons.14 Growth hormone is an anabolic hormone that also increases food intake. Growth hormone has been shown to reverse catabolism in older malnourished persons.15 However, a recent study in critically ill malnourished subjects suggested that growth hormone increases mortality.16

THE CENTRAL NERVOUS SYSTEM

Multiple anatomic connections within the central nervous system are involved in modulating food ingestion. These connections include the amygdala, nucleus accumbens, nucleus tractus solitarius, and the hypothalamus. Within the specific nuclei in these regions, multiple neurotransmitters interact with one another to form the “feeding cascade.”17,18

Animal studies have supported a role for decreased dynorphin stimulation of feeding in the pathophysiology of the anorexia of aging.19,20 Dynorphin produces its effect by activating the k-opioid

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receptor. Aging is associated with a decline in opioid-receptor function, further supporting the concept that opioids are involved in the anorexia of aging.

Neuropeptide Y is a potent orexigenic peptide. Its role in appetite regulation has been studied extensively. There is evidence that neuropeptide Y is involved in the anorexia of aging in rats but not in mice.

Animal studies have suggested that nitric oxide plays a major role in the central stimulation of food intake. However, one human study did not confirm that finding. A study in rodents has suggested that nitric oxide is involved in the anorexia of aging in this species.

Corticotropin-releasing factor (CRF) is an anorectic peptide that also stimulates the sympathetic nervous system, resulting in catabolism. The CRF-2 receptor seems to be the one involved in appetite regulation. There is no evidence that CRF is directly involved in the anorexia of aging. However, CRF might be important for the anorexia associated with depression in older persons.

The role of other peptides in the anorexia of aging remains to be determined.

**TESTOSTERONE, LEPTIN, AND SARCOPENIA**

Testosterone levels decline with aging in males. As sex-hormone–binding globulin levels increase with age, there is an even more dramatic fall in free or bioavailable testosterone. This decline in testosterone has been shown to be the major factor associated with the decline in muscle mass and muscle strength that occurs with aging. In addition, it is associated with a decline in functional status, i.e., the ability to perform simple tasks necessary for the maintenance of the activities of daily living. Testosterone replacement increases muscle mass and muscle strength in men. Testosterone also increases muscle strength in women.

Leptin is a peptide hormone that is produced by adipose cells. Leptin produces anorexia and increases metabolic rate. In women,
leptin levels increase with the increase in fat mass at middle age and declines in old age.43 These increased leptin levels decrease food intake in postmenopausal women.44 In men, leptin levels continue to increase over the life span, despite a decrease in body fat in old age.45 Several studies have shown that females have higher leptin levels than males even when corrected for fat mass. In a longitudinal study, I and my colleagues showed that testosterone is the factor most closely associated with the increase in leptin levels in older men.46 In addition, testosterone treatment results in a decrease in leptin levels.47

Food intake decreases to a greater extent in males than females with aging.47 Increased leptin secondary to androgen deficiency in aging males appears to play an important role in the pathogenesis of this phenomenon. In addition, the age-related fall in testosterone plays a key role in the development of age-related sarcopenia.

Cytokines, Aging, and Weight Loss

As people age, they develop numerous minor ailments (e.g., arthritis, recurrent infections, tumors, and pressure ulcers) that result in inflammatory responses. Such inflammatory responses result in the elaboration of cytokines. Elevated cytokines, especially interleukin (IL)–6, have been associated with a decline in function and frailty in older persons.48,49 The mechanisms by which cytokines do this are not clear but include anorexia and muscle protein catabolism, resulting in weight loss and decreased muscle strength. With the development of malnutrition, a vicious cycle is developed in which the older person develops recurrent infections and/or pressure ulcers, leading to further cytokine release and the cachexia, or wasting, syndrome (Fig. 1).

A number of cytokines have been implicated in the pathogenesis of anorexia and muscle wasting. Tumor necrosis factor-α, IL-1, IL-6, γ-interferon, leukemia inhibitory factor, and ciliary neurotrophic factor have all been shown to be involved in anorexia. Many of these cytokines belong to the same superfamily as leptin and are thought to produce their anorectic effects by stimulating the leptin receptor.50 The interleukins appear to stimulate CRF.51 CRF is a potent anorectic agent.52 In addition, cytokines inhibit the release of orexigenic peptides such as neuropeptide Y, dynorphin, galanin, and melanin concentrating hormone. Cytokines increase prostaglandin E1, a potent anorectic agent.53

Leptin belongs to the helical cytokine family, which includes IL-6, IL-11, leukemia inhibitory factor, and ciliary neurotrophic factor. Many of these cytokines cause leptin to be released. In addition, the leptin receptor is homologous to the gp130 signal-transducing molecule that also is associated with the IL-6 receptor.54 This signaling pathway results in the activation of signal transducers 1 and 3 and activation of transcription in the hypothalamus.55 Endotoxin, lipopolysaccharides, and the anorectic cytokines activate the same postreceptor pathway, suggesting mechanisms by which these cytokines might produce anorexia.56 With aging there is a decline in signal-transducer 3 activity, whereas signal-transducer 1 does not change.57 Signal-transducer transcription factors seem to be the molecular basis for the cytokine-related anorexia in older persons.

Cytokines such as IL-1 also block the release of luteinizing hormone by luteinizing hormone-releasing hormone.58 This will decrease testosterone levels with an acceleration of the sarcopenic process. Lowering testosterone also increases leptin levels, further aggravating the anorectic process.

Martinez et al.59 characterized a condition that they called idiopathic senile anorexia. In this condition, production of IL-6 and tumor necrosis factor-α is increased in peripheral blood mononuclear cells from anorectic as opposed to non-anorectic elderly.59 Interestingly, tumor necrosis factor-α is decreased in the cerebrospinal fluid of anorectics. The investigators suggested that those changes were an attempt of the body to adapt to the anorexia of aging. Those patients also had increased circulating levels of cholecystokinin.60

Megestrol acetate has been used successfully to treat cancer and anorexia caused by acquired immunodeficiency syndrome.61 There are limited studies in older humans. However, Yeh et al.62 showed that megestrol acetate causes weight gain in older males and that this weight gain is related to suppression of cytokines. Whether the effect of megestrol acetate on feeding requires cytokine suppression or is due to a direct progestational effect on neurotransmitters in the central nervous system is not clear.

Pathologic Anorexia and Weight Loss

As alluded to in the section on cytokines, disease is a major cause of protein-energy malnutrition. Whereas cancer is an obvious cause of anorexia, recent studies have shown that malnutrition in most older persons has treatable causes.63 Weight loss in older persons can be caused by anorexia, increased metabolism (e.g., hyperthyroidism), and malabsorption (e.g., gluten enteropathy). Depression is the most common cause of weight loss in older persons.63,64 In general, the more severe the depression, the greater the weight loss. In addition, successful treatment of depression reverses the weight loss. Approximately one-third of older persons with severe weight loss appear to have depression. Table 1 provides a simple mnemonic listing of the treatable causes of weight loss in older persons.

Table 1. Meals-on-Wheels Mneumonic for the Causes of Weight Loss in Older Persons

<table>
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<th>Cause</th>
<th>Example</th>
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| Medications (e.g., digoxin, theophylline, cemetidene) | |}

References


