Perspectives in Cancer Research

Cancer Anorexia-Cachexia Syndrome: Are Neuropeptides the Key?1

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Abstract

Progressive wasting is common in many types of cancer and is one of the most important factors leading to early death in cancer patients. Weight loss is a potent stimulus to food intake in normal humans and animals. The persistence of anorexia in cancer patients, therefore, implies a failure of this adaptive feeding response, although the weight loss in the patients differs from that found in simple starvation. Tremendous progress has been made in the last 5 years with regard to the regulation of feeding and body weight. It has been demonstrated that leptin, a hormone secreted by adipose tissue, is an integral component of the homeostatic loop of body weight regulation. Leptin acts to control food intake and energy expenditure via neuropeptidergic effector molecules within the hypothalamus. Complex interactions among the nervous, endocrine, and immune systems affect the loop and induce behavioral and metabolic responses. A number of cytokines, including tumor necrosis factor-α, interleukins 1 and 6, IFN-γ, leukemia inhibitory factor, and ciliary neurotrophic factor have been proposed as mediators of the cachectic process. Cytokines may play a pivotal role in long-term inhibition of feeding by mimicking the hypothalamic effect of excessive negative feedback signaling from leptin. This could be done by persistent stimulation of anorexigenic neuropeptides such as corticotropin-releasing factor, as well as by inhibition of the neuropeptide Y orexigenic network that consists of opioid peptides and galanin, in addition to the newly identified melanin-concentrating hormone, orexin, and agouti-related peptide. Information is being gathered, although it is still insufficient, on such abnormalities in the hypothalamic neuropeptide circuitry in tumor-bearing animals that coincide with the development of anorexia and cachexia. Characterization of the feeding-associated gene products have revealed new biochemical pathways and molecular targets for pharmacological intervention that will likely lead to new treatments. Although therapeutic intervention using neuropeptide agonists/antagonists is now directed at obesity treatment, it may also have an effect on treating cancer anorexia-cachexia, especially when combined with other agents that have effects on muscle and protein breakdown.

Introduction

Cachexia is a debilitating state of involuntary weight loss complicating malignant, infectious, and inflammatory diseases and contributing significantly to mortality. Anorexia, also a frequent complication of these diseases, is a major contributor to the development of cachexia, although the pattern of weight loss in cachexia differs from that seen with pure nutrient deprivation (1).

The word “cachexia” is derived from the Greek “kakos” meaning “bad” and “hexis” meaning “condition” (1). About half of all cancer patients show a syndrome of cachexia, characterized by anorexia and loss of adipose tissue and skeletal muscle mass. In general, patients with solid tumors have a higher frequency of cachexia (2). At the moment of diagnosis, ~80% of patients with upper gastrointestinal cancers and 60% of patients with lung cancer have had substantial weight loss (2). Cachexia is more common in children and elderly patients and becomes more pronounced as disease progresses (2).

The anorexia-cachexia syndrome is a complex interplay of metabolic and behavioral variables that is correlated with poor outcomes and compromised quality of life (1–3). Although the etiology of cachexia is not well defined, several hypotheses have been explored including cytokines, circulating hormones, neuropeptides, neurotransmitters, and tumor-derived factors (4–6). An emerging view is that the anorexia-cachexia syndrome is caused predominantly by cytokines either produced by cancer or released by the immune system as a response to the presence of the cancer, as well as other tumor products that induce profound lipolysis or protein degradation (1, 7).

The application of molecular and genetic techniques to the study of body weight regulation have produced exciting new insights into the physiological systems governing appetite, energy expenditure, and metabolic signaling (8–11). Recent studies led to the hypothesis that body weight is regulated by a feedback loop in which peripheral signals report nutritional information to an integratory center in the hypothalamus of the brain, and neuropeptides are essential effector molecules within the hypothalamus (8–11). In this report, I review data that point to the hypothesis that dysregulation of the neuropeptidergic circuitry controlling food intake and energy expenditure, and thus energy homeostasis, is playing a major role in the cancer anorexia-cachexia syndrome.

