Neural control of the anorexia-cachexia syndrome

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THE ANOREXIA-CACHEXIA SYNDROME is a debilitating condition characterizing the clinical journey of patients suffering from chronic diseases including cancer, chronic obstructive pulmonary disease, tuberculosis, chronic heart failure, and end-stage renal insufficiency (64). As an experimental model, it represents a reliable and unique tool for the investigation of the mechanisms regulating energy intake and homeostasis. Beyond its relevance to human physiology, this syndrome impacts on clinical practice since it is highly prevalent and negatively impacts on patients’ morbidity and quality of life, ultimately accelerating death. The pathogenesis is multifactorial and reflects the complexity and redundancy of the mechanisms controlling energy homeostasis under physiological conditions. Accumulating evidence indicates that, during disease, disturbances of the hypothalamic pathways controlling energy homeostasis occur, leading to profound metabolic changes in peripheral tissues. In particular, the hypothalamic melanocortin system does not respond appropriately to peripheral inputs, and its activity is diverted largely toward the promotion of catabolic stimuli (i.e., reduced energy intake, increased energy expenditure, possibly increased muscle proteolysis, and adipose tissue loss). Hypothalamic proinflammatory cytokines and serotonin, among other factors, are key in triggering hypothalamic resistance. These catabolic effects represent the central response to peripheral challenges (i.e., growing tumor, renal, cardiac failure, disrupted hepatic metabolism) that are likely sensed by the brain through the vagus nerve. Also, disease-induced changes in fatty acid oxidation within hypothalamic neurons may contribute to the dysfunction of the hypothalamic melanocortin system. Ultimately, sympathetic outflow mediates, at least in part, the metabolic changes in peripheral tissues. Other factors are likely involved in the pathogenesis of the anorexia-cachexia syndrome, and their role is currently being elucidated. However, available evidence shows that the constellation of symptoms should be considered, at least in part, as different phenotypes of common neurochemical/metabolic alterations in the presence of a chronic inflammatory state.

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repair injured tissues. Mobilization of lipids from adipose depots may likewise contribute to these processes and counteract the energy debt imposed by the disease. During chronic illness, however, the anorexia-cachexia syndrome becomes detrimental since it progressively depletes protein and energy stores, compromises organ and tissue function, and facilitates the development of complications, eventually accelerating death (46).

In the clinical setting, patients suffering from chronic diseases usually present with the anorexia-cachexia syndrome rather than solely anorexic or cachectic symptoms. In contrast with this clinical picture, the research into the pathogenic mechanisms has focused frequently on the neurochemical alterations or the metabolic derangements. Little attention has been devoted to the investigation of possible common pathways. This has prompted the assumption that anorexia and cachexia could be only incidentally diagnosed in the same patient. Accumulating evidence now challenges this approach by suggesting that anorexia and cachexia represent in part different phenotypes of common neurochemical/metabolic alterations. Indeed, body weight loss and poor nutritional status are reliable predictors of mortality in chronic diseases (66). Weight loss due to cachexia is not completely accounted for by the degree of anorexia and reduced food intake (46). Notwithstanding this, anorexia represents an independent negative prognostic factor (37), suggesting the existence of a common pathway linking anorexia and cachexia.

The Melanocortin System

Under physiological conditions, the homeostasis of food intake and body weight is controlled by complex and redundant mechanisms. Neural, metabolic, and humoral signals from peripheral tissues inform the brain whether energy stores are being repleted or depleted. The hypothalamus receives and integrates peripheral signals (18). Within the hypothalamus, the arcuate nucleus in rodents (i.e., the infundibular nucleus in humans), situated between the third ventricle and the median eminence, is considered to act as an important sensor of alterations in energy stores to control appetite and body weight. Involved in this role are two distinct subsets of arcuate neurons.

