Physiological and non-physiological age-related changes associated with reduced food intake in older persons

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Abstract

Dietary intake changes during the course of aging. Normally an increase in food intake is observed around 55 years of age, which is followed by a reduction in food intake in individuals over 65 years of age. This reduction in dietary intake results in lowered levels of body fat and body weight, a phenomenon known as anorexia of aging. Anorexia of aging has a variety of consequences, including a decline in functional status, impaired muscle function, decreased bone mass, micronutrient deficiencies, reduced cognitive functions, increased hospital admission and even premature death. Several changes during lifetime have been implicated to play a role in the development of anorexia of aging. These changes are both physiological, involving peripheral hormones, senses and central brain regulation and non-physiological, with differences in psychological and social factors. In the present review, we focus on the physiological and especially on the non-physiological age-related changes that play a role in the etiology of anorexia of aging. At the end we conclude with suggestions for future nutritional research to gain greater understanding of the development of anorexia of aging which could lead earlier detection and better prevention.

Keywords: aging, anorexia, food, hormones, depression, loneliness

1. Introduction

Aging in humans is associated with a failure to maintain energy homeostasis in response to changes in physiological and non-physiological factors, resulting in a decrease in body fat and body weight in older individuals (above 60 years of age) (Steen 1988, Shimokata et al. 1989). The changes in the maintenance of energy homeostasis have been elucidated in several epidemiological studies. A cross-sectional follow-up study in the USA, for example, reported a decline in average daily energy intake of 1165 kcal in males and 405 kcal in females when comparing individuals of 20 and 75 years of age (Briefel et al. 1995). A similar study performed in Mexico, reported a decrease of 19.3 kcal/day/year in women and 25.1 kcal/day/year in men who were above 60 years of age (Koehler 1994). Furthermore, an Australian study revealed that older persons lost height (1.8 cm) and weight (1.9 kg) during the 84 months of the study which was related to a significant decrease in carbohydrate, fat and protein consumption (Zhu et al. 2010). Besides changes in the amount of food and type of food intake, it is also shown that older persons eat fewer snacks between meals (de Castro 1993), that they experience less cravings for food (Pelchat and Schaefer 2000) and that they feel less hungry and more satiated than younger individuals (Clarkson et al. 1997). These age-related changes in food consumption lead to decreased energy intake in older persons which is associated with a reduction in body fat and body weight. These reductions can lead to a variety of health-related consequences, including a decline in functional status, impaired muscle function, decreased bone mass, micronutrient deficiencies, reduced cognitive functions, increased hospital admission and even premature death (Roberts 2000, Ahmed and Haboubi 2010). Overall, the reduced food intake and the decreased body fat and body weight in older persons, is referred to as anorexia of aging (Morley 1997, Kmiec 2010, Hays and Roberts 2006).

Anorexia of aging is a nationwide issue with currently 16% of those older than 65 years who are affected (Ahmed and Haboubi 2010, Guigoz et al. 2002). It is especially a severe problem among institutionalized older persons of which 15 % of the community-dwelling and home-bound older persons, 23 to 62% of the hospitalized patients and up to 85% of the nursing home residents suffer from malnutrition (Ahmed and Haboubi 2010, Guigoz et al. 2002). The development of anorexia of aging is multifactorial, involving both physiological and non-physiological aspects (Hays and Roberts 2006). Preceding reviews on the anorexia of aging focused mainly on the physiological changes involved in the development of this type of anorexia. However, we will outline both physiological (peripheral hormones, senses and central brain regulation) and non-physiological (psychological and social) changes to show that not only the physiological factors but also the non-physiological aspects play a significant role in the development of anorexia of aging.

2 Physiological changes

There are several physiological factors associated with reduced food intake in older persons. Some of these factors are known to be associated with feelings of hunger or satiety while the effects of others remain unknown. Most of the physiological factors involved in lower dietary intake in elderly are related to changes in peripheral hormones, senses and central brain control. Here, we will discuss the most important age-related changes in these three aspects affecting energy intake regulation and their role in the development of anorexia of aging.

2.1 Peripheral hormones

Several peripheral hormones are important in food consumption and are associated with altered energy intake in older persons, including cholecystokinin (CCK), leptin, ghrelin, insulin, peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). These peripheral hormones are released in the gastrointestinal (GI) tract in response to food ingestion and they mainly influence food intake by affecting activity in key brain areas like the hypothalamus, where the blood-brain-barrier is less tight due to a fenestrated capillary endothelium (Bear et al. 2006, Kastin and Pan 2000).

2.1.1 Cholecystokinin

One of the hormones involved in short-term regulation of food intake is CCK. It is usually referred to as the satiety hormone because it induces feelings of satiety. CCK is released from inclusion (I) cells of the small intestine in response to stimulation of the intestines by certain types of food. Furthermore, CCK is co-released with PYY from specialized gut endocrine cells (L cells) in the intestine (Sam et al. 2011). The main effect of CCK is activation of neurons in the nucleus of the solitary tract (a viscerosensory cell group in the brain stem (NTS)), possibly involving vagal afferents. This activation changes in eating behavior by reducing meal frequency and meal size (Bear et al. 2006). Other functions of CCK include slowing of gastric emptying (Morley 1987), inhibiting ghrelin production (a hormone involved in increasing appetite) (Sam et al. 2011) and down regulating NPY gene expression (a neuropeptide involved in eating behavior) (Simpson et al. 2009). When focusing on age-related changes in CCK, it has been shown that older adults have more CCK immuno-reactive cells in the duodenum compared to younger individuals. The increased number of CCK reactive cells might be related to the high prevalence of GI disorders like appendicitis and inflammatory bowel disease, observed in older persons (Såndstrom and El-Salhy 1999, Goldacre 2009). Furthermore, baseline plasma CCK concentrations are higher in older than in younger adults and fasting levels of CCK have found to be about 5-fold higher in older than in younger adults (MacIntosh et al. 1999). These higher levels were associated with increased feelings of satiation and a subsequent

reduction in food intake. Moreover, comparing underweighted older persons with healthy individuals, CCK8 levels (a specific splice-variant of the CCK hormone involved in the adaption of gut motility to the digestive status [Buéno 1993]) have found to be significantly higher in the underweighted subject group (Martinez et al. 1993). Another study performed by Serra-Prat and colleagues (2009), showed no differences in CCK concentrations following a meal in older participants, while younger participants showed enhanced CCK concentrations. The impaired response of CCK after a meal, the higher plasma CCK concentrations in older persons observed by MacIntosh and colleagues (1999) and especially the increased CCK concentration in underweighted older persons compared to healthy controls, support that high CCK concentrations results in a reduction in dietary intake. This effect can be mediated by CCK itself or CCK-induced inhibition of ghrelin production which both increase feelings of satiety. Overall, CCK might play an important role in the development of anorexia of aging.

