The Anorexia of Aging

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Introduction

Protein-energy malnutrition is a frequent condition in the elderly, it is associated with a reduction in the adaptive response to the physiological and pathological conditions of aging [1]. The pathogenesis of malnutrition is likely to be multifactorial. A low-calorie intake represents one of the main risk factors for malnutrition: this condition has been referred to as ‘anorexia of aging’ [2]. Many factors are involved with the pathogenesis of anorexia in the elderly.

Both cross-sectional [3] and longitudinal [4, 5] observations have shown that energy intake is reduced in the elderly as compared to younger subjects. The mean calorie reduction between 20 and 80 years of age was 1,300 kcal/day for men and 600 for women [3], while from 40 to 70 years of age food intake was reduced by 25% [4]. At more advanced ages, energy intake declined constantly by 13 kcal/day/year in women and 25 in men [5]. The consistent reduction of food intake in the elderly is only partly balanced by reductions in energy expenditure, so old men and women mainly lose body weight [5].
Many of the social, psychological and organic conditions which characterize aging are also recognized causes of reduced food intake and malnutrition (fig. 1). Among social factors, economic problems and isolation are the most frequent. Depression more frequently plays a role in weight loss in the elderly than in young people [2]. Depression causes malnutrition, as meals are frequently ignored or refused. Ageusia of swallowing may also be recognized, particularly in postischemic dementia [2].

Several diseases which are frequently associated with the elderly lead to weight loss, mainly by elevating energy expenditure, but also because they depress hunger sensation. Patients with chronic obstructive pulmonary disease suffer from both the consequences of energy dispersion (due to respiratory inefficiency) and anorexia, caused by inflammatory mediators. Similarly, neoplasia and heart failure cause cachexia for higher energy requirement but also for anorexia. In these conditions, high concentrations of cytokines such as IL-6 and TNF-α have a strong anorexigenic effect [6].

Dysphagia and poor mastication interfere with nutritional status either directly or indirectly, by reducing taste sensation. Many drugs, which are widely used in the elderly, may cause anorexia. Table 1 shows a list of the most common. Even when old and young people are compared in the same setting, in paired health and social conditions, energy intake has been reported to be lower in the elderly. A primitive alteration in the mechanisms regulating energy balance has been hypothesized [7].

Aging is associated with an impairment in the ability to regulate body weight. A study from Roberts et al. [8] demonstrated that after a few weeks of a hypocaloric diet both elderly and young subjects lost weight, however the elderly were unable to spontaneously regain weight by a compensatory hyperphagia as was observed in young adults. On the contrary, after overfeeding only the young spontaneously reduced food intake and thus lost extra weight, while older subjects maintained excess weight [8].

Short-term regulation of food intake also seems to be impaired with aging. A preload with a snack (yogurt) was not compensated in a subsequent buffet meal and the older subjects showed a 10–30% excess in calorie intake [9].

Single food-specific sensory satiety contrasts the excessive intake of a single food even in a normocaloric meal. In the elderly this kind of satiety seems to be impaired thus facilitating monotonous single food intake [9]. Furthermore, a reduction in the hedonist component of eating and an elevated threshold of taste and smell restricts the pleasure of eating to only a few foods in the elderly. These conditions often lead to a poor alimentary

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**Table 1.** Drugs that may cause anorexia in the elderly

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Amiodarone, Furosemide, Digoxin, Spironolactone, Theophylline</th>
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<tbody>
<tr>
<td>NCS</td>
<td>Levodopa, Fluoxetine, Lithium</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>H₂-antagonists, PPI, Psyllium</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Griseofulvin, Metronidazole</td>
</tr>
<tr>
<td>Chemotherapies</td>
<td>Any</td>
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<tr>
<td>Anti-inflammation</td>
<td>Colchicine, AINSD, Penicillamine</td>
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variety of choice which increases the risk of quantitative malnutrition due to low-calorie intake and qualitative low intake of single nutrients [10].