Leptin and Body Weight Regulation

The concept that appetite-restraining signal(s) from adipocytes are integral components of the feedback loop between the periphery and the brain for energy homeostasis gained firm ground with the cloning of the ob1 gene and its encoded protein, leptin, from adipocytes (10–13). Leptin is an afferent signal from the periphery to the brain that regulates adipose tissue mass (10, 13, 14). The level of leptin is positively correlated with body fat mass, and dynamic changes in plasma leptin concentrations in either direction activate the efferent energy regulation pathways (10, 11). Leptin reduces appetite and increases energy expenditure and evidently elicits these effects via the central nervous system (10, 11). In the absence of leptin, such as in ob/ob mice, animals fail to restrain their food intake and become massively obese.

Leptin acts via the leptin receptors with alternatively spliced forms (10, 15). The short forms may function in the transport of leptin across the BBB. The long (transmembrane) form of the receptor is expressed massively ob/ob mice, animals fail to restrain their food intake and become massively obese.

3 The abbreviations used are: ob, obese; BBB, blood-brain barrier; ARC, arcuate nucleus of the hypothalamus; DMH, dorsomedial nucleus of the hypothalamus; POMC, pro-opiomelanocortin; NPY, neuropeptide Y; MCH, melanin-concentrating hormone; AGRP, agouti-related peptide; CTR, corticotropin-releasing factor; GLP-1, glucagon-like peptide 1 7-36 amide; CART, cocaine- and amphetamine-related transcript; UCP, uncoupling protein; TNF, tumor necrosis factor; IL, interleukin; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic factor; CCK, cholecystokinin; MC, melanocortin; MSH, melanocyte-stimulating hormone.
energy homeostasis (16). The association of mutations in leptin and its receptor with massive obesity are observed in both rodents and humans (17–19).

Neuropeptidergic Cascade Downstream of Leptin Signaling

Fig. 1 shows a simplified model for the interaction of leptin with hypothalamic neuropeptidergic effector molecules within a regulatory feedback loop. The model emphasizes the feeding-drive systems that would underlie the hypothalamic response to starvation. NPY is the most potent orexigenic (feeding-stimulatory) peptide activated by the fall of leptin and consists of an interconnected orexigenic network that includes galanin, opioid peptides, MCH, orexin, and AGRP (8, 9, 11, 20–23). Most of these peptides are up-regulated in ob/ob mice, and their expressions are increased through fasting in wild-type mice and are inhibited by leptin administration (11). Other effector molecules functioning in this homeostatic loop are the anorexigenic neuropeptides such as CRF, melanocortin, GLP-1, neuropeptide, and CART, expression of which is down-regulated in ob/ob mice and stimulated by leptin (6, 8, 9, 11). The administration of the receptor antagonists of these peptides effectively blocks the reduction of food intake and body weight by leptin (11). The orexigenic and anorexigenic neuropeptides decrease and increase sympathetic nervous activity, respectively, which regulates energy expenditure by activating thermogenesis in brown adipose tissue and possibly in other sites such as white adipose tissue and muscle, through induction of the mitochondrial uncoupling protein UCP-1 and the newly identified UCP-2 and UCP-3 (24–27). Thus, if a disease process were to produce factors that induce or mimic the hypothalamic effect of excess negative feedback signaling from leptin, the expected outcome would be sustained anorexia and weight loss that is not accompanied by the usual compensatory response.

Cytokine Actions within the Regulatory Feedback Loop and Cancer Anorexia-Cachexia

Numerous cytokines, including TNF-α, IL-1, IL-6, and IFN-γ have been postulated to play a role in the etiology of cancer anorexia-cachexia syndrome (Refs. 1, 4, 5, and 28–30; Fig. 1). Cytokines are protein molecules released by lymphocytes and/or monocyte macrophages. They may be released into the circulation and transported to the brain through the BBB and circumventricular organs (leaky areas in the BBB), as is the case for IL-6 (29–34). Peripheral cytokines may influence the brain via neural pathways or second messengers such as NO and prostanoids. Vagotomy was reported to attenuate the acquisition of and facilitate the extinction of conditioned taste aversion induced by i.p. IL-1β or TNF-α administration (35). Cytokines are also produced by neurons and glial cells within the brain, partly in response to peripheral cytokines (29–34). Although the site of synthesis of cytokines within the brain is dependent on the nature of the stimulus, systemic disease seems to predominantly influence the expression in the hypothalamus, the area with highest densities of receptors for most cytokines being observed (33).