2.1.2 Leptin

Another hormone which is released by the body in response to food ingestion is leptin. This hormone is released by adipocytes and it regulates body mass by reducing appetite and increasing energy expenditure via inhibition of NPY/AgRP neurons and stimulation of αMSH/CART neurons in the hypothalamic arcuate nucleus (ARC) (Hays and Roberts 2006). Several studies have examined age-related effects on leptin and most of these studies show increased circulating leptin levels in older individuals (Zoico et al. 2004, Ruhl et al. 2004). Furthermore, a study on the effects of re-nutrition (increased nutrition in underweighted individuals) in older persons, found that leptin was the only biological parameter that increased after 6 weeks of successful re-nutrition. This makes this hormone a candidate for monitoring the efficacy of re-nutrition in malnourished older individuals (Nivet-Antoine et al. 2011). However, Robert and colleagues (1997) found no effect of age on the relationship between circulating leptin and body fat mass. Therefore, they concluded that changes in leptin concentration are not linked with changes in body fat in older humans. These contradictive results suggest that, although leptin might be involved in malnutrition and re-nutrition in older persons, other mechanisms seem to be more important in the development of anorexia of aging.

2.1.3 Insulin

Another peripheral signal involved in food intake is insulin. This hormone is released into the bloodstream by β cells of the pancreas and it forms a necessary prerequisite for transport of glucose into body cells. Insulin regulates the levels of glucose in the blood via production of glucose transporters (Ferrannini et al. 1999) and, similar to leptin, insulin is able to inhibit

NPY/AgRP neurons and to stimulate αMSH/CART neurons in the ARC, resulting in reduced food intake (Kmiec et al 2005). Moreover, it can act as a satiety signal by decreasing ghrelin levels (Serra-Prat et al. 2009). As shown by Gutzwiller and colleagues (1999), aging is characterized by elevated insulin levels in the blood and reduced glucose tolerance followed by increased blood glucose levels. These changes in glucose tolerance, increased insulin and glucose levels (Hays and Roberts 2006) might lead to decreased feelings of hunger resulting in reduced food intake in older persons, which is the main issue in anorexia of aging.

2.1.4 Peptide YY

PYY is a peptide that is secreted from L-cells in the gastrointestinal tract and pancreatic polypeptide producing (PP) cells in the pancreatic islets of Langerhans. It serves as an anorectic signal, causing a reduction in food intake via Y4 receptors in the brainstem and the ARC (Sam et al. 2011). Besides its anorectic properties, PYY is involved in delayed gastric emptying (Suzuki et al. 2010). In a fasted state, PPY concentrations are low but these concentrations rapidly increase after eating a meal. Enhanced levels are shown to peak at one to two hours after the meal and they remain elevated for several hours (Adrian et al. 1985), thereby reducing appetite during this period. PYY levels have also shown to be altered in anorexia nervosa and obesity patients (Alvarez et al. 2002, Misra et al. 2006) suggesting that this peptide plays a major role in pathological eating behavior. So far, age-related PYY differences have only been observed in animal experiments. In mice, an age-dependent increase of PYY cells has been found and a similar pattern was shown in rats (Sandström et al. 1998, Sweet et al. 1996). In humans, these differences in PYY cells have not been studied and further research is needed to elucidate the effects of PYY on feelings of hunger and satiety. Also, studies on the modulations of age on these PYY effects remain necessary.

2.1.5 Glucagon like peptide-1

Another hormone involved in food intake is GLP-1, which is released from L cells in the intestine, pancreas and brainstem (Simpson et al. 2009). GLP-1 can reduce food intake behavior via an effect of vagus nerve and directly via GLP-1 receptors located in the brain stem (Dossat et al. 2011, Suzuki et al. 2010). Furthermore, GLP-1 can suppress glucagon secretion, delay gastric emptying, inhibit PYY release and modulate insulin functioning (Nåslund et al. 1999, Suzuki et al. 2010), all affecting eating behavior. Overall, GLP-1 promotes satiety and suppresses energy intake (Flint et al. 1999). Di Fransesco and colleagues (2010) performed a study to determine the effect of different macronutrients on GLP-1 serum concentrations and hunger in both older and younger participants. They found

that GLP-1 concentrations were higher after a fat meal in the older persons but not in the younger participants. This indicates that fat increases GLP-1 concentration, thereby reducing hunger in older persons. However, a study of MacIntosh and colleagues (1999) in which fasting blood samples were examined after infusion of either lipid or glucose followed by a test meal, did not support these findings. Although they observed a GLP-1 related decrease in feelings of hunger after intraduodenal lipid infusion in younger but not in older participants, no differential effects of plasma GLP-1 concentrations were found between these groups.

2.1.6 Ghrelin

The hormone that is able to increase appetite and dietary intake is ghrelin**.** Grelin is produced and released from the fundus when the stomach is empty. It increases appetite and food intake by activating NPY/AgRP neurons of the ARC (Bear et al. 2006). Rigamonti and colleagues (2002) found that older persons showed lower ghrelin levels compared to younger individuals. Moreover, Bauer and colleagues (2010) revealed that older persons did not show the generally observed reduced ghrelin levels after eating a meal. Furthermore, these older persons reported to feel less hungry and more satiated after food intake compared to younger participants. Another study found that older persons showed reduced levels of ghrelin after a two-year period, which was related to a worse nutritional status of these individuals (Serra-Prat et al. 2010). If comparing old frail persons with healthy controls of the same age, no differential ghrelin suppression was observed after eating a meal and in both groups postprandial ghrelin recovery was absent (normal fluctuations of ghrelin levels before, during and after eating a meal). Frail participants did show lower fasting ghrelin concentrations compared to healthy controls (Serra-Prat et al. 2009). Stomach size may also play a role in ghrelin secretion and food intake. This relation between food intake and stomach size is based on the observation that individuals who receive gastric bypass surgery report to have reduced appetite and they consume less (Hafner et al. 1991). Unfortunately, no experiments have been performed to elucidate the effects of aging on stomach size. Taken together, older persons have lower ghrelin levels and dysregulated ghrelin responses after eating a meal. This results in higher feelings of satiety which can lead to reduced food intake. These age-related effect of ghrelin are relevant risk factors for the development of anorexia of aging.

An overview of the above mentioned effects of peripheral hormones on eating behavior and age-related modulations of these effects are provided in table 1.