Malnutrition has a dramatic impact on health in the elderly; it impairs the immune system thus increasing the frequency and severity of infectious diseases. In fact malnourished old people have particularly low levels of CD4+ T-helper cells [11]. Malnutrition may cause anemia as well as cognitive decline, osteopenia, altered drug metabolism and sarcopenia. Malnourished elderly run a higher risk of hospitalization, delayed discharge from the hospital and mortality [12]. Unfortunately, malnutrition is a frequent condition at older ages. It has been reported that 17–65% of hospitalized older subjects and 5–59% of institutionalized suffer from malnutrition [13].

In many cases, reduced food intake caused by unbalanced hunger-satiety sensation appears to be the only cause of malnutrition. Control mechanisms and possible abnormalities of aging are described below.

**Central Hypothalamic Hunger-Satiety Control**

Figure 2 summarizes the hypothalamic role in hunger-satiety control. The nucleus arcuatus (ARC) has neurons which release NPY (neuropeptide Y), the most common and potent orexigenic mediator, and AgRP (agouti-related peptide), another hunger mediator. Axons from ARC neurons release NPY and AgRP in the paraventricular nucleus (PVN), referred to as the ‘satiety center’, and inhibit it. Other neural terminations from ARC reach the lateral hypothalamic area (LHA), known as the ‘hunger center’, and stimulate it. The net effect of NPY and AgRP tone is hunger stimulation and satiety inhibition leading to increased food intake [14].

Adjacent to orexigenic neurons in the ARC, other neurons express POMC (pro-opiomelanocortin), the precursor of melanocortins, such as α-MSH, that inhibit LHA and stimulate PVN. Other neurons with similar action express CART (cocaine-amphetamine-related...
peptide). MSH and CART are inhibited by NPY neurons [14].

Leptin produced by the adipose tissue and insulin from the pancreas rise in the blood as a long-term signal of adiposity (i.e., they refer the presence of a positive energy balance to the hypothalamus). CCK and peptide YY (PYY) produced after meals by the upper and lower intestine elicit short-term signal of satiety. Leptin, insulin, CCK and PYY inhibit NPY/AgRP neurons and stimulate POMC neurons, thus causing satiety [14, 15].

Ghrelin, a hormone produced by the stomach during fasting, stimulates NPY neurons in the ARC, potentiates hunger and triggers eating [16].

Along the vagal nerve, stimuli from stretching receptors of the stomach rise after gastric filling by food and reach the nucleus of the tractus solitarius (NTS). NTS evokes the sensation of satiety and contrasts excessive food ingestion. In the same neural way, CCK, produced by the intestine in the presence of lipids and amino acids in the lumen, also stimulates NTS and thus postprandial satiety. NTS receives inhibitory fibers from LHA and excitatory fibers from PVN. In this complex system hunger prevails in fasting conditions, satiety after meals [14, 15].

NPY is one of the most abundant peptides in the whole brain and is able to integrate the metabolic and behavioral systems [17] pushing towards the search and intake of food, as a potent survival instinct. NPY impairment may potentially be involved in the pathogenesis of anorexia in the elderly. Studying this system in humans is very difficult for obvious reasons, so most of the data have been obtained from observations in rats. Aged rats exhibited low drinking and eating responses when NPY was injected into the PVN [18]. Surprisingly however, when plasma and cerebrospinal NPY levels were evaluated in anorectic elderly, NPY was found to be high [19].

At the level of the CNS, endogenous cannabinoids stimulate hunger since they potentiate the pleasure of and desire to eat [20]. It has been postulated that in analogy with animal studies, endocannabinoid tone in the elderly may be diminished [21]. Although some authors found lower concentrations of plasmatic endocannabinoids in elderly as compared to young people [22], the opioid inhibitor naloxone showed the same suppressive action on hunger in both young and older subjects, suggesting that there is no difference in the basal endocannabinoid tone. On the basis of these findings, MacIntosh et al. [23] concluded that age is not associated with reduced opioid feeding drive.

