

Pathophysiology and treatment of inflammatory anorexia in chronic disease

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Abstract Decreased appetite and involuntary weight loss are common occurrences in chronic disease and have a negative impact on both quality of life and eventual mortality. Weight loss in chronic disease comes from both fat and lean mass, and is known as cachexia. Both alterations in appetite and body weight loss occur in a wide variety of diseases, including cancer, heart failure, renal failure, chronic obstructive pulmonary disease and HIV. An increase in circulating inflammatory cytokines has been implicated as a uniting pathogenic mechanism of cachexia and associated anorexia. One of the targets of inflammatory mediators is the central nervous system, and in particular feeding centers in the hypothalamus located in the ventral diencephalon. Current research has begun to elucidate the mechanisms by which inflammation reaches the hypothalamus, and the neural substrates underlying inflammatory anorexia. Research into these neural mechanisms has suggested new therapeutic possibilities, which have produced promising results in preclinical and clinical trials. This review will discuss inflammatory signaling in the hypothalamus that mediates anorexia, and the opportunities for therapeutic intervention that these mechanisms present.

Keywords Cachexia · Anorexia · Hypothalamus · Inflammation · Melanocortin

Decreased appetite (anorexia) and catabolism of lean tissues are common co-morbidities of a multitude of chronic diseases. In such diseases, the synergistic effects

of decreased energy intake on the one hand, and increased energy expenditure on the other generate an ongoing loss of body weight in which muscle mass is not appropriately preserved [1]. Loss of muscle mass accompanying involuntary weight loss in association with chronic disease is known as cachexia. The consensus definition of cachexia is “... a complex metabolic syndrome associated with underlying illness and characterized by the loss of muscle with or without loss of fat mass” [2]. The presence of cachexia is a negative prognostic indicator in a multitude of conditions including cancer [3], chronic renal failure [4], congestive heart failure (CHF) [5], and HIV [6]. Although cachexia is not always associated with overt anorexia, they often occur together [7]. Unlike starvation, where adipose tissue is predominantly lost, muscle mass and adipose tissue are both affected in cachexia [8]. In accordance with this, correction of the nutritional deficit by intravenous nutrition in cachexia, while beneficial, has been unsuccessful in completely reversing the catabolic features of this syndrome [9]. Therefore, a therapeutic modality that corrects both decreased appetite and the catabolism of lean mass is the most desirable for treating cachexia associated with anorexia.

1 Cachexia as an inflammatory disease

One of the common features uniting all conditions associated with cachexia is an increase in the levels of circulating inflammatory cytokines. In chronic heart failure, circulating levels of tumor necrosis factor (TNF) [10–12] and interleukin-6 (IL-6) [11] are increased, and correlate with the degree of exercise impairment in these patients. In chronic renal failure, increased levels of circulating cytokines and C-reactive protein are correlated with increased

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mortality [13]. Likewise, in cancer patients suffering from cachexia, multiple inflammatory cytokines have been found at increased levels relative to non-cachectic cancer patients including IL-6 [14, 15] and TNF [16, 17]. Furthermore, multiple studies have implicated leukemia inhibitory factor (LIF) as a pathogenic factor in cancer cachexia. LIF is found at high levels in cancer patients [18], and is released from human tumor cell lines [19]. While serum LIF levels are a negative prognostic indicator in sepsis [20], no studies have been performed to date correlating the circulating LIF levels with the degree of cancer cachexia. Others have failed to find elevated levels of the aforementioned inflammatory mediators [17, 21] in cancer cachexia, likely reflecting heterogeneity in the type and severity of cancer studied as well as the intermittent nature of inflammatory processes. The ability of these inflammatory molecules to act directly on peripheral tissues to elicit catabolic processes is well characterized [22, 23]. Increased inflammatory signaling in skeletal muscle potentiates myofibrillar atrophy by suppressing protein synthesis and increasing protein degradation. While clearly a critical pathway in the pathogenesis of cachexia, there is at present no evidence for the direct regulation of skeletal muscle catabolism by the CNS, and it is therefore beyond the scope of this review.