Table 1 - Age-related changes in peripheral hormones influencing food intake
CCK: cholecystokinin, PYY: peptide YY, GLP-1: glucagon like peptide-1, I cell: inclusion cell, L cell: specialized gut endocrine cell, PP cell: pancreatic polypeptide producing cell

Stimulate food intake			Inhibit food intake		
Hormone	Secretion site	Aging effect	Hormone	Secretion site	Aging effect
Ghrelin	Stomach cell	↓ decline after meal, ↓ postcranial recovery, ↓ prandial rhythm	CCK	I cell and L cell intestine	↑ CCK immunoreactive cells, ↑ CCK8 levels
			Leptin	Adipocyte	Contradictive results
			Insulin	Pancreatic β cell	↑ levels, ↑ blood glucose levels
			PYY	L cell intestine, pancreatic PP cell	↑ PYY cells in mice and rats
			GLP-1	L cell intestine and pancreas	Macronutrient effect on GLP-1 levels, ↓ GLP-1 related hunger

2.1.7 Other physiological factors

With aging, there is a well-known change in gastric emptying that can be related to changes in CCK (Morley 1987), PPY (Suzuki et al. 2010) and GLP-1 (Suzuki et al. 2010) levels. These hormones are all involved in slowing the emptying process. Several studies have outlined the differences in gastric emptying between young and older participants; the older persons showed a decreased rate of gastric emptying either for liquids, solids or both compared to young persons (Horowitz et al. 1984, Moore et al. 1983, Klingensmith et al. 2010). Delayed emptying and its prolonged intragastric mechanisms have been linked to a reduction in feelings of hunger and an increase in satiation (Clarkston et al. 1997), which are important factors in the reduction of food intake in older persons and therefore in the development of anorexia of aging.

Xerostomia, also known as dry mouth syndrome can also affect eating behavior (Schiffmann 1997). Xerostomia is known to cause discomfort and difficulties with eating, alterations in speech, changes in taste and smell and it makes individuals more vulnerable for infections and severe dental caries (Närhi et al. 1999, Vissink et al. 1992**).** The development of xerostomia is associated with several diseases and the use of medications. (Schiffmann 1997, Närhi et al. 1999). Since xerostomia can lead to problems with eating and changes in taste and smell, it may play an important role in the development of anorexia of aging.

Other age-related changes that might be involved in reduced food intake in older in persons include differences in metabolic rate (Saltzman and Roberts 1996) and an inability to return to a normal eating behavior after overfeeding or underfeeding (Moriguti et al. 2000). With increasing age metabolic rate generally decreases, this may contribute to reduction in

food intake but also lower physical activity since metabolic rate is known to be influences by both food intake and exercise (Fukagawa et al. 1990). Concerning the second factor, an impaired ability to regulate food intake following under or overfeeding, a reduction in perceived frequency of hunger may be a contributing factor since these older persons report to feel less hungry compared to younger individuals. This could result in disturbances in restoring normal food intake patterns (Moriguti et al. 2000).

2.2 Senses

The enjoyment of food products is produced by olfactory, gustatory and visual processes. Age-related changes in these processes have been observed in several studies.

2.2.1 Olfactory processes

Studies focusing on age-related changes in olfactory processes showed that older individuals exhibit a significantly reduced capacity to identify different odors and that they perceive odors less intense than younger individuals (Koskinen et al. 2003, Makowska et al. 2011). Among these older adults, impaired olfaction is observed in about 50% of those over 65 years and in 75% of those over 80 years of age (Duffy 2007). More specific research on nasal epithelium in older individuals reveals a loss of olfactory receptors at a rate of 10% per decade over the lifespan (Loo et al. 1996). In addition, studies on the piriform cortex, which is the brain area involved in smell perception, have revealed a decrease of 18% in the dendrites and spines in this specific region (Curcio et al. 1985). Moreover, brain areas involved in olfactory processing showed high presence of amyloid plaques and neurofibrillary tangles, which can kill olfactory neurons due to reduced nutrient availability. Reduction in olfactory neurons can result in reduced smell perception (Attems et al. 2005). Furthermore, there are several age associated diseases involved that can influence smell perceptions in older adults, including upper respiratory infections, Alzheimer's disease, Parkinson's disease, and dementia (Doty 1989). The age-related effects on olfactory processes can lead to reduced dietary intake with increasing age because the positively influences of smell on food perception and food-related odors that increase appetite, disappear (Yeomans 2006).

2.2.2 Gustatory processes

Besides impairments in olfactory processes, changes in taste sensitivity and taste and texture discrimination have been observed with increasing age (Forde and Delahunty 2002, Mojet et al. 2003, Kremer et al. 2007). Interestingly, Landis and colleagues (2010) found an interaction between altered smell and taste perception. Concerning the perception of the five basic tastes (bitter, sweet, sour, salty and umami), the greatest age-related changes have been observed for salty and umami tastes (Mojet et al. 2003). However, when wearing a

nose clip, only the perception of salty tastants diminished with increasing age. With respect to taste perception, gender differences have also been observed; males appear to have a more pronounced decline in taste sensitivity than females (Mojet et al. 2003). These age-related changes in taste perception are related to altered neural activity. Jacobson and colleagues (2010) examined age-related changes in gustatory processing using functional magnetic resonance imaging (fMRI). They found more activation in gustatory and reward processing regions in older persons compared to younger adults. Moreover, older persons showed increased activity in regions not commonly associated with taste perception. Due to the decline in taste sensitivity, it is not surprising that older people often recall that their food is tasteless. Reduced taste perception might diminish the pleasure gained from eating and thereby contribute to the development of anorexia of aging.

There are several physiological factors associated with the decline in taste sensitivity with aging. These factors include differences in taste bud density (Kano et al. 2007), tooth loss (Morales-Suárez-Varela et al. 2011), mouth hygiene (Kanli et al. 2005), xerostomia (Schiffmann 1997), periodontal diseases (Morales-Suárez-Varela et al. 2011) and zinc decline (Coneyworth et al. 2009). However, non-physiological factors are also involved in the reduced taste perception in older adults. In a recent study older individuals from four different countries performed a signal detection theory approach to detect threshold for bitter, sweet, sour and salty tastants. Analysis revealed that besides age also sex, social class and country were major predictors of taste acuity (Simpson et al. 2011). In addition to physiological changes, non-physiological changes including socio-demographic and cultural factors should therefore be taken into account when investigating age-related changes in taste perception and anorexia of aging.