**Peripheral Control of Energy Balance**

Taste and flavor, but also the sight of pleasant food, enhance hunger by acting on the orexigenic mediators and by cortical integration of past experience. Ghrelin is the only orexigenic signal which comes from peripheral districts; it is produced in a pulsatile manner by the empty stomach. All other peripheral short- and long-term signals inhibit hunger and produce satiety. Anorexigenic signaling from the gastrointestinal tract counteracts food intake over digestive and absorption ability [24]. Adiposity signals from leptin and insulin indicate to the central system energy storage in the adipose tissue, thus they potentiate central satiety sensation. Long- and short-term signals interact so that insulin inhibits ghrelin and leptin enforces the CCK signal and vice versa [14].

Finally, nutrients themselves influence food intake, in particular blood levels of fatty acids and glucose, directly or indirectly, regulate hunger and satiety control centers [14, 19].

**Taste and Smell Alterations**

The elderly have a reduced sensor-specific satiety. As a consequence they may consume a large amount of a single food, but, on the other hand, they may feel satiety for any food after a single food ingestion. For instance, a young person who has eaten a yogurt would avoid intake of further yogurt but not necessarily other kinds of food; an older subject would lose not only desire for yogurt but also for any other food [7]. The possible mechanism for reduced sensory-specific satiety could be impairment of taste and smell senses in the elderly. This latter condition also causes reduced food intake, since taste and smell normally potentiate the sensation of hunger [25].

Taste is impaired with aging. Fukunaga et al. [26] found higher thresholds for recognizing sweet, bitter, salty and acid in the elderly as compared with young controls. Oral taste receptors were not found to be reduced, since taste buds count was similar between the different age groups. However, impaired cell turnover and structural abnormalities have been reported with aging [27].

Olfactory deficit has been demonstrated in the elderly and this may also reduce hunger [28]. Food consumption increased when elderly subjects were offered food with flavor enhancement [29]. Difficulty in recognizing flavors may be the consequence of age-related modification of olfactory epithelium, receptors and neural pathways. Furthermore, several drugs, commonly prescribed to old patients, impair taste and smell sensitivity [25].
Both flavor and taste of food perception are involved not only in specific food recognition, but also in the pleasantness of food. For this reason age-related sensory impairment may affect the hedonistic enhancement of food intake and contribute to the anorexia of aging [2]. Unfortunately, instead of improving the flavor and taste of their food to make it more appetizing, older people often renounce with the pleasure of eating and choose a monotonous diet, increasing their risk of malnutrition.

Gastrointestinal Motility

Abnormalities in gastrointestinal motility may play a crucial role in the hunger/satiety unbalance observed with aging. In particular, delayed gastric emptying may cause prolonged postprandial satiety [30–35]. Studies on gastric motility in the elderly have shown controversial results, mostly due to differences in test meals and methods of evaluation. Scintigraphic observations with radiolabeled food showed delayed emptying of both liquid and solid components of food [31, 34], but in one study only liquid food emptying from the stomach was delayed [32].