2 The central nervous system as a target of inflammatory signaling

It is well established that inflammatory cytokines have potent effects on feeding in animal models. The peripheral administration of cytokines such as interleukin-1 beta (IL-1 β) [24–26] and TNF [26] or the inflammatory bacterial cell wall product lipopolysaccharide (LPS) [24, 25] potently induce anorexia in laboratory animals. Furthermore, intercerebroventricular (ICV) injection of inflammatory cytokines such as IL-1 β [27], LIF [28, 29], and TNF [30] also reduce food intake, suggesting that the brain can respond directly to inflammatory signals. Peripheral or central cytokine injection leads to a rapid induction of cFOS immunoreactivity, a marker of neuronal activation [31], in multiple brain regions, including areas that are critical for food intake and energy metabolism such as the arcuate nucleus of the hypothalamus [32]. A negative correlation has been reported in tumor-bearing animals between food intake and interleukin 1 alpha concentration, further implicating inflammatory cytokines in the pathogenesis of anorexia [33].

Additional studies have suggested that inflammatory cytokine production in the CNS itself is critical in the generation of the anorectic response. Animals injected peripherally with LPS display a rapid increase in the expression of inflammatory cytokines in the hypothalamus

[24, 25]. IL-1 β appears to be particularly critical, as ICV infusion of IL-1 receptor antagonist (IL-1Ra) significantly reduces the anorexia resulting from peripheral LPS administration, and normalizes hypothalamic cytokine expression [34]. These results suggest that local cytokine production within the brain may function as a critical signaling intermediate and a feed forward mechanism for sustaining the response to inflammation. Additional studies have further implicated cytokine production within the brain as a critical mediator of anorexia. Myeloid differentiation primary response protein 88 (MyD88) is a signaling adaptor downstream of toll-like receptor-4 (the cellular receptor for LPS) and the type 1 interleukin-1 receptor (IL-1R1). Mice lacking functional MyD88 evolve a normal or increased serum cytokine response to LPS, presumably via MyD88-independent pathways [24, 25]. However, these mice are completely resistant to LPS- or IL-1 β -induced anorexia and show attenuated induction of hypothalamic cytokine production. These data demonstrate the MyD88 dependence of LPS-induced anorexia, and suggest that elevated hypothalamic cytokine expression might be a critical intermediary.

The induction of IL-1 β [35, 36] and TNF [36] expression in the hypothalamus has been documented in tumor-bearing animals. Further support for the critical nature of hypothalamic cytokines comes from experiments demonstrating that ICV administration of the TNF neutralizing antibody infliximab or IL-1Ra increases food intake and reduces the febrile response in a cecal ligation and puncture model of sepsis, and modestly increases survival [37]. Additionally, ICV infliximab or IL-1Ra improve food intake and survival in animals implanted with the Walker-256 tumor [37], in which hypothalamic levels of TNF and IL-1 β are both increased. While promising, the modest effects seen in these experiments point to likely redundancies in the inflammatory control of anorexia in more complex disease models. While many cytokines have the capability of inducing anorexia when injected centrally, the mRNA for multiple inflammatory mediators are simultaneously induced in the hypothalamus after peripheral LPS challenge or in tumor-bearing animals. It is therefore likely that in the true disease state, anorexia is due to the additive or synergistic effects of multiple inflammatory cytokines acting on both overlapping and non-overlapping targets. Infusion of multiple cytokines at doses that provoke only slight anorexia alone can lead to dramatic anorexia when given in combination [27]. Furthermore, the chronic administration of IL-1 β , TNF, IL-6 or interleukin-8 results in an initial anorectic period with rapid desensitization and complete recovery of food intake by the end of 1 week [38, 39]. In contrast, adenoviral delivery of LIF to the CNS can generate a chronic anorexia and weight loss that shows no signs of desensitization [40]. These findings indicate that the generation of long lived disease-

associated anorexia likely results from the complex interplay of multiple CNS cytokines, which are likely specific to the patient and condition.