Impaired smell and taste perception in older persons is not only associated with a reduction in food intake but it is involved in food choices, as well. Older persons consume a lower variety of energy-dense food products, which might results in inadequate nutrient intake in these individuals compared to younger persons (Roberts et al. 2005, Wu et al. 2011). Zhu and colleagues (2010) performed a 84 months, population based longitudinal study, to determine the changes in nutrient and dietary intakes in older women. They found that during the 84 month period participants lost body weight and the intake of energy and macronutrients significantly declined. Furthermore, intake of vitamins and minerals was found to decrease with age and the consumption of potatoes, meat, milk, bread and vegetables was also reduced significantly over time (Zhu et al. 2010). In the context of reduced variety in meals, sensory-specific satiety is a well-studied phenomenon, which refers to the observation that when a food is eaten to satiety, the pleasantness of that specific food product decreases more than food items that have not been eaten (Rolls et al. 1981). Based

on this phenomenon, one might expect that high variation in meals should delay satiation and increase food intake. This might explain why low weighted older persons who often choose meals with less variation, are satiated earlier and thus stop eating sooner and as a results show reduced dietary intake compared to individuals who consume high variation meals.

2.2.3 Visual processes

In addition to the age-related reduction in the sensation of smell and taste, deteriorations in visual perception may also influence food intake, since vision is strongly involved in identification, discrimination and selection of food products. Vision especially affects taste quality and hedonic ratings of food items (Verhagen and Engelen 2006, van Beilen et al. 2011). Furthermore, visual input can alter the perception of odors (Engen 1972) and because smell affects appetite, this can influence food intake. It is well known that with aging, vision declines (Sekuler et al. 1980) and based on the observations mentioned here, this reduction in visual perception might influence eating behavior in affected individuals. Unfortunately, no studies have been performed to evaluate the relationship between reduced vision and food choice in older persons and therefore no conclusion can be drawn about this aspect of food choice in older persons as well as its relevance for the development of anorexia of aging.

2.3 Central brain control

Besides changes in peripheral hormones and senses, some neurotransmitter and neuropeptides involved in central control of eating behavior also show age-related changes. Most of these neurotransmitters and neuropeptides influence eating behavior by acting on the most important area involved in regulation of eating behavior; the hypothalamus (Bear et al. 2006). In the hypothalamus, there are several distinct regions associated with feelings of hunger and satiety. Of these, the lateral hypothalamic area (LHA) is responsible for feelings of hunger and an increase in food intake and is therefore originally called the ‘hunger center’ of the brain, whereas the ventromedial hypothalamus nucleus (VMH) is activated after food consumption resulting in feelings of satiety. This region is known as the ‘satiety center’. These brain areas were determined about half a century ago mainly due to animal electrophysiological and lesion studies (Anand and Brobeck 1951, Brobeck et al. 1943). In the last decades, additional important food regulation areas were identified, including the dorsomedial hypothalamic nucleus (DMH), hypothalamic arcuate nucleus (ARC) and paraventricular nucleus (PVN). The DMH is connected to several regions of the hypothalamus involved in eating behavior including the LHA, VMH, ARC and PVN (Ter Horst and Luiten 1986, Renner et al. 2010) and this brain area itself is believed to be involved in satiety, circadian rhythm of food intake, energy balance and body weight homeostasis

(Gooley et al. 2006, Yang et al. 2009, Renner et al. 2010). The ARC affects eating behavior via two different types of cells; neurons that produce neuropeptide Y (NPY) and agouti-related peptide (AgRP) and neurons that secrete cocaine-amphetamine-regulated transcript (CART) and alpha-melanocyte-stimulating hormone (αMSH). NPY and AgRP both increase food intake while αMSH and CART serve as anorexic peptides. NPY/AgRP and αMSH/CART neurons project to different parts of the hypothalamus (Kmiec et al 2005). Most peripheral hormones can reach the ARC neurons via the blood-brain-barrier which is less effective in this region than in other parts of the brain. These hormones either activate or inhibit ARC or NTS neurons, resulting in pronounced effects on food intake (Kastin and Pan 2000) (figure 1). The paraventricular nucleus (PVN) of the hypothalamus is responsible for the humoral, somatic motor and visceromotor responses in the body. These responses result in a decrease in appetite and a subsequent reduction in food intake (Bear et al. 2006).

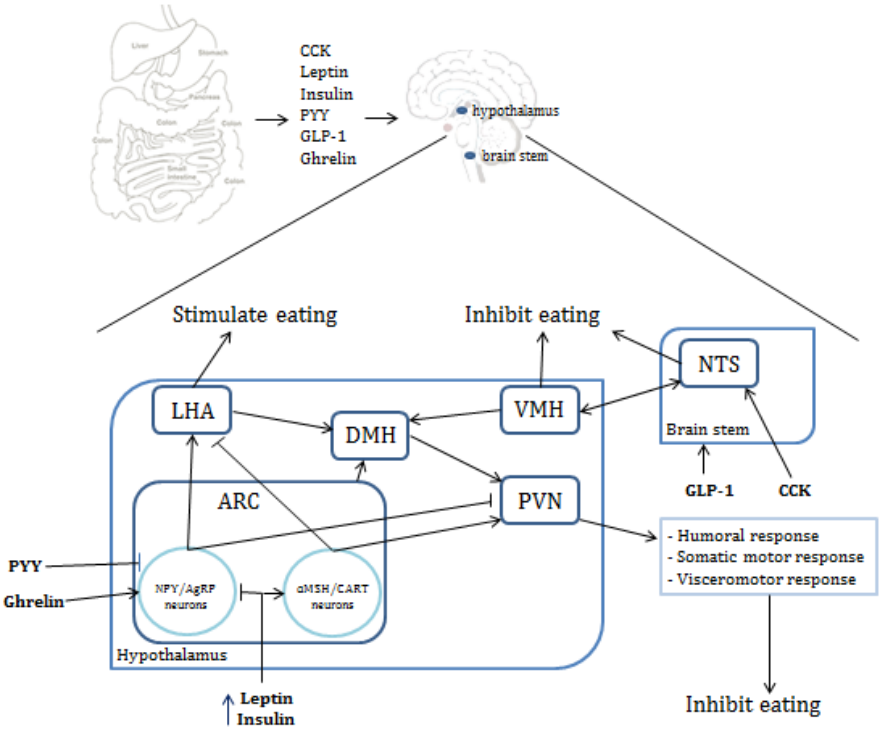

Figure 1 - The relation between peripheral hormones involved in eating behavior and specific brain structures

LHA: lateral hypothalamic area, DMH: dorsomedial hypothalamic nucleus, ARC: hypothalamic arcuate nucleus, PVN: paraventricular nucleus, VMH: ventromedial hypothalamic nucleus, NTS: nucleus of the solitary tract, CCK: cholecystokinin, PYY: peptide YY, GLP-1: glucagon like peptide-1, NPY: neuropeptide Y, AgRP: agouti-related peptide, αMSH: alpha-melanocyte-stimulating hormone, CART: cocaine-amphetamine-regulated transcript

The peripheral hormones mentioned above are involved in central food regulation by acting on different parts of the hypothalamus and brain stem. Besides the effects of these hormones, neurotransmitters and neuropeptides can stimulate or inhibit eating behavior by influencing this food regulation system. Unfortunately, most studies to identify the effects of

neurotransmitters on food intake and their involvement in aging have used animal experiments and therefore conclusion about the influence of these factors on human aging remains difficult. Here, we will outline the most important findings involving neurotransmitters and their regulatory effects. Where possible, we will outline the effects of human aging on these different factors.