The first population of neurons express proopiomelanocortin (POMC). In rodents, the majority of POMC cells also coexpress the anorectic peptide CART (cocaine- and amphetamine-regulated transcript), whereas in humans CART is absent from the perikarya and axons of POMC neurons (64). POMC is an inert polypeptide precursor that is cleaved into smaller biologically active peptides, among them the melanocortins, i.e., α-, β-, and γ-melanocyte-stimulating hormone (MSH). The biological effects of melanocortins are mediated through a family of five melanocortin receptors termed MC1R–MC5R (67). These receptors show considerable homology, with all of them being seven-transmembrane domain G protein-coupled receptors. However, MC4R is a crucial molecular component of the homoeostatic circuit that regulates energy balance by mediating anorectic and catabolic responses (18). Interestingly, recent data show that the effects of the melanocortin system on food intake and energy expenditure are dissociated, being related to the activity of specific POMC neurons located in different hypothalamic areas (1).

The second subset of arcuate neurons expresses the potent orexigenic peptide neuropeptide Y (NPY) and agouti-related protein (AgRP). Interestingly, AgRP is the endogenous antagonist of MC4Rs, thereby antagonizing the anorexigenic effects of α-MSH. This evidence underlines the reciprocal functional relationship between the two subsets of arcuate neurons. The POMC/CART and NPY/AgRP neurons project to related hypothalamic nuclei, and these downstream second-order neurons expressing melanocortin receptors are included in the hypothalamic melanocortin system.

The melanocortin system plays a crucial role in the homoeostasis of energy metabolism. During the last few years, anatomical and functional evidence has accumulated and led to development of a widely accepted model of regulation of energy intake and body weight (18). In the presence of excess energy, POMC neurons are activated and trigger the release of melanocortins from POMC axon terminals, which activate MC4R, thereby leading to suppressed food intake and increased energy expenditure. Simultaneously, the activity of the arcuate AgRP/NPY system is suppressed, which would otherwise antagonize the effects of α-MSH on MC4R. In contrast, in times of energy depletion, the activity of anorexigenic POMC neurons is decreased but the activity of orexigenic NPY/AgRP neurons is increased.

The anorexia-cachexia syndrome is characterized by hypothalamic inappropriate response to normal homeostatic feedback. Under physiological conditions, low levels of the anorexigenic hormone leptin, which derives mainly from fat tissue, decrease the activity of POMC/CART neurons and elicit energy intake. Similarly, increased levels of the orexigenic hormone ghrelin increase energy intake by interacting with NPY/AgRP neurons (13). In the presence of the anorexia-cachexia syndrome, leptin levels are decreased (51), whereas ghrelin levels are normal or elevated (46). Nevertheless, energy intake is not increased as expected.

The hypothalamic inappropriate response to these peripheral signals appears to be mediated by the persistent activation of POMC/CART neurons. Consistent evidence indicates that
MC4Rs are key factors in mediating anorexia and body weight loss during wasting diseases. In experimental models of cancer, MC4R knockout mice, but not MC3R knockout animals, resist the loss of lean body mass without influencing tumor growth (59, 60). Similar results have been obtained in nephrectomized mice mimicking uremia-associated anorexia-cachexia (15), which suggests that the involvement of central melanocortin system is a common feature in wasting diseases. Further supporting this view, the blockade of MC4Rs achieved via central infusion of the endogenous MC4R antagonist AgRP (34) or via peripheral/oral administration of an MC4R antagonist (12, 16, 58, 87) or inverse agonist (72) ameliorates anorexia, prevents body weight loss and particularly muscle wasting, and improves basal metabolic rate, which is frequently found accelerated in wasting diseases. More recently, it has been shown that ghrelin administration in a model of chronic kidney disease reduces the activity of the enzyme cleaving POMC into α-MSH, with this effect being associated with improved energy intake and increased lean body mass (18b).