High serum levels of TNF-α, IL-6, and IL-1 have been found in some, but not all, cancer patients, and the levels of these cytokines seem to correlate with the progression of some tumors (36–38).
Chronic administration of these cytokines, either alone or in combination, is capable of reducing food intake and reproducing the different features of the cancer anorexia-cachexia syndrome (1, 36–39). The problem with ascribing specific tissue responses to individual cytokines is that considerable overlap and redundancy exists in the cytokine network (28, 31–34). Administration of either TNF-α or IL-1 will induce the synthesis of a variety of other proinflammatory cytokines such as IL-6. Thus, studies that use pharmacological administration of recombinant cytokines may not discriminate between biological responses induced directly by administered cytokine and those induced secondarily by other cytokines stimulated. Systemic disease such as cancer and inflammation may elicit a cytokine cascade in which several cytokines are induced simultaneously (28). More direct evidence of cytokine involvement comes from the experiments in which specific neutralization of cytokines can relieve anorexia and cachexia in experimental animal models (1, 37, 38, 40). Examples are the anti-TNF-α, anti-IL-6, anti-IL-1, and anti-IFN-γ antibodies, although no single antibody has been proven to reverse all of the features of wasting seen in cancer cachexia (37). These studies revealed that cachexia can rarely be attributed to any one cytokine but rather is associated with a set of cytokines and other cachectic factors that work in concert.

**Leptin**

The crystal structure of leptin indicates that it is a member of the helical cytokine family (41), which includes the IL-6 family of IL-6, IL-11, LIF, and CNTF. Most of these cytokines are able to cause body weight loss and/or anorexia (42). It was demonstrated that weight loss-inducing cytokines such as TNF-α, IL-1 and LIF increase the expression of mRNA for leptin in adipose tissue and plasma levels of leptin, despite the decrease in food intake that would normally suppress leptin expression (43–45). The increased leptin could thus contribute to anorexia by preventing the normal compensatory mechanisms in the face of decreased food intake. However, these cytokines have also been shown to cause anorexia even in the absence of leptin (46, 47), and failure to see elevated leptin levels was reported in tumor-bearing rats (48) and in patients with cancer cachexia (49–51).

CNTF is a pluripotent neurocytokine expressed by Schwann cells in peripheral nerves and glial cells in the brain. CNTF was reported to have more profound and longer lasting anorectic effects than other cytokines and to reduce leptin gene expression (52, 53). Cytokines may elicit effects on energy homeostasis that mimic leptin in some regards, and the increased hypothalamic actions may contribute to anorexia and body weight loss. This appears to be a likely explanation because leptin receptor is homologous to the gp130 signal-transducing molecule associated with the IL-6-type cytokine receptor and shares the same postreceptor signaling pathway via activation of the signal transducers and activators of the transcription family (54). Previous studies demonstrated that leptin activates the Stat3 protein in the hypothalamus of normal mice but not in db/db mice that have a defect in the long form of leptin receptor (55). This action was shared by cytokines of the gp130 family (54), as well as endotoxin LPS, which causes anorexia and induces cytokines including IL-6 family members. Therefore, if Stat3 protein is essential for leptin-induced anorexia, the cytokines that share with leptin the same postreceptor signaling pathway could likewise induce anorexia and unopposed weight loss.

**NPY**

NPY, a 36-amino acid peptide, is one of the most abundant and widely distributed neurotransmitters in the mammalian brain (20, 21, 56–59). The ARC is the major site of expression for NPY within neurons in the hypothalamus that project to PVN, DMH, LHA, and other hypothalamic sites. Although NPY has been demonstrated to produce diverse effects on behavior and other functions, its most noticeable effect is the stimulation of feeding after central administration (20, 21, 57–59). The feeding-stimulatory effect of NPY is robust and ~500 times more potent on a molar basis than norepinephrine, an amineergic neurotransmitter (58). Multiple injections of NPY into the PVN or cerebral ventricle result in obesity, indicating that NPY is capable of overriding powerful inhibitory signals on food intake and body adiposity (60, 61). NPY produces a shift to positive energy balance by increasing food intake, by decreasing energy expenditure primarily with a reduction in thermogenesis in brown adipose tissue (62), and by facilitating fat deposition in white adipose tissue partly through increased insulin activity (63).