2.3.1 Cocaine-amphetamine-regulated transcript

CART is an anorectic neurotransmitter that is released by αMSH/CART neurons in the ARC. CART levels in the brain vary in response to leptin levels in the blood (high levels of leptin stimulates αMSH/CART neurons, resulting in a decrease in food intake [Vicentic and Jones 2007]). NPY neurons are able to inhibit CART function (Di Fransesco et al. 2010). The inhibiting effect of CART on feeding behavior is shown in several animal studies in which CART injections reduced food intake (Asakawa et al. 2001). On the other hand, fasting, which decreases CART expression, resulted in reduced food intake inhibition and therefore in increased food intake (Van Vugt et al. 2006). Age-related changes in CART levels have been demonstrated in animal experiments in which CART messenger ribonucleic acid (mRNA) levels in the ARC were higher in old rats compared to young animals (Sohn et al. 2002). Similar results were obtained by Wolden-Hanson and colleagues (2004) who compared three different age groups of rats and found that in old rats, arcuate CART mRNA levels were increased. Furthermore, fasting-induced changes in gene expression were attenuated with age (Wolden-Hansen et al. 2004). Although these findings suggests an involvement of aging on CART food regulation, no experiments on humans have been performed so far to identify the exact involvement of CART in the development of anorexia of aging.

2.3.2 Neuropeptide Y

NPY is also involved in eating behavior. NPY is synthesized by the peripheral nervous system and NPY/AgRP neurons in the hypothalamus and it strongly stimulates food intake. This stimulation is shown by animal research in which injection of NPY into the PVN results in significantly increased food intake (Morley 1987). Martinez and colleagues (1993) found a significant increase in NPY levels in both plasma and cerebrospinal fluid (CSF) in underweighted older persons compared to healthy controls. This finding is contradictive to several animal studies showing that old rats have lower levels of ARC NPY mRNA than younger animals (Gruenewald et al. 1996) and that old male rats show decrease hypothalamic NPY levels compared to young male rats (Kowalski et al. 1992). Due to these contradictive results between animals and human studies, the exact age-related changes in

NPY levels in humans and its involvement in the development of anorexia of aging remain unclear.

Based on animal experiments, there is an indication that NPY and leptin actions are closely related. NPY knock-out mice eat normally, are not underweighted and re-feed normally after fasting normally. However, they are twice as sensitive to the effects of leptin compared to wild-type mice (Hollopeter et al. 1998, Palmiter et al. 1998). This suggests that NPY has inhibitory actions on leptin satiety signals. Unfortunately, no human experiments have been performed to confirm a relationship between NPY and leptin.

2.3.3 Agouti-related peptide

Another peptide involved in central brain regulation of feeding behavior is AgRP. This peptide is released from NPY/AgRP neurons in the hypothalamus and increases appetite and food intake. When comparing old and young rats, it is shown that hypothalamic AgRP expression is suppressed in old rats (Wolden-Hanson et al. 2004). Moreover, old AgRP knock-out mice show reduced body weight and body fat compared to young knock-out mice (Wortley et al. 2005). Another animal study used RNA interference to reduce AgRP mRNA levels with 50%. This reduction in AgRP mRNA resulted in lower body weight while the amount of food intake did not change in these animals (Makimura et al. 2002). This last finding indicates that AgRP influences body homeostasis, however, other factors may be of more importance in affecting food intake.

2.3.4 Alpha-melanocyte-stimulating hormone and pro-opiomelanocortin

αMSH and its precursor POMC are released from αMSH/CART neurons in the hypothalamus and both decrease feelings of hunger (Wolden-Hanson et al. 2004). Both peptides have only been studied in animals in relation with aging. These studies have shown a significantly higher decrease in POMC mRNA after fasting in older rats compared to younger rats (Wolden-Hanson et al. 2004). However, another study did not show differences in POMC expression between young and old rats (Pu et al. 2000).

2.3.5 Orexins

Orexins are neuropeptide hormones that are released from a small population of neurons in the LHA which have projections to several brain areas. There are two types of orexins; orexin A and orexin B (Sakurai and Mieda 2011). Orexin A is responsible for the stimulating effects on eating while orexin B is mainly involved in circadian rhythms and sleep (Chapman 2004, Sakurai et al. 2010). Orexin A injection into the brain ventricles or the lateral hypothalamus increases food intake and orexin deficiency causes weight loss in animals (Matsumura et al. 2002). Moreover, administration of anti-orexin antibodies or an orexin receptor antagonist,

reduced food intake (Sakurai and Mieda 2011). A study on human narcolepsy patients (orexin A and B are both associated with this disorder [Chapman 2004]), showed a decrease in the amount of food intake in patients compared to controls although an increase in body mass index in these patients has also been observed (Sakurai and Mieda 2011). The effects of increasing age on orexin A/B show contradictive results. Matsumura and colleageus (2002) showed a significantly higher concentration of plasma orexin A in the group older than 60 years of age compared to the group younger than 39 years. However, animal research found no significant increase in orexin levels in relationship to increasing age (Lin et al. 2002). Moreover, the number of orexin neurons in the lateral hypothalamic area was 28% lower in old rats, administration of orexin A did not stimulate food intake in old rats and a significantly lower amount of orexin receptor type 1 has been observed in the brain of old rats compared to young animals (Kmiec 2006).

2.3.6 Dopamine

Dopamine is involved in the corticolimbic pathways of the brain. These pathways are important in reinforcement of eating behavior and the rewarding experiences gained from food (Fulton 2010, Suzuki et al. 2010). When focusing on the effects of aging, significant age-dependent losses of dopamine receptors and dopamine transporters have been observed in regions of the prefrontal cortex, the striatum and the thalamus (Kaasinen et al. 2000, Dreher et al. 2008). Also, a reduction in the number of dopamine neurons in the substantia nigra has been found with increasing age (Anglade et al. 1997). Dreher and colleagues (2008) performed a study in which they combined Position Emission Tomography (PET) with fMRI to identify age-related changes in the reward system. They found that older persons had a significant lower activation of the dorsolateral prefrontal cortex compared to younger individuals, reflecting a decreased neural sensitivity to reward in older persons. This decrease in reward sensitivity can have pronounced effects on the reward gained from food, resulting in a decrease in reinforcement behavior followed by a decrease in food intake. However, an fMRI study in which different taste stimuli were used revealed a greater activation in gustatory and reward processing areas in older individuals compared to younger participants (Jacobson et al. 2010). The observed differences in reward processing with age and the age-related changes in dopamine receptors and transporters suggest that differences in the dopamine reward system might be of major importance in the development of anorexia of aging.