Ultrasound studies extrapolate gastric volume modifications, and thus gastric filling and emptying, by measuring the area at the level of the antrum, in fasting conditions and at regular intervals after meals. Using this technique, liquid meal emptying was found to be accelerated in the early postprandial phase in elderly patients [33]. The authors hypothesized an age-related reduction adaptation of the stomach to the alimentary (liquid) bolus. Morley [2] demonstrated a reduced production of nitric oxide at the level of the fundus, leading to a loss of gastric compliance and more rapid antral filling, while another US study with a liquid meal failed to find any differences between younger and older subjects [35]. Under more physiological conditions where subjects were given a mixed solid-liquid meal, ultrasonographic antral dynamics demonstrated delayed gastric emptying in the elderly [30, 36]. A study conducted in our institution showed complete gastric emptying after an 800-kcal meal to be delayed by more than 2 h in the elderly [30]. Satiety consistently lasted longer and hunger was suppressed during the 4 h of postprandial observation; satiety was directly and hunger inversely correlated with gastric emptying time. Nonetheless, satiety remained high in the elderly even at the end of the observation, when only a small quantity of food was present in the antrum. This suggests a possible sensory hypersensitivity. Ultrasonography can only evaluate antral emptying and cannot study fundus filling or emptying, nor distinguish between the liquid and solid components of food. Nevertheless, complete gastric emptying time, extrapolated by ultrasound antral area dynamics, proved to be reliable when compared with ‘gold-standard’ scintigraphy [36]. Therefore, the use of ultrasound monitoring after physiological meals is probably the best non-invasive way of evaluating gastric motility at more advanced ages. Furthermore, in physiological conditions, antropyloric motility leads neurohormonal response to a meal, which regulates food intake and digestion, according to antral filling and nutrient delivery from the antrum to small intestine [37]. Reduced fundus compliance has been suggested in the elderly but, again, this may reduce food intake because of distension of the antrum due to earlier delivery of food [2].

Slower gastric emptying in elderly persons may be a consequence of a reduced digestive ability of the stomach; it could also be the consequence of an ‘ileal brake’ effect, caused by a neurohormonal response to the presence of nutrients in the small intestine over its digestive and absorptive ability. Furthermore, a primitive age-related decline of gastric motility might be involved. Finally, chronic gastritis or medications may cause hypochlorhydria, which further retards gastric emptying [38].

Altered gallbladder contraction has also been postulated in elderly persons. A recent study [30] shows minor postprandial gallbladder contraction in healthy elderly compared with young controls. Postprandial gallbladder volume was inversely correlated with satiety. Nevertheless, previous ultrasound studies [35, 39] failed to demonstrate any gallbladder contractility abnormality in elderly persons. In the experiment of Di Francesco et al. [30], the administration of a meal rich in calories (800 kcal) and lipids (45%), requiring a submaximal digestive response, probably unmasked the difference between younger and older participants.

The approximate mean volume of bile reversed into the duodenum by the gallbladder in young controls and elderly subjects may be calculated by the percentage of volume reduction after the meal. Gallbladder bile volume output was nearly half in the elderly (7.5 vs. 14.5 cm$^3$) [unpubl. data]. These findings seem to be in contrast with the high levels of CCK in elderly subjects, but CCK may maintain the role of anorexigenic signal and it may be less effective on gallbladder motility due to a CCK resistance [30].

Gastric and cholecystic emptying is coordinated after ingestion of a meal, and the gallbladder only starts to refill when the stomach is almost empty. Gastric emp-
tying leads to gallbladder contraction by delivering nutrients into the small intestine where CCK is produced [40]. For this reason, slower gastric emptying coincides with reduced gallbladder contraction. Only one other study simultaneously evaluated gastric and cholecystic emptying by ultrasonography in elderly subjects [35]. However, Wedmann et al. [35] did not find any gastric or cholecystic motor abnormality after a lighter liquid meal.

Abnormalities in gastric motility may cause early satiation due to reduced fundus compliance [2], and prolonged satiety caused by slower gastric emptying [30]. Using satiety scores, younger subjects crossed hunger sensation 2 h after their meal and had scores comparable to fasting values after 4 h. In their elderly counterparts, the sensation of satiety still prevailed over hunger 4 h after their meal. Satiety was directly and hunger inversely correlated with gastric emptying time. Gallbladder volume was inversely correlated with satiety [30].

Intestinal motility also influences the hunger/satiety balance at the level of colon-rectum, in particular colonic stasis delays gastric emptying by a colon-gastric reflex, indirectly prolonging the sensation of satiety [2]. Gastrointestinal motility in the elderly has received little attention, even though breath-H₂ test orocea transit time and radiopaque label transit time were found to be normal in healthy elderly subjects [41]. Constipation, which is a common finding in advanced ages, is an exclusion criteria for motility studies of this kind, but it should be taken into account as a possible cause of impaired motility along the whole gastrointestinal tract, and thus as a risk factor for anorexia.