NPY synthesis in the ARC and its release into the PVN, the most abundant projection, are regulated by afferent signals such as leptin, insulin (both inhibitory), and glucocorticoids (stimulatory; Refs. 14, 20, 21, 58, 59, and 61). NPY synthesis and secretion are all up-regulated in models of energy deficiency or increased metabolic demand such as starvation, insulin-dependent diabetes mellitus, lactation, and physical exercise (20, 21, 59, 61, 64). The primary physiological role of the ARC NPY neurons may thus be to restore normal energy balance and body fat stores under conditions of energy deficit, the signals of which are falling leptin and/or insulin occurring in these conditions. The exact position of NPY in the hierarchy of neuropeptide signaling cascade, however, remains to be determined, and the relatively normal food intake and body weight of NPY-knockout mice suggest that other systems cooperate to control energy homeostasis under various circumstances (65, 66).

Previous studies demonstrated that NPY feeding systems are dysfunctional in anorectic tumor-bearing rats. NPY injected intrahypothalamically stimulated feeding less potently in rats bearing methylcholanthrene-induced sarcoma than in controls, which was observed prior to the onset of anorexia and became more severe as the rats developed anorexia (67). The reduced affinity of hypothalamic NPY receptors as well as refractory adenylate cyclase in response to NPY suggests that the postsynaptic NPY-signaling systems are altered in the hypothalamus of tumor-bearing rats (68, 69). The level or release of NPY in the PVN or the hypothalamus is also reduced in tumor-bearing rats, whereas it is increased in fasting animals and in nutritional controls that have their food restricted to match their body weight. 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seen in tumor-bearing rats such as hyperammonemia may also reduce
NPY-induced feeding and hypothalamic NPY concentrations (68, 81).
However, no change or even increase in NPY mRNA levels were
reported in the hypothalamus of tumor-bearing rats (49, 82), suggest-
ing the involvement of other orexigenic and/or anorexigenic signals in
the anorexia and cachexia.

MCH and Orexin

MCH is a cyclic 19-amino acid peptide originally isolated from
salmon pituitaries that is expressed in the mammalian brain, specifi-
cally the lateral hypothalamus and the zona incerta (8–11, 83, 84).
The expression of this peptide was found to be increased in ob/ob
mice and also in fasting wild-type mice (22). Intracerebroventricular
administration of MCH produced a dose-dependent stimulation of
food intake in rats (22, 83). MCH-deficient mice have recently been
generated that have reduced body weight and leanness due to reduced
feeding and an inappropriately increased metabolic rate (85). Another
family of neuropeptides in the LH was recently identified simulta-
neously and independently by two groups of investigators, who named
them orexins (23) or hypocretins (86). Orexins stimulate feeding when
injected intracerebroventicularly, and the expression of orexin
mRNA is increased by food deprivation (85). Immunohistochemical
studies demonstrate projections from NPY neurons in the ARC to
MCH and orexin cells in the LH, suggesting that the latter two
peptides may function as downstream effector molecules of NPY in
the appetite-regulating pathways (87, 88). Although alterations in the
NPY system may affect MCH and orexins in the LH, it is not yet
known whether these newly identified peptides are involved in the
anorexia and cachexia of cancer.

Galanin and Opioid Peptides

Other peptides that are known to consist of an interconnected
orexigenic network with NPY are galanin and the opioids, β-endor-
phin and dynorphin (89). Galanin is a 29–30 amino acid peptide that
is widely distributed in the brain, including the PVN of the hypothal-
amus (90–92). Central administration of galanin increases food intake
in rats, and reduction of central galanin levels by antisense oligonu-
cleotide or central administration of galanin receptor antagonist de-
creases food intake. Although the NPY system is closely associated
with carbohydrate ingestion and carbohydrate utilization, channeling
nutrients toward the synthesis of fat, galanin appears to act preferen-
tially in the ingestion of fat and may enhance fat deposition through
a reduction in energy expenditure (90). A high fat diet can enhance
galanin production in the PVN, which was closely linked to body
adiposity (92).