2.3.7 Opioids

In addition to dopamine, opioids are also involved in reward processing of eating. Opioid receptors have a wide distribution in the human brain. Activation of these receptors increases

appetite and food intake (Suzuki et al. 2010). Opioids are thought to act on the hypothalamus, amygdala and nucleus accumbens to increase appetite (Chapman 2004). Administration of opioid agonists including ketocyclazocine and morphine increase food intake in animals (Kavaliers and Hirst 1985) and opioids antagonists like buta-funaltrexamine and naloxone decrease food intake in both animals and humans (Shin et al. 2010, Trenchard and Silverstone 1983). Martinez and colleagues (1993) found that the amount of beta-endorphin, an endogenous opioid synthesized from POMC in the hypothalamus, is significantly reduced in older persons suffering from anorexia of aging compared to healthy controls. This decline in opioid levels has also been found in animals studies. For example, in rats, beta-endorphin levels in the hypothalamus and corpus striatum declined significantly with age (Gambert et al. 1980) and in mice, age-related alterations have been observed in beta-endorphin neuronal system (Miller and Zhu 1992). Furthermore, opioid agonists increase food intake in young mice but not in old mice and opioid antagonists reduce food intake only in young mice (Kavaliers and Hirst 1985, Gosnell et al. 1983). All these observations imply that opioids are important for age-related changes in food intake.

2.3.8 Serotonin

Serotonin is a neurotransmitter mainly known for its involvement in mood and mood disorders (Baldwin and Rudge 1995). However, serotonin is also involved in dietary intake as shown by increasing serotonin levels in the hypothalamus in anticipation of food and enhanced serotonin concentrations during the consumption of food products (Bear et al. 2006). Age-related changes in serotonin levels have not been determined so far but it is shown that the binding of ligands to serotonin transporters significantly declines with increasing age (Pirker et al. 2000). This suggests that the number of serotonin transporters, similar to dopamine transporters, are reduced in older individuals. Furthermore, the relation between mood and eating is an important topic in nutritional research since mood can have pronounced effects on food intake. For example, stress can result in significant changes in eating behavior (Macht 2008) and binge eaters eat in response to negative affect (Bohon et al. 2008). Furthermore, serotonin levels have shown to be altered in eating disorders like anorexia nervosa and bulimia nervosa (Kaye 2008). Another implication of the effects of serotonin on eating behavior can be found in its relation with antidepressant medication, which inhibits serotonin uptake resulting in increased levels of serotonin. It is shown that during the first few weeks of treatment with antidepressants body weight decreases, followed by an increase in body weight (Hainer et al. 2006). Furthermore, some antidepressant medications have found to be effective in treating in eating disorders and obesity (Hainer et al. 2006). The effects of mood changes, which involve altered serotonin levels, on eating behavior in older persons will be further outlined in the next session.

An overview of the abovementioned neurotransmitters and neuropeptides and the age-related effects of these factors on eating behavior is given in table 2.

Table 2 - Age-related changes in neuropeptides and neurotransmitters influencing food intake
NPY: neuropeptide Y, AgRP: agouti-related peptide, CART: cocaine-amphetamine-regulated transcript, αMSH: alpha-melanocyte-stimulating hormone, POMC: pro-opiomelanocortin, CSF: cerebrospinal fluid, mRNA: messenger ribonucleic acid

Stimulate food intake		Inhibit food intake	
Neuropeptide/ neurotransmitter	Aging effect	Neuropeptide/ neurotransmitter	Aging effect
NPY	↑ plasma and CSF level, ↓ mRNA*	CART	↑ mRNA*, attenuated fasting gene expression*
AgRP	↓ expression*	αMSH/POMC	↓ POMC expression*
Orexin	↑ plasma level, ↓ neurons*, ↓ receptors*, no stimulation after injections*		
Dopamine	↓ receptors, ↓ transporters*, ↓ activation		
Opioids	↓ beta-endorphin, no stimulation of agonist/antagonist injection*,		
Serotonin	↓ ligand binding		

* results from animal experiments

3. Non-physiological changes

In addition to the age-related physiological changes, the nutritional status of older persons is affected by psychological and social factors. In this part of the review we will outline the most important age-related changes in these non-physiological factors and their involvement in decreasing food intake and the development of anorexia of aging.

3.1 Psychological factors

3.1.1 Depression

One of the psychological factors that can influence food intake in older persons is depression. Depression is a common disorder in older individuals, especially in women, and it frequently involves a loss of appetite, reduced food intake and unintended weight loss (Quandt et al. 2000). Comparing old and young individuals, it is shown that depression is associated with weight loss only in individuals of above 55 years while it is associated with weight gain in younger participants (DiPietro et al. 1992). When focusing specifically on depression in older persons, weight loss has been found to be an important symptom in relation to higher mortality rates in depressed institutionalized older persons. Moreover, successful treatment of depression in these individuals was associated with weight gain (Donini et al. 2003). Another study determined the association between nutritional deficits in depressed older persons using questionnaires to identify malnutrition and depression. Results showed that 22% of the participants had nutritional deficits that were significantly related to depression (Cabrera et al. 2007). Furthermore, physical disabilities in older individuals, impeding food intake related activities, such as shopping and cooking, can also have pronounced consequences on eating behavior. This was demonstrated by Anyanwu

and colleagues (2011) who found that participants who were unable to shop or prepare meals were more likely to show depressive symptoms and difficulty with eating, which were both involved in reduced food intake.

The exact mechanisms by which depression can influence food intake remain to be determined although it is shown that during a period of induced depressive mood, the hedonic value of food products declines (Willner and Healy 1994). This decline can result in lower food intake in depressed individuals. Furthermore, dysregulation of certain neurotransmitters involved in depression can also be involved in reduced food intake of depressed older persons. Here, serotonin might be important since serotonin concentrations are reduced in depressive disorder and this neurotransmitter is known to be involved in eating regulation, as well (Weltzin et al. 1994). Finally, depression can lead to enhanced alcohol consumption which in turn can result in reduced dietary intake (see below) (Lewis 2011).

Apathy is a motivational state characterized by a lack of interest and/or emotions that frequently occurs as a symptom of depression or cognitive decline but it can also occur independently from other disorders (Bakker et al. 2010). Apathy can have serious effects on the quality of life of affected individuals (Bakker et al. 2010). Although there have not been any studies determining the effects of apathy on food intake in older persons, we hypothesize that apathy can lead to a reduced motivation to eat, which is frequently observed in older persons (Donini et al. 2003), resulting in decreased food intake and an higher risk for developing anorexia of aging.