The mechanisms by which MC4R antagonism in models of chronic diseases exerts its metabolic effects are still a matter of investigation. Recent data suggest that the improvement of basal metabolic rate is mediated partly by the normalization of the expression of uncoupling proteins (16) that are involved in the increase of energy expenditure associated with chronic diseases. Much less is known about the mechanisms leading to preserved body weight and lean body mass. In particular, it is yet to be determined whether central melanocortin antagonism influences the activity of the peripheral ATP-dependent ubiquitin-proteasome system, the main proteolytic system involved in muscle wasting in animal models and human diseases (68). Nevertheless, based on the large amount of data available (12, 15, 16, 36, 58, 59, 60, 72, 87), the existence of a “brain-muscle axis,” in which the brain not only regulates energy intake but influences metabolic rate and the balance in muscles between anabolism and catabolism, is likely. The exact mechanisms of the interplay between central and peripheral pathways await better detailing; however, it appears to involve the balance between inhibitory and stimulatory factors of the regulation of muscle mass, as recently demonstrated in an animal model of uremic cachexia. In particular, Cheung et al. (17) demonstrated that the expression of myostatin, an important inhibitory factor of muscle mass accretion, is increased in the muscles of uremic rats. In contrast, the expression of insulin-like growth factor I, a factor promoting muscle accretion, is reduced. Interestingly, the injection of AgRP in the third ventricles of uremic rats partially corrected these uremia-induced changes, resulting in a gain of body mass.

Central infusion of AgRP in cachectic animals ameliorates anorexia and improves body composition (36). This suggests that decreased activity of NPY/AgRP neurons should parallel the hyperactivation of POMC/CART neurons during disease. Immunocytochemical studies in tumor-bearing rats with anorexia-cachexia show decreased NPY innervation of hypothalamic nuclei (52), which is reversed by tumor resection (53). Direct measurement of NPY concentrations in the hypothalamus of tumor-bearing rats with anorexia-cachexia reveals a significant decrease of this orexigenic peptide (63) despite the fact that increased mRNA levels for NPY have been also reported (11). Furthermore, mRNA levels and immunostaining of the NPY receptor, the Y1 receptor, are decreased in the hypothalamus of tumor-bearing rats (11), whereas tumor resection restores normal hypothalamic NPY levels (75).

In humans, data on hypothalamic NPY levels and activity during wasting diseases are lacking. However, significantly lower plasma levels of NPY have been measured in anorectic cancer patients compared with controls (34). Furthermore, animal studies show that megestrol acetate, an orexigenic drug used in the treatment of human anorexia-cachexia, increases hypothalamic NPY levels (61).

Based on the large and consistent amount of evidence, it appears that the anorexia-cachexia syndrome is related, at least in part, to dysfunction of the melanocortin system, consisting of hyperactivity of POMC/CART neurons and decreased activity of NPY/AgRP neurons, leading to hypothalamic resistance to peripheral inputs signaling energy depletion. Most importantly, the hypothalamus appears to mediate the onset of not only anorexia but of cachexia as well by influencing the balance in muscles between catabolism and anabolism.

Hypothalamic Serotonergic Activity and Its Interplay With Proinflammatory Cytokines

The mechanisms responsible for the dysfunction of the melanocortin system have been investigated in experimental studies, and results suggest the involvement of proinflammatory cytokines and hypothalamic serotonergic neurons. The role of proinflammatory cytokines, and particularly interleukin-1 (IL-1) and tumor necrosis factor-α (TNFα), in the pathogenesis of the anorexia-cachexia syndrome has been recognized for many years (33). In tumor-bearing rats with anorexia, hypothalamic IL-1 mRNA expression is significantly increased (74). Also, IL-1 levels in the cerebrospinal fluid of anorectic tumor-bearing rats are increased and inversely correlate with energy intake (73), whereas intrahypothalamic injection of the IL-1 receptor antagonist ameliorates anorexia in the same experimental model (43). The role of TNFα in mediating cancer-associated anorexia is supported by the evidence that intraperitoneal injection of recombinant human soluble TNF receptor improves anorexia in tumor-bearing animals (84). In humans, IL-1 appears to play a significant role in mediating anorexia-cachexia, since megestrol acetate has been shown to exert its effects via reduced expression of IL-1 by mononuclear cells (55) beyond its influence on hypothalamic NPY concentrations (61). Interestingly, POMC/CART neurons in the arcuate nucleus of hypothalamus express the type 1 IL-1 receptor, and intracerebroventricular injection of IL-1 increases the frequency of action potentials of POMC/CART neurons and stimulates the release of α-MSH (80). These data strongly suggest that IL-1 is involved in mediating the dysfunction of the melanocortin system by increasing the activity of POMC/CART neurons in the arcuate nucleus of hypothalamus.