Opioid peptides are also involved in the regulation of food intake,
although the increase in feeding after the administration of opioids or
opiates is not only short lasting in its effect but generally is mild
relative to the increase in feeding after NPY or galanin administration
(89, 93). Opioids may alter taste and nutrient selection, eliciting a
preference for high-fat diets. Opioid receptor antagonists decrease
feeding induced by fasting, as well as by galanin or NPY administra-
tion (89, 93, 94). The intimate connectivities among β-endorphin,
galanin, and NPY were indicated by the immunohistochemical obser-
vation of synaptic contact among a population of these peptide-
producing neurons in the hypothalamus (89).

It was reported that by using naloxone, a nonsel ective opioid
receptor antagonist, IL-1α and IL-1β are able to stimulate the activity
of the hypothalamic endogenous opioid peptide system to inhibit
luteinizing hormone-releasing hormone secretion (95). However,
a nocturnal depletion of hypothalamic dynorphin was reported in an-
orexic Walker-256 carcinosarcoma rats that coincides with the phase
of tumor-induced anorexia (96). This suggests that dynorphin, an
dogenous kappa opioid receptor agonist, may be involved in the
reduction of food intake, although the sensitivity or binding capacity
of kappa opioid receptors does not appear to be altered in tumor-
bearing rats (96). Physiological anorexia of aging was reported to be
due, in part, to a decreased opioid (dyncorphin) feeding drive (97).
However, it is not apparent how opioid systems are involved in the
development of cancer anorexia and cachexia. This is also the case for
galanin, despite the fact that gonadal steroids show excitatory effects
on galanin expression in the PVN (90), and postgestrational drugs may
stimulate appetite and body weight gain in cancer patients (98).

Glucagon and Glucagon-like Peptide I

A single proglucagon gene in mammals gives rise to an identical
proglucagon RNA transcript that is translated and processed differen-
tially in the brain, pancreatic islets, and intestine. Glucagon pro-
duced in the pancreas and GLP-I in the intestine and brain are potent
anorexigenic peptides (99, 100). A large body of evidence indicates
that the peripheral administration of glucagon produces satiety and
reduces food intake in experimental animals and in humans, and
afferent fibers of the hepatic vagus are the key element supporting this
behavioral effect (99). The administration of a highly specific anti-
glucagon antibody increases food intake in rats, suggesting a physi-
ological role of glucagon in controlling food intake. GLP-I was shown
recently to elicit a potent suppression of food intake and to reduce
body weight after intracerebroventricular administration (100). GLP-
I-producing neurons are located in the brain, primarily in the nucleus
of the solitary tract. Administration of exendin 9–39, a specific GLP-I
receptor antagonist, increases food intake in several animal models,
suggesting also that endogenous GLP-I in the brain is an inhibitor of
feeding (100).

The tumor-bearing state is associated with a decrease in the host
insulin:glucagon ratio. Hyperglucagonemia in the tumor-bearing state
may be the most important hormonal alteration causing abnormal
carbohydrate metabolism in cancer anorexia (101–104). Increased
glucagon levels can lead to anorexia, as well as increased hepatic
 gluconeogenesis and utilization of gluconeogenic amino acids at the
expense of protein synthesis, leading to a negative energy balance.
Inhibiting glucagon secretion may increase carcass weight, preserve
muscle protein, and even inhibit tumor growth (103, 104). Cytokines
such as IL-6 stimulate glucagon secretion in humans (105). Recently,
transplantable rat glucagonoma has been isolated, which shows
highly increased circulating levels of glucagon and GLP-I, and is
associated with severe anorexia, adipsia, and weight loss (49). A
highly significant increase in hypothalamic NPY mRNA levels was
found in the anorectic rats. It thus appears that the glucagonoma
releases circulating factor(s) that override the hyperphagic action of
NPY. Given that the satiety effect of glucagon is vagally mediated
(99), the lack of effects of vagotomy in this model may exclude
glucagon as a causative agent. GLP-I is a likely candidate for the
anorectic effects of the tumor because GLP-I can promote satiety and
reduce food intake after continuous peripheral administration (106)
and because GLP-I can inhibit NPY-induced feeding in the brain
(100). The glucagonoma syndrome in humans is also characterized by
elevated levels of circulating proglucagon-derived peptides and is
frequently associated with weight loss beyond what would be ex-
pected for a relatively small tumor (107).