3.1.2 Alcoholism

Alcoholism may also be involved in reduced food intake and weight loss in older persons (Hays and Roberts 2006), because the prevalence of alcohol abuse and dependence is very high among the older population, especially in men (5% to 23% in at home living individuals and 8% to 21% in hospitalized persons (Reid et al. 1998)) and alcoholism is known to influence nutritional intake (Lewis 2011). One of the mechanisms by which high amounts of alcohol can reduce food intake is by inhibition of brain regions involved in food regulation. One of these brain areas is the hypothalamus; high amount of alcohol lead to altered metabolic and behavioral signaling in this brain areas, resulting in lowered nutritional intake (Lewis 2011). Furthermore, alcohol is high in calories and among addicted individuals calories derived from alcohol may eventually make up 50% of their total daily energy intake. Alcohol abuse can therefore lead to major nutrient deficiencies and changes in body metabolism (Lewis 2011). The effects of chronic alcohol abuse on body weight was elucidated by Addolorato and colleagues (1998) who found that persons who suffer from

alcoholism showed a significantly lower body weight caused by fat mass reduction, compared to controls. Based on the high prevalence of alcoholism in older persons and the effects of alcohol on food intake, we suggest that alcohol abuse in older persons is a risk factor for the development of anorexia of aging, particularly in men. Moreover, increased alcohol consumption increases the risk of depression and vice versa (Boden and Fergusson 2011). Therefore, alcohol abuse in people at old age may also contribute to the development of a depressive disorder, resulting in lower food intake due to reduced hedonic values of food items.

3.1.3 Mood

As mentioned above, depressive mood is related to decreased food intake, showing the effect of negative feelings and emotions on eating behavior. This effect of mood on dietary intake was shown by Patel and Schlundt (2001), who followed the eating patterns of their participants for two weeks. Results showed that meals eaten in a positive or negative emotional state were significantly larger than meals eaten in a neutral mood. Another study disentangled the differences between positive and negative emotional effects on food intake (Macht et al. 2002). In this study, emotional states were experimentally induced by showing film clips. Results showed that sadness induced a decrease in appetite whereas joy increased appetite and pleasantness of food products (Macht et al. 2002). Although it should be kept in mind that the mood manipulations used, induced a temporal emotional state and not a longer lasting mood, like the negative feelings and emotions in a depressive disorder, these findings do highlight the importance of emotions in food regulation. In this context, negative emotions in older persons can be important in reducing dietary intake and the development of anorexia of aging.

In addition to emotion-related changes in eating behavior, the consumption of specific products can influence emotional states, as well. Consumption of specific products can be a rewarding experience, which might result in the desire to eat that product again (Gibson 2006). The impact of food consumption on emotions is experienced by most individuals and it is part of a reinforcement mechanism. This mechanism involves a liked product that activates the reward system, which in turn enhances mood and reinforces the desire to eat the product again (Dovey 2010). The reward system plays a key role in this reinforcing mechanism and it is shown that aging induces functional (Dreher et al. 2008) and structural (Marschner et al. 2005) alterations in (parts of) the reward system. Furthermore, age-related changes in dopamine neurons, dopamine receptors and transporters (Jacobson et al. 2010) and opioid levels (Martinez et al. 1993) have been observed. Since dopamine and opioid are

both involved in activation of the reward system, these changes may be of significant importance for reward-related food intake in older individuals.

3.2 Social factors

Besides psychological factors, social factors like loneliness, widowhood, lack of social support and social isolation are problems experienced by older persons (Ramic et al. 2011). These factors and their effects on eating behavior will be outlined in the following session.

3.2.1 Living alone

Ramic and colleagues (2011) performed a study to determine the differences in food intake between older persons living alone and controls, who lived in family surroundings. They found that participants who lived alone had a higher nutritional risk because they consumed fewer meals per day, had significant lower daily intake of protein, fruits and vegetables and showed significant loss of appetite (Ramic et al. 2011). This difference was also outlined by Wham and colleagues (2011), who found that living alone results in a higher nutritional risk than living with others. Moreover, they found that alone-living participants showed a lower level of physical activity, which may result in disturbances in the balance between food intake and energy expenditure. The disturbance in energy balance was also mentioned by Hays and Roberts (2006), who stated that older men had a substantial reduction in the ability to maintain a constant energy balance, where young men did not. These changes in energy balance place older persons at risk for weight loss and related health problems (Wilson and Morley 2003).

3.2.2 Widowhood

Among older persons, becoming a widow/widower is common and it is shown that widows and widowers are more likely to be at nutrition risk than those who are married/partnered, divorced/separated or never married (Wham et al. 2011). Rosenbloom and Whittington (1993) performed the first study on eating behavior and being a widow/widower. In this study, a group of recently widowed older persons were interviewed about their eating behaviors and compared with married controls of similar age. The researchers found that changes in social environment of the participants altered the social meaning of eating which resulted in negative effects on eating behavior and food intake (Rosenbloom & Whittington 1993). A similar study was performed by Quandt and colleagues (2000), who also interviewed recently widowed older women about the impact of widowhood on their eating behavior. Their results showed that the lack of structure due to becoming a widow, made these women more vulnerable for undernutrition. A study performed in 2001 focused more directly on the effects of recent widowhood on weight, dietary intake and dietary habits (Shahar et al. 2001). This

study included a group of recently widowed older persons and a group of married controls and results revealed that weight loss was significantly higher among widowed participants. Furthermore, the findings indicated that recently widowed participants eat more meals alone, enjoy their eating less and consume fewer snacks and homemade meals (Shahar et al. 2001). The possible underlying consequences of widowhood involved in reducing food intake in older persons are, changes in social relationships, reduced participation in social activities, reduced food preparations and changes in the patterns of food consumption.

3.2.3 Social isolation

Another factor associated with widowhood and loneliness, which is also involved in anorexia of aging is social isolation. Older persons may become isolated from society due to widowhood or lack of social support, which can result in reduced social contact and an increased risk for the development of depression (McIntosh et al. 1989). Social isolation results in a higher number of meals eaten alone, which was found to be associated with 30% lower energy intake (de Castro and de Castro 1989). Also, it can lead to less variety in meals which can result in lower food intake due to early satiation (Wham et al. 2011). One of the few studies that determined the direct relationship between social isolation and food intake in older persons revealed that in a group of 100 participants, 22% to 31% of the individuals showed social problems and these problems were more pronounced in underweighted individuals (Volkert et al. 1989).