3 Afferent pathways for inflammatory signaling

Visceral sensory afferents have been proposed as a potential mechanism by which peripheral inflammation might generate an anorectic response. In particular, the vagus nerve appears to play a role in mediating behavioral responses to inflammation. Sub-diaphragmatic vagotomy was shown to attenuate the induction of IL-1 β mRNA expression in the hypothalamus after intraperitoneal LPS challenge [41] or IL-1 β injection [42]. However, other studies have demonstrated that vagotomy does not prevent increases in hypothalamic IL-1 β protein content in LPS treated animals [43]. In agreement with this, vagotomy was reported to attenuate the anorexia seen with LPS administration [44] while others have seen no alteration in the anorectic response to LPS or other inflammatory stimuli in vagotomized animals [45]. An explanation for the discordance of these studies is not immediately apparent; however, these data are suggestive of a vagally mediated anorectic pathway in response to inflammatory stimuli that may be critical under certain circumstances. It seems clear however, that the vagus is not necessary for the anorectic response to intravenous IL-1 β [46] suggesting that inflammatory cytokines in circulation may signal to the CNS via a pathway independent of the vagus. There is some evidence to suggest that tumor growth may stimulate anorexia via a vagal pathway. Anorexia was attenuated in tumor-bearing rats when a sub-diaphragmatic vagotomy was performed prior to tumor implantation, or when vagal afferents were chemically ablated [47].

In contrast multiple lines of evidence suggest that circulating cytokines act directly on CNS neurons. The best-studied cytokine with regard to its neuronal action is leptin, a negative regulator of body mass and appetite. While implicated as a mediator of uremic cachexia [48] and elevated levels of leptin have been reported in CHF [49] studies demonstrating the critical role for leptin in the pathogenesis of other forms of cachexia have yet to be performed. However, leptin is closely related to IL-6 and LIF in structure and signaling [50]. Thus leptin may serve as an effective prototype for cytokine access to the CNS, despite extensive evidence for it being an essential mediator of cachexia. Inflammatory cytokines are generally believed to be too large to cross the blood brain barrier (BBB) by simple diffusion [51]. However, CNS structures collectively referred to as circumventricular organs have specialized fenestrated capillaries. The median eminence is one such region, where the permeable capillaries of the portal

vasculature play a critical role in the neuroendocrine communication between the hypothalamus and the anterior pituitary. Neurons in the adjacent arcuate nucleus of the hypothalamus (ARC) are thought to have processes that lie outside of the BBB [52] and are also responsive to circulating factors via median eminence capillary fenestrations [51]. Furthermore, the ARC is a critical site for the integration of physiologic leptin signals. Thus, the ARC represents a possible location for the detection of circulating cytokine signals. Additional areas of the brain respond directly to leptin signals [53, 54], yet lie behind the BBB. Active transport across the BBB and the blood-CSF barrier is well characterized for leptin [55, 56]. In addition, evidence exists for active transport into the CNS of multiple inflammatory cytokines implicated in cachexia including IL-1 β [57] IL-6 [58], and TNF [59]. These data suggest the possibility that areas of the brain that are behind the BBB may be able to respond to circulating cytokines.

Another mode by which inflammatory cytokines may influence neuronal activity is the synthesis of prostaglandins along the BBB, either in endothelial cells or perivascular macrophages. Prostaglandins are small lipid soluble inflammatory mediators, which diffuse across the BBB [60, 61]. Consistent with the notion that prostaglandins serve as a signaling intermediate, endothelial and perivascular cells express the receptors for inflammatory cytokines [62, 63], and are activated under inflammatory conditions [63, 64]. Furthermore, inflammatory insults appear to activate endothelial cells more rapidly than neurons. This suggests that under inflammatory conditions, endothelial cells may be responsible for conveying the activating signal to neurons [64]. In accordance with this, neurons are known to express receptors for prostaglandins [65]. Under inflammatory conditions, the mRNA for synthetic enzymes for prostaglandin E₂ (PGE₂), the most studied of the centrally acting prostaglandins, are induced in endothelial cells and perivascular macrophages [66]. When cyclooxygenase (COX), the proximal biosynthetic enzyme for prostaglandins, is blocked pharmacologically, animals display attenuated anorectic responses to peripheral IL-1 β [67] and LPS [68, 69]. In some studies, tumor-bearing animals display attenuated anorexia and weight loss when treated with COX inhibitors [70, 71].