**Role of Hormones**

CCK is the prototype of satiety hormones: it is released by the proximal small intestine in response to the delivery of nutrients from the antrum, particularly of lipids and proteins [24]. Several studies have demonstrated the presence of higher CCK concentations in the blood of aged compared to young persons [30, 37, 39, 42]. Intraduodenal infusion of either glucose solution or lipid suspensions showed a greater difference between the age groups after lipid infusion [43].

Motor gallbladder sensitivity to CCK seems to be impaired with aging, but a CCK satiating effect sensitivity seems to be preserved [44]. High levels of CCK are probably among the major causes of the anorexia of aging as they were correlated to abnormally higher satiety sensation after meals [37]. In a recent study we confirmed higher fasting and postprandial CCK serum concentration in the elderly [30]. At the end of the observation, when the antrum contained small volumes of food, the elderly group still had circulating CCK levels which correspond to high satiety and low hunger.

CCK may have a primitive role in the genesis of anorexia and malnutrition, since higher CCK levels were found in malnourished aged subjects compared to well-nourished elderly [42].

PYY is released by the distal intestine in response to the presence of nutrients in the lumen. PYY inhibits the NPY-mediated appetite stimulus [44].

A previous study [37] on postprandial PYY did not find any differences between young and older people, but the observations were limited to 120 min after the meal. A recent observation showed a greater rise of PYY in late postprandial period in the elderly as compared to young controls [30]. In analogy with CCK, abnormally high postprandial PYY levels may inhibit the search for a second meal, thus leading to longer fasting intervals resulting in a risk of malnutrition in elderly persons.

Both CCK and PYY are enteric peptides involved in gastrointestinal motility in response to eating, they provide a potent anorexigenic signals to the hypothalamus. They also mediate slowing of gastric emptying induced by the presence of nutrients in the small intestine [37]. Abnormally high levels of fasting and postprandial CCK and PYY may further and indirectly prolong satiety by slowing antral emptying.

The glucagon-like peptide-1 (GLP-1) is an active byproduct from glucagon metabolism. GLP-1 is produced by the distal small intestine after food ingestion and carries a strong anorexigenic signal [45]. The role of GLP-1 in anorexia in the elderly needs to be further investigated since its concentrations after different stimuli have been shown to be similar in older and younger subjects [37, 42].

Insulin, a well-known regulator of glucose metabolism, is also a satiety hormone. Insulin probably acts indirectly by enhancing the leptin signal to the hypothalamus and by inhibiting the ghrelin orexigenic stimulus. Aging is characterized by reduced glucose tolerance and elevated insulinemia. This condition may facilitate anorexia [45].

Higher concentrations of plasma insulin may amplify the anorexigenic signal of leptin, since insulin stimulates central leptin action and sensitivity at the level of the ARC [46]. Hyperinsulinemia in the elderly could also be responsible for inhibiting ghrelin gastric expression and central sensitivity [47].

Di Francesco et al.
Leptin is another possible actor of anorexia in the elderly. This cytokine is a hormone which is mainly produced by adipose cells, whose main role consists in long-term energy balance, by giving the CNS a sign of energy storage. Low leptin levels signal loss of body fat and a need for energy intake, while high leptin levels testify the presence of adequate body fat and no need for further food intake [14].

Fasting leptin in healthy elderly subjects was found to be elevated when compared to young persons, even after adjusting for body fat mass [48]. Serum leptin was found to be significantly higher in the elderly group after a meal. Interaction was not significant, as well as the effect of time, so that mean values of leptin showed a flat line in both young and older persons; younger subjects showed lower mean values compared to older subjects [49]. These findings are in line with previous observations in adults, suggesting that leptin concentrations do not change significantly shortly after a meal [50] and confirming that leptin is more involved in long-term food control than in short-term modulation of food intake.