CCK

Of several putative satiety signals, the small-intestinal hormone
CCK has received the most attention (99). Systematic administration
of CCK reduces short-term food intake in many animal species and in
CCK delays the rate of gastric emptying, which may contribute to reduced food intake. Evidence for the importance of endogenous CCK for normal termination of feeding has come from studies in which administration of highly potent and selective CCK antagonists increased food intake or hunger sensations in animals and humans. The CCK-evoked satiety signals are carried by vagal afferent fibers and subsequently processed to the nucleus tractus solitarius and PVN of the hypothalamus, although further work is required to identify the brain sites and brain pathways involved (99, 109). CCK is also localized within the brain, with particularly high concentrations being found in the hypothalamus and cerebral cortex (109). CCK administered into the cerebral ventricle or PVN reduced feeding, whereas CCK antagonists reliably increased feeding (108, 110, 111). The release of endogenous CCK octapeptide (CCK-8), a predominant molecular form in the brain, at hypothalamic sites has been demonstrated after intra gastric administration of nutrients in animals (112, 113).

The initial studies demonstrated that plasma concentrations of immunoreactive CCK were not significantly altered in either Walker-256 carcinosarcoma or the methylocholanthrene-induced sarcoma animal model of cancer anorexia (114). Furthermore, levels of immunoreactive CCK were significantly reduced in the hypothalamus and cerebral cortex of animals bearing the methylocholanthrene sarcoma during mild and severe anorexia (114). However, the RIA used at that time, unfortunately, did not recognize active CCK-8, leaving the possibility of CCK involvement in producing anorexia and cachexia. It was demonstrated that the repeated (but not single) administration of CCK-8 facilitates anorexia and body weight loss in Walker-256 carcinosarcoma rats compared with controls (115, 116). This was particularly evident during the early stages of tumor growth and without the development of behavioral tolerance (116). CCK mediates, at least in part, IL-1β-induced anorexia and gastric stasis (117). Injection of IL-1β increased plasma CCK levels including CCK-8 and decreased food intake and emptying of gastric contents. Pretreatment with CCK-A (peripheral type) receptor antagonist partially blocked the decrease in food intake and gastric emptying rate by IL-1β (117). Because CCK rapidly mobilizes leptin from the stomach (118) and interacts synergistically with leptin (119), increases in the release and/or sensitivity to either factor might play a role in inducing anorexia. Peripherally administered CCK was reported to decrease NPY-induced food intake and hypothalamic NPY levels (59).

Melanocortin and AGRP

The agouti mouse is similar to ob/ob, a monogenic model of obesity that has an increased propensity to develop tumors (120). The gene defect in this mouse model was found to involve a 133-amino acid peptide that competes with MCs such as α-MSH for binding to their receptors (121). Agouti antagonized several members of MC receptors, including the MC-1 receptor in the hair follicle (expressing the yellow coat color) and the MC-4 receptor in the brain when expressed ectopically (developing obesity; Refs. 8–11). α-MSH, produced from proopiomelanocortin precursors, decreases feeding after central administration, whereas MC-4 receptor antagonist increases feeding (8–11, 122). Inactivation of the MC-4 receptor by gene targeting produces a syndrome of obesity similar to that of the agouti mouse (123). Both the yellow mice and MC-4 receptor knockout mice have increased NPY levels in the DMH of the hypothalamus (124). Recently, AGRP was discovered as a homologue of agouti, which is downstream of leptin (125). AGRP acts as an antagonist of the MC-4 receptor and is expressed in the ARC of the hypothalamus in close association with NPY (126). The ectopic expression of AGRP in transgenic mice produces obesity closely resembling that of the MC-4 receptor knockout mice (125). The output from the feeding inhibitory MC-4 receptor may thus be determined by the ratio of agonist (MSH) and antagonist (AGRP) at MC-4 receptor neurons in the DMH and PVN of the hypothalamus (8, 127).