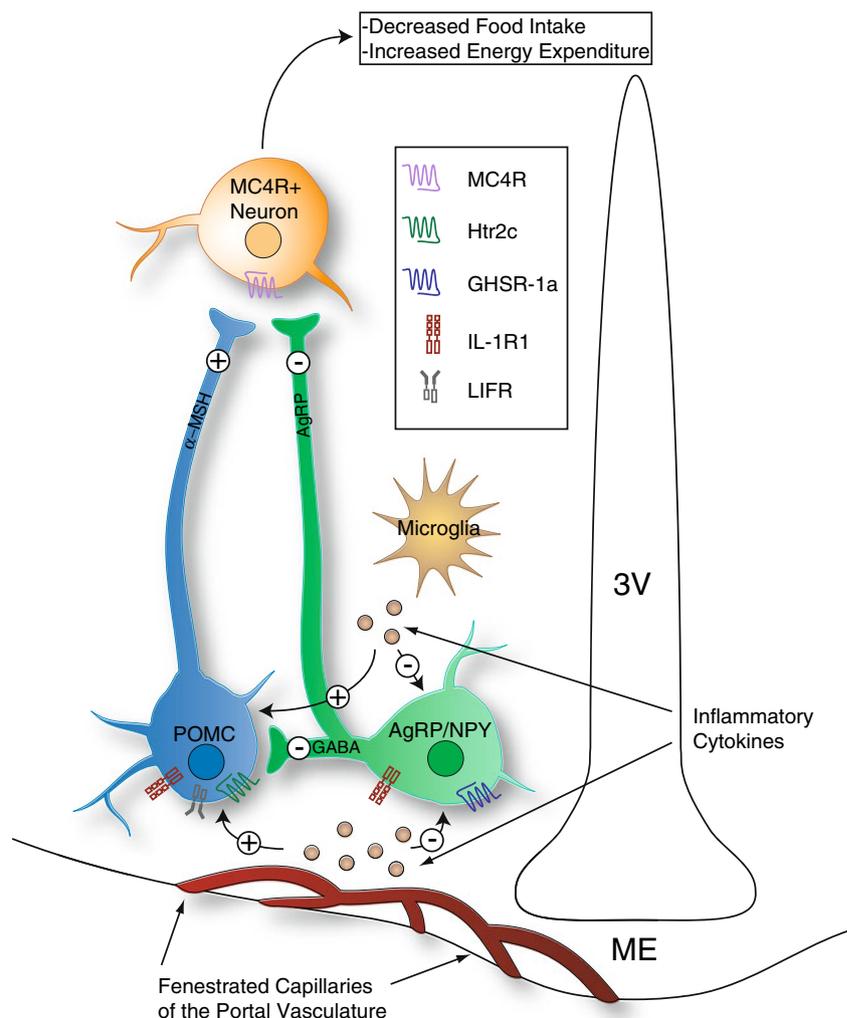
The precise mechanisms by which COX inhibition is protective remains somewhat unclear, as certain tumors show attenuated growth when treated with COX inhibitors [72], suggesting that tumor regression rather than inhibition of anorectic pathways may be responsible for these effects. Furthermore, it appears that some experimental tumors produce anorexia and weight loss in a COX-independent manner, as COX inhibition is not effective in reversing anorexia or weight loss in certain models [71]. While the non-steroidal anti-inflammatory