Serotonin is a classical neurotransmitter that orchestrates diverse behavioral and physiological processes, including energy balance (82). Its role in mediating satiety through its effects in the hypothalamus is well established (62). This prompted studies on its influence in inducing anorexia-cachexia during catabolic states. In experimental tumor models, the onset of anorexia is associated with increased hypothalamic serotonin levels, as assessed by in vivo microdialysis (4), and
increased expression of serotonin receptors (5-HTRs) (53). Strengthening the link between serotonergic neurotransmission and disease-related anorexia, tumor resection has been demonstrated to restore energy intake, which is associated with normalized hypothalamic serotonin concentrations (4) and receptor expression (53). Furthermore, intrahypothalamic injection of the serotonin antagonist mianserin improves energy intake in anorectic tumor-bearing rats (43).

Serotonin is also a precursor in the synthesis of the hormone melatonin, produced by the pineal gland and modulating the activity of the hypothalamic suprachiasmatic nucleus, which regulates biological rhythms. Both melatonin synthesis (2) and secretion profile (19) have been shown to be changed in cachectic patients and animals. Disrupted melatonin synthesis could, therefore, contribute to increased serotonin accumulation in the hypothalamus.

In humans, the role of serotonin in disease-associated anorexia has been inferred by detecting increased plasma and cerebrospinal fluid levels of the precursor of serotonin, the amino acid tryptophan, in anorectic-cachectic cancer patients (8) and in patients with liver cirrhosis (42). Also, therapeutic strategy aimed at reducing brain supply of tryptophan has met with improved energy intake and nutritional status in cancer, uremic, and liver cirrhotic patients (45). The brain accumulation of tryptophan during disease may exert catabolic effects beyond its role as precursor of serotonin. Brain tryptophan is also involved in the synthesis of kynurenine and its derivatives, compounds with immune modulating effects (48). The most critical is the kynurenine pathway, because tryptophan is degraded mainly via this pathway, producing free radical generators (i.e., 3-hydroxykynurenine and 3-hydroxyanthranilic acid). The rate of tryptophan degradation via the kynurenine pathway is inflammation driven. Therefore, increased brain concentrations of tryptophan coupled with increased expression of proinflammatory cytokines could sustain tryptophan metabolism toward increased free radical generator production, leading to increased oxidative stress. It should be noted that in anorectic tumor-bearing rats, increased levels of markers of oxidative stress have been detected in hypothalamic areas involved in the regulation of energy metabolism (20).

Intriguingly, the anorectic effects of serotonin appear to be mediated by the melanocortin system. The administration of fenfluramine, a serotonin reuptake inhibitor, has been shown to activate central melanocortin pathways (27). More recently, new insights into the relationship between serotonin and the melanocortin system have been provided. Although at least 14 functionally different subtypes of 5-HTRs have been identified (29), studies have particularly focused on the 5-HT3R and 5-HT1bR. These two subtypes of receptor display a complementary distribution within the arcuate nucleus; 5-HT2cRs are expressed in anorexigenic POMC/CART neurons, whereas 5-HT1bRs are expressed in orexigenic NPY/AgRP neurons (28). The use of agonists at these receptors influenced the activity of both cell populations in a reciprocal manner, since they hyperpolarized NPY/AgRP neurons while suppressing inhibitory postsynaptic potentials in POMC/CART neurons (28).