A lack of social support can also result in social isolation of older persons, especially in women (McIntosh et al. 1989, Kendler et al. 2005). Since older individuals become more dependent on others for obtaining, preparing and eating food products (McIntosh et al. 1989), reduced social support can result in lower food intake. Furthermore, social support can serve as a buffer against the negative effects of poor appetite on dietary intake, because social control can improve healthy behaviors and stimulate individuals to eat proper amounts of food (McIntosh et al. 1989). The effects of social isolation on dietary intake makes social isolation in the older population a risk factor for reduced nutritional intake and the development of anorexia of aging.

3.2.4 Environmental changes

Moving from an independent living environment into a nursing home or hospital is another social change that a large group of older persons encounter. Changes in environment can influence eating behavior, because eating is no longer based on personal preferences but instead it is dictated by the time schedules in institutionalized environments (Donini et al. 2003). Also, the environment of the nursing home and the ambiance in which meals are consumed can influence food intake. This was demonstrated by Mathey and colleagues

(2001), who manipulated the ambiance of food consumption in nursing homes by improving the physical environment, atmosphere of the dining room, food service and organization of the nursing staff assistance. They found that these improvements resulted in a better nutritional status of their participants. Also the quality of the food in the new environment is of significant importance and has to be taken into account when considering the nutritional status of older persons. Especially since it is shown that only 23% of the older persons living in a nursing home is very satisfied with the served food (Donini et al. 2003). Furthermore, the way of eating may change if individuals move to a new environment. For example, in some nursing homes it is common to eat in groups and in other nursing homes individuals have to eat alone. All these factors may contribute to changes in food intake. Unfortunately, there has not been any study comparing dietary intake in older persons before and after moving to a new environment. Therefore, a direct relationship between this life event and changes in dietary intake remains to be determined.

3.2.5 Poverty

Important social factors that can influence nutritional intake in older persons are an inability to shop and/or cook and poverty. Of these, poverty is a common problem among older persons and it is known to be a risk factor for depression (Neri et al. 2011). Ramic and colleagues (2011) demonstrated that in participants who lived alone there were significantly more individuals in poverty and depression compared to the participants who were living with others. This suggests that poverty might be involved in depression and loneliness which both can lead to reduced food intake. Poverty can also lead to an inability to buy specific food products resulting in a lower variety in meals (Hays and Roberts 2006). As mentioned earlier, a reduction in dietary variety can have major consequences on food intake because lower variety decreases the amount of food eaten (Bhutto and Morley 2008). This reduction in food intake related to poverty might therefore be a risk factor for the development of anorexia of aging.

Most of the psychological and social problems observed in older individuals, are related (figure 2) and can be linked to important life events like becoming a widow/widower or changes in the living environment. Such life events can increase stress levels and it is known that stress can influence eating behavior by either increasing or decreasing dietary intake (Adam and Epel 2007). How stress changes eating behavior and whether it increases or decreases food intake is influenced by inter-individual and gender differences (Greeno and Wing 1994). At this moment it is still unknown which psychobiological mechanisms underlie these differences (Adam and Epel 2007). However, it is known that daily psychological stressors increase food intake and body weight while long-term stress tends to decrease

eating behavior in humans (Melhorn et al. 2010). Interestingly, recent research has revealed a relationship between the hypothalamic-pituitary-adrenal (HPA) axis and leptin, insulin and NPY although no effects of aging on this relationship have been determined yet (Adam and Epel 2007). Furthermore, cortisol is associated with inhibition of neurogenesis in the hippocampus which has been implicated in the development of depression, increased food avoidance and a reduced sucrose preference (Snyder et al. 2011). In addition to this effect of cortisol on the hippocampus, aging is accompanied by a functional decline of the hippocampus (Choi and Won 2011). These effects of aging and stress can be of significant importance in food regulation in older persons. Chronic stress in older persons may contribute to reduced dietary intake via the development of depression or reduced food preference which are both risk factors for the development of anorexia of aging.

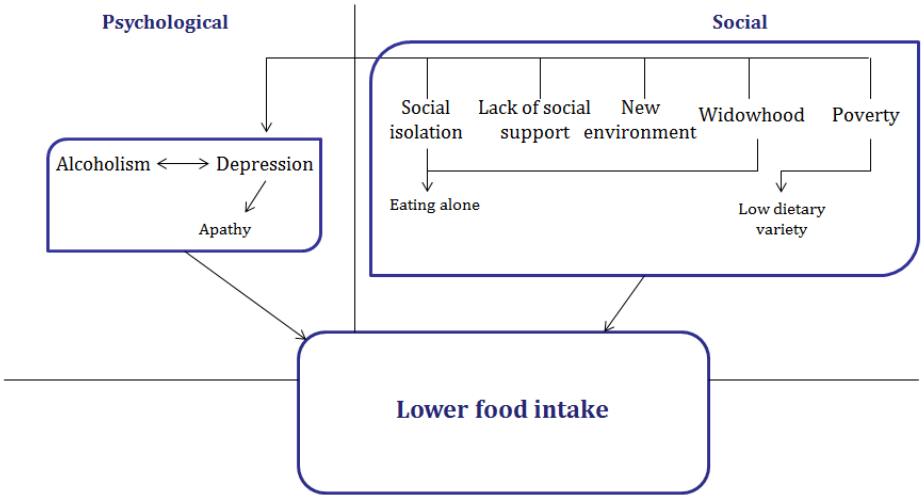

Figure 2 - Interactions between social and psychological factors influencing food intake in older persons

4. Conclusion

Anorexia of aging is a major problem among persons older than 65 years of age. It involves reduced food consumption which is followed by lowered body fat and body weight. This reduction in body fat and body weight is associated with several consequences, including premature death. The development of anorexia of aging is influenced by both physiological and non-physiological age-related changes. Although most research on this type of anorexia has focused on the physiological factors associated with food intake, the non-physiological factors mentioned in this review are, as shown, of significant importance. Therefore, we suggest to include non-physiological data in future research on anorexia of aging to elucidate the effects of depression, alcoholism, poverty, widowhood, environment changes, social isolation and loneliness, on dietary intake in older individuals. Furthermore, since reduced food intake is also observed in healthy older individuals, changes in physiological and non-physiological factors in this healthy population should be outlined in more detail. However, to

determine the exact mechanisms by which anorexia of aging develops, it is necessary to conduct more studies in which eating patterns of older persons who are suffering from anorexia of aging are compared to healthy controls. Also, a better understanding of the relationship between the physiological, psychological and social factors associated with food consumption should lead to a better knowledge about the development of anorexia of aging. Here, the context of food consumption, including for example neophobia and negative associations, should be outlined in more detail because these can be major factors influencing food intake. All the above mentioned suggestions for future research should lead to new insides in why some older individuals develop anorexia of aging, which can lead to earlier detection and better prevention.

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