(NSAID) agents used to inhibit COX are generally regarded as specific, recent evidence demonstrates that many of the commonly used compounds also have the ability to inhibit other inflammatory pathways including nuclear factor- κ B (NF- κ B) [73]. This complicates the interpretation of NSAID data, as the effects seen cannot be solely attributed to decreases in prostaglandin biosynthesis, and instead effects on other more general inflammatory pathways must be considered. Additional evidence for the role of prostaglandins in driving anorexia and weight loss comes from studies in mice lacking the terminal biosynthetic enzyme for PGE₂, microsomal prostaglandin E synthase. These mice display complete resistance to anorexia from LPS injection or tumor implantation [74]. Interestingly, hypothalamic expression of inflammatory cytokines is normally induced under inflammatory conditions in these animals suggesting parallel pathways for prostaglandin and cytokine signaling.

4 Neural targets for inflammatory cytokine action: the melanocortin system

One important target for inflammatory signaling in the CNS is the hypothalamic central melanocortin system, which consists of two neuronal populations expressing peptide neurotransmitters with opposing actions (Fig. 1). Proopiomelanocortin (POMC) neurons are located in the ARC, and the nucleus of the solitary tract of the brain stem [75]. These neurons express the POMC precursor peptide, which is cleaved into many bioactive products including the anorectic peptide alpha melanocyte-stimulating hormone (α -MSH). The anorectic effect of α -MSH is exerted by binding to its cognate receptor, the type four melanocortin receptor (MC4R), which is expressed in a broad array of hypothalamic and extra-hypothalamic areas in the CNS [76]. The net effect of signaling at the MC4R is decreased appetite [77] and increased energy expenditure [78]. It should be noted that the POMC peptide is cleaved into

Fig. 1 Inflammatory cytokines target hypothalamic feeding circuits in cachexia. Inflammatory cytokines from circulation or produced locally by microglia act directly on hypothalamic arcuate nucleus neurons. The activity of anorectic POMC neurons is stimulated while the activity of orexigenic AgRP/ NPY neurons is inhibited. This leads to increased signaling at the MC4R, which results in decreased food intake and increased energy expenditure. Ghrelin analogs act by stimulating AgRP/ NPY neurons through the GHSR-1a while melanocortin antagonists block the MC4R. Both approaches are successful in reducing pathologically elevated melanocortin tone in cachexia and improving food intake. 3V third ventricle, ME median eminence



multiple other peptides with diverse CNS and peripheral functions. However, these other cleavage products are not well described in cachexia, and have been extensively reviewed elsewhere [79]. Lying adjacent to the arcuate POMC neurons, are the Agouti-related peptide/neuropeptide Y (AgRP/NPY) neurons, which have orexigenic activity [75]. While NPY acts on specific NPY receptors, AgRP is an inverse agonist at the MC4R, increasing food intake and decreasing energy expenditure [80]. Importantly, α -MSH and AgRP immunoreactive fibers project to many of the same locations across the CNS, although AgRP projections are less dense [81–83]. In addition, AgRP neurons send inhibitory projections to neighboring POMC neurons, creating an additional level of control [84]. Both neuronal populations are cytokine responsive. Furthermore, both play a critical role in normal energy homeostasis in the response to leptin, and the maladaptive energetic response to inflammatory cytokines. In particular, POMC neurons express the IL-1R1, and increase their spontaneous firing rate in response to IL-1 β administration. The release of α -MSH from hypothalamic explants after IL-1 β treatment is also increased [85]. The converse is true of AgRP neurons, which, like POMC neurons express the IL-1R1, but instead decrease the spontaneous release of AgRP in response to IL-1 β [86]. Presumably, the net result of IL-1 β action on these two neuronal populations is to dramatically increase signaling at the MC4R, resulting in anorexia. In addition, recent work has shown that the acute anorectic effects of exogenous LIF are entirely mediated by LIF receptor signaling on POMC neurons [28], further demonstrating the importance of the melanocortin system in mediating the response to cytokines.