The MC-4 receptor may regulate the response to inflammatory cytokines (127). Intracerebroventricular administration of α-MSH has strong anti-inflammatory and antipyretic effects (127, 128). α-MSH is the most potent endogenous antipyretic hormone and inhibits fever induced by IL-1, IL-6, or TNF-α (128). COOH-terminal tripeptide of α-MSH antagonizes IL-1-induced anorexia (129). Anticytokine effects of α-MSH are not specific to a certain cytokine but rather they include antagonism of all proinflammatory cytokines (128). The MC system is thus involved in the central regulation of the immune response, but the role of this system in causing the cachexia seen in cancer patients has not been examined.

Corticotropin-releasing Factor and Urocortin

CRF, a 41-amino acid peptide, is one of the key mediators involved in stress-related endocrine, immune, visceral, and behavioral responses (130–132). The CRF peptide family consists of CRF itself, fish urotensin, frog sauviagin, and the recently characterized mammalian urocortin (133). Considerable evidence suggests a role for CRF systems in appetite regulation and energy balance (9–11, 132). Administration of CRF into the cerebral ventricle or the PVN of the hypothalamus, its primary site of biosynthesis, decreases food intake and increases sympathetic nervous activity, leading to increased thermogenesis, lipolysis, and blood glucose levels (132). Chronic administration of CRF causes sustained anorexia and progressive weight loss. Recently, CRF₁ and CRF₂ receptors have been cloned and characterized (130). The selective expression of CRF₂ receptor mRNA in the ventromedial nucleus and PVN of the hypothalamus suggests that CRF₂ receptor is involved in the regulation of food intake and energy expenditure (134). Urocortin is a potent activator of CRF₂ receptor, and central administration of urocortin produces appetite-suppressing effects more potent than CRF, with very low anxiogenic and aversive effects (133).

A well-studied endocrine effect of cytokine is activation of the hypothalamic-pituitary-adrenal axis, an action proposed to participate in the negative feedback control of the immune response (Fig. 1). Because glucocorticoids inhibit cytokine production, the ability of many cytokines such as IL-1, IL-2, IL-6, TNF-α, and IFN-γ to stimulate hypothalamic CRF expression and/or release may be an important mechanism for limiting cytokine production (4, 132). However, it could induce anorexia and weight loss if a sustained increase in one or more of these cytokines occurring in the brain or periphery caused persistent stimulation of CRF activity in the PVN. CRF blunts the adaptive hypothalamic response to weight loss through an inhibition of the NPY system (11, 131, 132). It was reported that stimulation of CRF by IL-1β is paralleled by a potent and sustained suppression of food intake (135) that can be elicited by intracerebroventricular administration at doses below those required to induce central effects such as fever (14). The immune neutralization of endogenous CRF by CRF antiserum inhibits IL-1-induced anorexia (136) as well as adrenocorticotropic hormone release, providing evidence for a role of hypothalamic CRF in the response. Rats bearing the Yoshida sarcoma displayed anorexia that was associated with increased rectal temperature (and thus energy expenditure; Ref. 71). Although food-restricted control rats showed a decrease in CRF levels in the PVN and ARC of the hypothalamus, the tumor-bearing rats had elevated CRF and reduced NPY levels in the PVN, suggesting increased CRF signaling during weight loss (71).

Substantial evidence shows that brain CRF plays a role in the
alterations of gastrointestinal motor function induced by stress (137). Recently, it was demonstrated that CRF₂ receptor is primarily involved in CRF-induced, long-lasting inhibition of gastric emptying of the meal (138). Gastric emptying plays an important role in regulating food intake, and a reduced rate of gastric emptying contributes to the inhibition of feeding (139). IL-1β inhibits gastric emptying that was antagonized by the central administration of CRF receptor antagonist (140). It is likely that CRF is responsible, at least in part, for the prolonged inhibition of gastric motor function seen in cancer, which also leads to anorexia and cachexia. The role of endogenous urocortin in stress responses is presently unclear, but investigation of the effects of CRF antagonists or antisera may not distinguish between a CRF or urocortin action (130).