It is likely that the interplay between serotonin and the melanocortin system is far more complex than is outlined in this review. Indeed, recent data show that subanorectic doses of 5-HT2cR agonists improve glucose tolerance and reduce plasma insulin levels in murine models of obesity and type 2 diabetes via MC4R signaling pathways (93).

Serotonin, IL-1, and TNFα do not appear to represent separate pathways influencing the activity of the central melanocortin system. Peripheral infusion of IL-1 induces anorexia and raises brain tryptophan levels, thereby increasing serotonin synthesis (79). Interleukin-1 intrahypothalamic injection depresses food intake and increases release of serotonin (91). TNFα, as well as IL-1, acutely regulates neuronal serotonin transporter (94). Also, it is likely that IL-1 and TNFα interact to mediate specific biological responses. Indeed, IL-1-induced anorexia in normal rats is more severe when a subeffective dose of TNFα is concurrently infused (90), suggesting that low concentrations of these cytokines, as produced endogenously, may have potential effects on different biological functions in vivo.

These data indicate that, during catabolic states, increased hypothalamic expression of IL-1 occurs in conjunction with increased release of serotonin. Serotonin and IL-1 interact within the arcuate nucleus to influence the activity of the melanocortin system, yielding and maintaining the inhibition of NPY/AgRP neuronal activity and the suppression of the inhibition of POMC/CART neurons. These biochemical events facilitate the release of the endogenous MC4R agonist α-MSH while suppressing the release of the endogenous MC4R antagonist AgRP, thus resulting in dysfunction of the melanocortin system. The mechanisms responsible for the failure of the intrinsic, melanocortin-mediated, anti-inflammatory circuitry remain to be ascertained. Indeed, α-MSH exerts anti-inflammatory activity by reducing TNFα secretion by macrophages/macrophages through the MC1R (32). However, this pathway appears not to function in experimental models and in many patients suffering from chronic diseases. The different genotype of patients may explain, at least in part, the phenotypic diversities occurring in the clinical setting.

Autonomic Nervous System

There is growing evidence that the autonomic nervous system is involved in the pathogenesis of the anorexia-cachexia syndrome by informing the brain on the peripheral challenges and by mediating at least some of the metabolic responses occurring in peripheral tissues.

In a classical paper, it was shown that brown adipose tissue thermogenesis is activated in an experimental model of tumor cachexia through the sympathetic nervous system (7). Also, the prevention of anorexia following vagotomy in tumor-bearing animals (3) suggests that the vagus might be involved in signaling to the brain about a tumor, and this signaling is important in the behavioral response (reduced food intake) to tumors. More recently, it has been demonstrated that peripherally growing hepatoma induces anorexia and reduced food intake by activation of brainstem neuronal structures, including the nucleus of the solitary tract, an area receiving extensive vagal innervation (78). Interestingly, the activation of the nucleus of the solitary tract appears to be independent of proinflammatory cytokines, as determined by the absence of increased cytokine levels in plasma, while inducing cytokine and cyclooxygenase expression in the brain (78). The nucleus of the solitary tract projects to the arcuate nucleus (18a), where at least part of POMC neurons have been demonstrated to
express cholinergic (39) and noradrenergic receptors (18a). These data complement previous observations showing that IL-1 does not appear to be key in activating POMC neurons (88), but it might be critical in maintaining their activation, since POMC neurons induce the hypothalamic expression of IL-1.

The mechanism(s) of vagal activation during peripheral challenge (either trauma, tumor growth, or cardiac failure, etc.) remains to be completely elucidated. It has been proposed that proinflammatory cytokines could be involved (25), but such interaction occurs locally rather than systemically because hepatic vagotomy does not appear to mediate IL-1-induced anorexia (41). Supporting the interplay between the vagus nerve and proinflammatory cytokines, the accumulation of brain tryptophan, frequently characterizing the course of chronic diseases and yielding to increased serotonin synthesis and oxidative stress, appears to be influenced by sympathetic activity (65).