Additional evidence for the critical nature of melanocortin signaling in cachexia comes from the finding that mice lacking functional MC4R resist anorexia associated with tumor growth [87, 88], chronic renal failure [48], or LPS administration [87, 88]. In addition, ICV administration of exogenous AgRP, or synthetic melanocortin antagonists also ameliorates anorexia induced by LPS, inflammatory cytokines [26, 89, 90] chronic renal failure [48], and tumor growth [88, 91].

As a result of these findings, multiple preclinical studies have begun to examine the potential therapeutic benefit of melanocortin antagonism in cachexia. Melanocortin antagonists have been developed that improve food intake and prevent the loss of lean mass when administered peripherally to tumor-bearing mice [90, 92]. Recently, melanocortin antagonists have been developed with oral bioavailability that attenuate anorexia and lean mass loss in tumor-bearing animals [93]. Preclinical studies have also demonstrated the efficacy of melanocortin antagonism in chronic renal failure. Peripheral administration of melanocortin antagonists improves food intake [48] and prevents the loss of

lean mass in subtotal nephrectomy-induced chronic renal failure [48, 94, 95]. As the preclinical data demonstrate, melanocortin antagonism is an exciting treatment possibility for anorexia associated with chronic disease. Future clinical studies will likely begin to explore the efficacy of melanocortin antagonism as a therapeutic modality in human cachexia.

5 Neural targets for inflammatory cytokine action: neuropeptide Y

NPY is another well-studied orexigenic neuropeptide, which increases food intake when administered exogenously. Co-expressed in the same neurons as AgRP, NPY is also regulated by inflammatory stimuli. Globally, NPY acts to increase food intake, and administration of exogenous NPY leads to hyperphagia and obesity [96]. Unlike starvation, which induces NPY mRNA in the hypothalamus, inflammatory stimuli such as LPS or IL-1 β either show no change [97] or demonstrate a reduction [98] in NPY mRNA levels. Furthermore, tumor-bearing animals show either no change [99], a decrease [100] or a slight increase [101] in NPY mRNA, depending on the report. Irrespective of the directionality of the change, inflammatory anorexia results in a marked suppression of NPY mRNA expression relative to that seen in animals restricted to an equivalent level of food intake. This suggests that inflammatory signaling disrupts the normal regulation of NPY in response to negative energy balance.

A functional antagonism has been demonstrated between IL-1 β and NPY, where IL- β decreases the NPY-induced feeding response in a dose-dependent manner [102]. A reduction is seen in the NPY content of hypothalamic microdialysates from tumor-bearing animals, suggesting impaired NPY release in cachectic states [103]. However, several studies have demonstrated a decreased efficacy of exogenous NPY in tumor-bearing animals as compared with healthy controls, suggesting functional resistance to the peptide in cachexia [91, 104]. Furthermore, resistance to continuous infusion of NPY develops rapidly in tumor-bearing animals [104], suggesting an NPY deficiency is not solely responsible for the anorexia in tumor-bearing animals. In accordance with these studies, radioligand binding assays performed in anorectic tumor-bearing rats demonstrated a dramatic decrease in NPY receptor affinity with a moderate reduction in receptor number [105]. Finally, decreases in NPY immunoreactive projections to various hypothalamic nuclei have been documented in anorectic animals [100]. These data collectively demonstrate that NPY is aberrantly regulated in cachectic states. There is evidence to suggest both a decrease in NPY production, and a decreased sensitivity to NPY in cachexia.

However, given the presence of apparent resistance to NPY in cachexia, a therapeutic strategy involving exogenous NPY replacement without correction of the underlying downstream defects may not be viable.

6 Neural targets for inflammatory cytokine action: the serotonergic system

The serotonergic system is a powerful regulator of food intake and energy metabolism. Serotonergic neurons are located in the brainstem raphe nuclei and project to a wide variety of cortical and subcortical regions. Serotonin or 5-hydroxytryptamine (5-HT) is released from the terminals of these neurons and binds to 5-HT receptors. There are seven families of serotonin receptors (5-HT₁₋₇R), each of which contains multiple members, with overlapping roles in cognition, memory, and autonomic functions such as vasomotor tone and GI motility [106]. As a result, serotonin biology is a complex field that cannot be fully reviewed here, and references will only be made to aspects that have been implicated in cachexia.

