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Peptides and aging: Their role in anorexia and memory

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ABSTRACT

The rapid aging of the world's population has led to a need to increase our understanding of the pathophysiology of the factors leading to frailty and cognitive decline. Peptides have been shown to be involved in the pathophysiology of frailty and cognitive decline. Weight loss is a major component of frailty. In this review, we demonstrate a central role for both peripheral peptides (e.g., cholecystokinin and ghrelin) and neuropeptides (e.g., dynorphin and alpha-MSH) in the pathophysiology of the anorexia of aging. Similarly, peripheral peptides (e.g., ghrelin, glucagon-like peptide 1, and cholecystokinin) are modulators of memory. A number of centrally acting neuropeptides have also been shown to modulate cognitive processes. Amyloid-beta peptide in physiological levels is a memory enhancer, while in high (pathological) levels, it plays a key role in the development of Alzheimer's disease.

The world's population is rapidly aging [1]. In 2012, 14% of the population of the USA is over 65 years of age and this is expected to rise to over 20% by 2030. At present, Japan has 23% of its population over 65 years of age and this is expected to grow to 32.2% by 2030. In 2030, 27.9% of the German population and 25.5% of the Italian population will be over 65 years of age. By 2050, over 25% of China's population will be over 65 years of age. This aging tsunami is requiring all of us to focus on the aging process and particularly on the factors that are involved in leading to the development of frailty [2]. The role of alterations in peptide function with aging has been underappreciated. Peptides play a key role in weight loss and memory disturbances that occur with aging. It is important to recognize that centrally acting neuropeptides have different effects, depending on where they are released neuroanatomically. This explains the different effects of peptides on memory and feeding within the central nervous system.

It is now well established that the anorexia of aging plays a key role in weight loss and the subsequent development of sarcopenia and frailty [3,4]. Peptides have been established to be major players in the physiological anorexia of aging [5,6]. Numerous peptides have been shown to play a role in the modulation of memory processing [7]. Of these, amyloid-beta peptide (AβP) is considered to play a key role in the pathogenesis of Alzheimer's disease [8–10].

The link between peripheral peptides that modulates both feeding and memory can be explained by the fact that feeding is key to species survival, so it is important for animals to remember what factors were successful or not successful during a foraging expedition. This review will highlight the role of peptides in the pathogenesis of the appetite and memory disturbances that occur with aging.

Peptides and the anorexia of aging

Weight loss in older persons is one of the major factors associated with frailty and mortality [11,12]. In 1988, Morley and Silver [13] postulated that there was a physiological anorexia of aging and that this placed older persons at increased risk of severe weight loss when they were exposed to the disease associated with aging. They further suggested that much of the anorexia of aging was due to changes in the peripheral and central peptide function that occurs during the aging process.

With aging, there is a reduction in the rate of gastric emptying, particularly in response to large meals [14]. In addition, there is a decrease in fundal compliance due to a decline in nitric oxide activity in the fundal wall [15]. These factors result in an increase in antral stretch, which, through ascending fibers in the vagus, sends increased satiety signals to the brain [16,17].

Cholecystokinin (CCK) is well established as playing a major role as a peripheral signal of satiation [18,19]. While CCK reduces feeding when given both peripherally and centrally, its major effect is due to stimulating the ascending fibers of the vagus nerve [20]. This is mediated through CCK-A receptors [18]. Central effects of CCK on

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food intake are mediated by both CCK-A and CCK-B receptors [21]. In old mice, CCK suppressed feeding to an extent greater than in young mice [22,23]. In older humans, circulating CCK levels and the response of CCK to a meal are greater than those in younger persons [24]. Frail older persons had an increased CCK peak compared with younger persons [25]. In addition, when CCK-8 was infused into older persons, the suppression of food intake was double that seen in younger individuals [26].

Ghrelin is produced by the fundus of the stomach, and its levels are increased during fasting. Ghrelin increases food intake and the release of growth hormone by activating nitric oxide synthesis [27]. In one study in rats, ghrelin infusion increased food intake and growth hormone equally in young and older animals [28], although in two others it was not as effective [29,30]. In a 24 h circadian rhythm study in humans, the active form of ghrelin, acyl-ghrelin, was found to be lower in older adults compared to younger persons [31]. In another study, the reduction in ghrelin with aging was associated with a fall in testosterone levels [32]. Active ghrelin levels decline less following a meal in older individuals than younger ones, suggesting a decreased response to ghrelin in older persons [33]. Ghrelin levels are higher in older persons with malnutrition [2]. Ghrelin agonists have been shown to increase food intake and growth hormone in older persons with cancer [34]. Overall, these studies support a role for ghrelin in the pathophysiology of the anorexia of aging. Anamorelin is an orally bioavailable drug that binds to the growth hormone secretagogue receptor in the hypothalamus. It mimics appetite and growth hormone secretory effects of ghrelin. Anamorelin has been shown to increase food intake in persons with cancer [35]. This suggests that it may be an excellent orexigenic drug in persons with the anorexia of aging [36].