The role of the hypothalamus in integrating immune function and metabolism is well recognized (26). Therefore, it should be considered as a key anatomical area, adapting behavior and peripheral metabolism to perceived challenges. Indeed, hypothalamo-medullary POMC projections mediate at least in part the reduction of food intake induced by MC4R agonists (92). The intrahypothalamic infusion of nicotine, a cholinergic agonist, increases hypothalamic serotonin concentrations (76), which are known to activate the melanocortin system (27, 28). Furthermore, central melanocortin agonists stimulate white adipose tissue lipolysis and brown adipose tissue thermogenesis through the sympathetic nervous system (5, 38). It should also be remembered that the vagus nerve modulates the inflammatory response by reducing the production of proinflammatory cytokines (85). However, in clinical practice, this physiological anti-inflammatory mechanism may frequently be ineffective because of the magnitude of the peripheral challenge and the individual profile of the factors involved (i.e., specific polymorphisms of specific genes conferring higher/lower biological activities).

In human diseases, alterations of sympathovagal balance and increased sympathetic activity have been demonstrated (14, 31, 77). Also, therapeutic interventions aimed at modulating sympathetic activity have been shown to result in favorable metabolic effects, including reduced basal metabolic rate and reduced lipolysis (23, 40). Direct evidence of the role of autonomic nervous activity on food intake and muscle protein degradation during human diseases is lacking. However, preliminary observations in anorexic cancer patients suggest that vagal activity, as assessed by measuring heart rate variability, is related to the degree of anorexia (Laviano A and Meguid MM, unpublished observations). Furthermore, ghrelin administration in patients with anorexia-cachexia results in improved food intake, reduced sympathetic nerve activity, and increased lean body mass (70, 71). Whether these are causally related or mere associations remains to be ascertained.

Based on the available data, a model of the pathogenesis of the anorexia-cachexia syndrome could be proposed (Fig. 2). Different peripheral challenges (i.e., tumors, renal failure, pulmonary disease, etc.) are sensed by the vagus nerve, possibly by local interaction with proinflammatory cytokines. This information is transmitted to brainstem areas and then to the hypothalamus yielding to the activation of the melanocortin system via cholinergic, noradrenergic, or serotonergic innervation. The activated melanocortin system induces the expression of proinflammatory cytokines to maintain the catabolic response. The metabolic and behavioral effects of melanocortin activation are then triggered in peripheral tissues, at least in part, via sympathetic outflow.

**Fatty Acid Oxidation**

As previously mentioned, the hypothalamic regulation of energy metabolism involves different pathways. Indeed, fatty acid metabolism within hypothalamic neurons controls food intake and energy metabolism in a leptin-independent way. In particular, inhibition of fatty acid synthase (FAS) blocks fasting induced upregulation of orexigenic neuropeptides and
downregulation of anorexigenic neuropeptides (30). As a result, food intake and body weight are significantly reduced (30). Hypothalamic malonyl-coenzyme A (CoA), a substrate of FAS, is an indicator of global energy status. Its concentration is low in fasted mice and rapidly increases on refeeding (30). Therefore, high intrahypothalamic malonyl-CoA induces anorexia by inhibiting fatty acid oxidation, whereas low levels have the converse effect and elicit food intake.

Malonyl-CoA has an inhibitory effect on carnitine palmitoyltransferase I (CPT I), which is the main regulatory enzyme involved in fatty acid oxidation. The FAS/malonyl-CoA pathway could be involved in the pathogenesis of disease-associated anorexia-cachexia syndrome, because in vitro studies show that proinflammatory cytokines, particularly TNFα and IL-1, inhibit fatty acid oxidation (69). If this effect also applies to the in vivo situation, then proinflammatory cytokines, and particularly IL-1, may cause an inappropriate switch in hypothalamic neurons from fatty acid oxidation to fatty acid synthesis, increase hypothalamic malonyl-CoA concentrations, and suppress food intake (Fig. 2). Interestingly, recent data show that the brain-specific CPT Ic is a key step in the regulation of energy metabolism, and knockout animals for CPT Ic display decreased rates of fatty acid oxidation and reduced food intake (89). Therefore, it is conceivable that the inhibitory effects of proinflammatory cytokines on fatty acid oxidation contribute to the dysregulation of the melanocortin system, thus leading to reduced energy intake. Inhibition of fatty acid oxidation within hypothalamic neurons influences metabolism in peripheral tissues. The “malonyl-CoA signal” is rapidly transmitted to peripheral tissues by the sympathetic nervous system, increasing mitochondrial biogenesis, fatty acid oxidation, and uncoupling protein-3 expression and thus energy expenditure (9, 10). Also, since mitochondria are among the main sources of reactive oxygen species production, it is postulated that this brain-muscle axis may contribute to increased oxidative stress, which in turn increases muscle protein degradation (48).