Concluding Remarks

In recent years, cachexia has been understood as the result of major metabolic abnormalities due to a combination of host cytokine release and tumor products rather than as a simple increase in energy consumption by the tumor and starvation by the patient (98). Hyperalimentation was thus unable to counteract wasting. Effective reversal of cachexia appears to require pharmacological intervention, which in turn requires knowledge of the mediators and the processes.

Since the discovery of leptin in 1994 (12), there has been an explosion of information about the role of various genes and gene products, including neuropeptides, in the regulation of body weight (8–11, 46). Although much of this knowledge has come from studies of obesity, there appear to be implications for clinical conditions associated with weight loss (132). Various cytokines are proposed to play a pivotal role in long-term feeding inhibition and wasting, including IL-1β, IL-6, its subfamily members CNTF and LIF, IFN-γ, and TNF-α (141). These cytokines affect the homeostatic loop of body weight regulation by mimicking leptin in some regards, and one of the key targets is neuropeptidergic effector molecules within the hypothalamus that regulate food intake and energy expenditure via the sympathetic nervous system.

The arcuate NPY neurons are in a strategic position to monitor the metabolic state of the animal and are activated normally in states of negative energy balance (11, 87, 132). NPY is a component of hypothalamic circuitry integrating aspects of feeding behavior and energy homeostasis. The NPY orexigenic network is composed of signals such as opioids and galanin, as well as the newly identified MCH, orexin, and AGRP. In cancer subjects, this compensatory response to weight loss is inhibited because of dysregulation of hypothalamic neuropeptidergic circuitry, as demonstrated by decreased orexigenic (e.g., NPY) and/or excess anorexigenic (e.g., CRF) signaling in tumor-bearing animals (Fig. 1). Because cancer cachexia is associated with a disproportionate loss of lean mass, it is likely that both the central and peripheral metabolic responses to weight loss are abnormal. It has recently been shown that cytokines increase UCP-2 mRNA levels, suggesting that activation of UCP in white adipose tissue and/or muscle might be a molecular mechanism underlying the increase in heat production and wasting (46).

Research into the regulation of body weight is so rapid that new peptides will almost certainly be identified soon that might play an important role and be a potential therapeutic target. CART is another hypothalamic peptide that exerts an inhibitory tone on feeding and has functional interactions with NPY (142, 143). Limited success to ameliorate cancer-related metabolic changes such as glucose metabolism and weight loss was reported in pharmacological insulin supplementation in cancer patients and tumor-bearing animals (144–148). However, this effect of insulin is based on its potent anabolic effect in peripheral tissues, apart from its effect in the brain as an adiposity signal where insulin promotes a state of negative energy balance (14). It is recognized that megestrol acetate, a synthetic progestosterone derivative, enhances appetite and causes body weight gain in a number of cachectic patients via stimulation of NPY and other mechanisms (98, 149). There is a large effort to develop the agonists and/or antagonists of neuropeptide receptors that have been specifically associated with food intake and energy expenditure (150), including NPY Y₁ and Y₂ receptors (21), opioid receptor, MC₄ receptor, CRF₂ receptor, CCK-A receptor, and GLP-I receptor, some of which are presently being evaluated in clinical trials. The augmentation of the NPY orexigenic network is apparently one of the key potential targets for the treatment of cancer cachexia. In this report, attention has been focused on neuropeptide and cytokine interactions within the regulatory feedback loop of body weight regulation. It is important, however, to keep in mind other hormones, neurotransmitters, enzymes, and substances that are likely to be involved in the cachectic process, notably lipid- and protein-mobilizing factors that can directly mobilize fatty acids and amino acids from adipose tissue and skeletal muscle, respectively (1, 7, 151–154). This is likely a unique feature of tumor-bearing hosts, as might be the case for an involvement of the brain serotonergic system in the development of cancer anorexia-cachexia (Refs. 59, 155, and 156; Fig. 1).

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References


35. Goehler, L. E., Busch, C. R., Tagartia, N., Relton, J., Sisk, D., Maier, S. F., and Watkins, L. R. Blockade of cytokine induced conditioned taste aversion by subd- 


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