While glucagon-like peptide 1 is suppressed in older persons with type 2 diabetes mellitus [37], it is not reduced in older persons [24]. Similarly, it would appear that there is no change in the effect of another anorectic hormone, amylin, with aging [38]. With aging, there is an increase in body fat and leptin levels [39]. In males, the decline in testosterone is associated with a greater increase in leptin levels [40]. Thus leptin may play a role in the greater decrease in food intake seen in older males compared to older females [41].

Multiple neuropeptides are involved in the central regulation of feeding. The kappa opioid peptide, dynorphin, is a potent enhancer of feeding [42]. Older rats have a decline in the opioid feeding drive [43]. However, in older humans, there were minimal differences in food intake in response to naloxone [44]. Cerebrospinal fluid levels of beta-endorphin were reduced in older persons with an idiopathic senile anorexia [45]. These decreased levels of beta-endorphin were reversed after 5 months of treatment with megestrol acetate.

Agouti-related peptide (AGRP) is co-secreted with neuropeptide Y (NPY) in the hypothalamus and stimulates food intake by inhibiting cAMP stimulation due to alpha-melanocyte-stimulating hormone. There is a decrease in AGRP mRNA with aging in the arcuate nucleus in rats [46]. The anorectic peptide cocaine-amphetamine-regulated transcript (CART) increased. AGRP had a more potent effect in increasing food intake in old compared with young rats after central administration. The aging effects on AGRP and CART appear to be related to the decline in testosterone with aging [47]. Intracerebroventricular infusion of alpha-MSH in older rats caused a marked decrease in food intake compared with 12-month-old rats [48,49]. Alpha-MSH also caused a decrease in muscle mass, suggesting a role in sarcopenia [50]. There is no evidence to support the role of neuropeptide Y (NPY), a potent regulator of feeding, in the aging effects on feeding [30,51]. Megestrol acetate, a corticosteroid/progestational/anabolic agent, increases food intake in older humans and in animals increases NPY [52]. Orexin-A is found in the lateral hypothalamus. In young and adult rats, it stimulates feeding, but was not effective in old rats [30].

As can be seen in Fig. 1, peptides play a major role in the peripheral and central regulation of the anorexia of aging. In males, the age-related decline in testosterone appears to play an important modulatory role in the physiological anorexia of aging [51,47]. Inflammatory cytokines (interleukin-1 and tumor necrosis factor-alpha) appear to play a central role as mediators of pathological anorexia and sarcopenia [53–55,6]. Depression is an important cause of disease-related anorexia in older persons [56,57]. Corticotrophin releasing factor (CRF) is an important mediator of anorexia [58], and it is increased in persons with depression [59,60].

Peptides as modulators of memory

With normal aging, there is a gradual decline in memory [61]. For some persons, this transitions to mild cognitive impairment (MCI) [62]. Over the age of 65 years, approximately 5% have dementia [63]. The most common cause of dementia is Alzheimer's disease, which is characterized by amyloid plaques and neurofibrillary tangles.

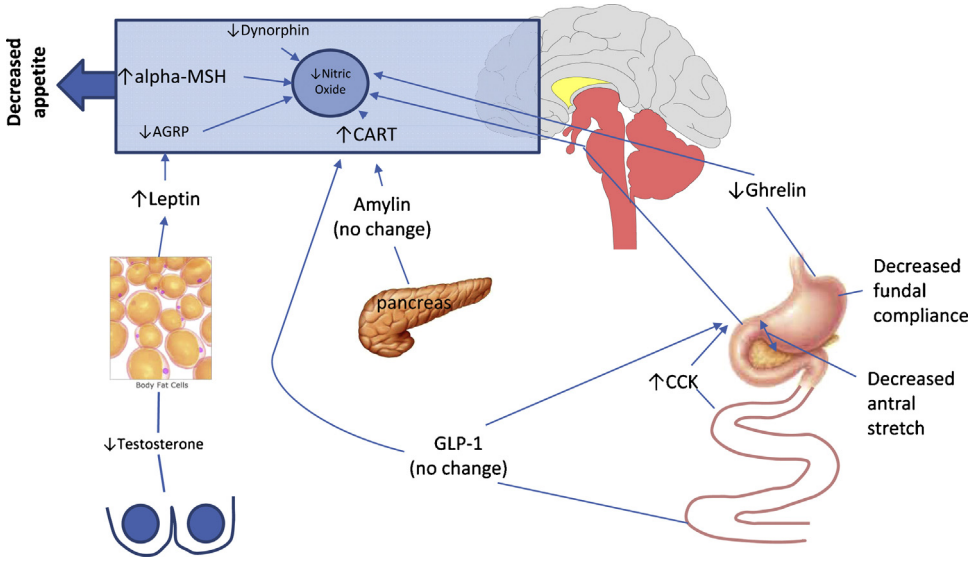

Fig. 1. Role of peptides in modulating the anorexia of aging. GLP-1, glucagon-related peptide-1; CCK, cholecystokinin; AGRP, agouti-related peptide; CART, cocaine amphetamine-regulated transcript.