The relevance of the “malonyl-CoA signal” to human anorexia-cachexia syndrome was recently suggested in animal models. In particular, the anorectic effects of tamoxifen are associated with increased malonyl-CoA concentrations in the hypothalamus and inhibition of FAS expression specifically in the ventromedial nucleus of hypothalamus (49). Furthermore, obese women treated with tamoxifen gained significantly less body weight over a 6 yr period than did obese women given placebo (49). These data indicate that changes in hypothalamic metabolism may occur during tumor growth, contributing to the onset of anorexia-cachexia. Supporting this view, studies investigating the effects of carnitine administration to patients with anorexia-cachexia demonstrate improved appetite and enhanced nutritional status (47). The mechanisms responsible for the favorable effects on patients’ energy intake and lean body mass need to be completely elucidated. Data suggest that, during disease, carnitine deficiency may occur, at least in specific clinical conditions (54). Therefore, it could be speculated that carnitine administration may enhance fatty acid oxidation beyond its role as an antioxidant agent.

Based on the available data, it appears that increased hypothalamic expression of proinflammatory cytokines, and particularly IL-1 and TNFα, following peripheral challenge may reduce fatty acid oxidation within hypothalamic neurons, leading to accumulation of malonyl-CoA. This signal contributes to the dysfunction of the melanocortin system and to the increased catabolic sympathetic drive leading to deranged metabolism in peripheral tissues.

The pathogenesis of the anorexia-cachexia syndrome is likely more complex than the pathways outlined in this review. Recent data suggest that autoantibodies toward α-MSH could be responsible for the onset of anorexia nervosa (19a), and it cannot be excluded that they may also play a role in disease-associated anorexia-cachexia syndrome. Macrophage inhibitory cytokine-1, a member of the transforming growth factor-β superfamily, has recently been shown to contribute to tumor-induced weight loss and anorexia (35). Prostaglandins have been shown to be involved in experimental models of anorexia-cachexia (86). Also, therapeutic strategies aimed at interfering with prostaglandin synthesis led to favorable clinical effects (50). Furthermore, oxidative stress is emerging as a causative factor in anorexia and cachexia (56). While awaiting cleared biochemical and molecular elucidation of the brain-muscle axis, available evidence shows repeatedly that the brain and particularly the hypothalamus is critical in triggering and maintaining the flow of catabolic stimuli toward peripheral tissues.

Conclusion

During the last few years, our knowledge of the neural mechanisms regulating the onset and progression of the anorexia-cachexia syndrome has significantly improved. However, the translation of the data obtained in experimental models into the clinical setting is limited by the heterogeneity of the symptoms characterizing the anorexia-cachexia syndrome during human disease. It is extremely likely that the different features of this syndrome even in patients suffering from the same disease are related to the polymorphisms of specific genes (6), which in turn modulate the individual neurochemical/metabolic response to similar challenges. In this light, it seems appropriate that the research on the anorexia-cachexia syndrome focuses on the identification of polymorphisms of key genes, including those expressing proinflammatory cytokines, MC4R, and 5-HTR. This would allow clinicians to predict the likelihood of developing anorexia-cachexia, thereby permitting the use of preventive measures or at least the timely start of antinflammatory therapeutic strategies.

REFERENCES

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