Nevertheless, the authors hypothesized that elevated serum leptin may have facilitated a postprandial prevalence of anorexigenic signals. As already discussed, aging is characterized by high postprandial CCK concentrations [2, 30]. In this condition, leptin passes more easily through the blood-brain barrier, inducing an increase in hypothalamic sensitivity to leptin [51]. Other authors claim the contrary for higher central CCK sensitivity in the presence of high leptin levels [50]. In any case, leptin and CCK collaborate to amplify the inhibitory message to NPY feeding drive.

Ghrelin is the only peripheral hormone known to stimulate appetite. Ghrelin is produced and secreted by the endocrine gastric mucosa to enhance food intake [16]. Ghrelin has a pulsatile secretion, with a maximal blood concentration just before the meal and a drop just after stomach filling. For these reasons, ghrelin is thought to be implicated in meal initiation. It has been suggested that ghrelin also encourages healing and growing. Therefore, hunger elicited by ghrelin could be considered as a warranty for energy surplus need in case of growth and tissue repair [14–16].

Ghrelin also seems to regulate long-term energy balance, and it rises under conditions causing negative balance such as anorexia nervosa, cachexia or hypocaloric diet; on the contrary, ghrelin secretion is suppressed in obese subjects with a positive energy balance [52].

Only relatively few data are presently available on ghrelin dynamics with aging. One study showed fasting ghrelin elevated values in the elderly [53]. Two other observations showed no significant age-related difference even in the postprandial period [42, 49]. Postprandial ghrelin was not significantly different in young and old subjects. In both age groups ghrelin dropped after the meal and returned to basal values within 4 h. Nevertheless, hunger did not follow a postprandial ghrelin raise in the elderly. Concurrent high concentrations of leptin and insulin may have been responsible for the low sensitivity to ghrelin [47, 52]. Furthermore, ghrelin is produced by the stomach in two major molecular forms: an active acylated ghrelin that stimulates food intake, and a second desacyl ghrelin that has been thought to have no hormonal action [54]. However, very recently, in animal models, it has been demonstrated that, in contrast with the acylated form, desacyl ghrelin decreases the intake of

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food [52]. The ratio of acylated to non-acylated ghrelin may have a role in different responses to ghrelinemia in the elderly and further studies are necessary in this direction.

Conclusions

In summary, the risk of malnutrition in the elderly is high even in the absence of clinical or social risk factors due to the primitive so-called ‘anorexia of ageing’. In adult life we face the risk of overeating and gaining body weight due to the prevalence of hunger (mostly central) signals, warranting survival in the presence of small quantities of food.

In the elderly there is a prevalence of both short- and long-term satiety signals (mostly peripheral), which contrast energy balance and cause malnutrition (fig. 3). In this case it seems that species survival prevails and less active (aged) people spontaneously consume less community food resources. Notwithstanding the presence of large amounts of food, at least in developed countries, this mechanism leads to malnutrition and thus to higher morbidity, disability and mortality at older ages.

A pharmacological approach to this problem does not seem to be realistic at this stage, but data coming from recent studies already suggest a possible intervention strategy in order to contrast anorexia and prevent malnutrition. For example, slow gastric emptying may be contrasted by fractioning food intake in small digestible meals. Improving taste and flavor of the dishes may enhance blunted hunger. Excessive CCK signal may be reduced by limiting the intake of CCK-stimulating foods such as fats and proteins.

Finally, the large amount of recent data has not yet clarified all of the aspects of anorexia in the elderly. Many more peptides and mediators involved in energy homeostasis need to be tested in the elderly, the complex integration of peripheral and central circuits needs to be further studied in humans, little attention has been paid to the role of digestive and absorptive dysfunction with aging on hunger and satiety control. Basic scientific research but also on-the-road nutritional intervention protocols will help to clarify these issues.