Global activation of the serotonin system appears to suppress feeding. Administration of the drug fenfluramine, which is believed to globally increase serotonin release and simultaneously block reuptake, suppresses feeding in animals and humans [107–109]. Furthermore, lesions of the raphe nuclei [110] or ICV injection of a serotonin antagonist [111] result in hyperphagia and obesity. The majority of studies have focused on the 5-HT_{2C}R as the predominant receptor mediating the effects of serotonin signaling on appetite. Mice lacking functional 5-HT_{2C}R resist the effects of fenfluramine or a specific 5-HT_{2C}R agonist [112, 113] on food intake and develop obesity secondary to hyperphagia [114]. Interestingly, ARC POMC neurons express 5-HT_{2C}R and are activated electrophysiologically by fenfluramine [115]. In the context of the 5-HT_{2C}R deficient mouse, selective restoration of 5-HT_{2C}R expression in POMC neurons corrects the obese phenotype [116].

Experimental evidence for the involvement of serotonergic signaling in disease-associated anorexia comes from work examining the serotonin content of the hypothalamic ventromedial nucleus (VMH). Microdialysis experiments revealed an increase in VMH serotonin content in tumor-bearing animals, which returned to baseline with tumor excision [117]. Furthermore, injection of a serotonin antagonist into the VMH of tumor-bearing animals resulted in improved food intake [53]. Another study, however, found no effect on the appetite of tumor bearing mice treated with tricyclic antidepressants, which are generally believed to inhibit serotonin reuptake and potentiate its signaling [118]. While serotonin signaling seems a likely

candidate for therapy, future studies will have to be performed to examine receptor subtypes involved in inflammatory anorexia.

7 Neural targets for inflammatory cytokine action: ghrelin

Ghrelin is a growth hormone releasing peptide, which is produced in the stomach in response to hunger or starvation [119]. Ghrelin is present in two forms: acylated ghrelin which is active, and desacyl ghrelin which is inactive. Acyl ghrelin binds to the growth hormone secretagogue receptor-1a (GHSR-1a) which is found on ARC AgRP/NPY neurons, increasing their activity and peptide release [120]. There is some experimental evidence for the involvement of ghrelin in the pathophysiology of cachexia. Ghrelin exerts anti-inflammatory effects on immune cells and endothelium [121, 122], decreasing proinflammatory cytokine production. In animals and humans experiencing anorexia due to inflammatory arthritis, serum ghrelin levels are decreased compared with controls [123]. Furthermore, ghrelin levels are acutely decreased by LPS administration [124], which results in an IL-1R1 and prostacyclin-dependent signaling mechanism decreasing ghrelin secretion by the stomach [125]. In contrast to the acute inflammatory state however, ghrelin is found at increased levels in chronic inflammation. Furthermore, exogenous ghrelin administration attenuates the anorectic response to LPS [122], most likely due to an attenuation of the inflammatory response and activation of hypothalamic AgRP/NPY neurons.

However, plasma levels of ghrelin are increased in patients with cachexia from multiple etiologies as compared with non-cachectic patients suffering from the same underlying conditions [126–129] although some do report that levels fall in advanced cancer patients [130]. This suggests that in cachexia, ghrelin may be elevated as a compensatory mechanism for negative energy balance. Based on these human data, an overt ghrelin deficiency does not appear to be involved in the pathogenesis of anorexia associated with chronic disease, although the possibility remains that the ghrelin response is inappropriately low given the level of negative energy balance.

Despite the lack of conclusive evidence for a clear role for ghrelin in chronic anorexia, multiple preclinical studies have demonstrated promising results in experimental models of cachexia. When administered to tumor-bearing animals [99, 131, 132] or rats with chronic renal failure [133], ghrelin ameliorates anorexia and improves lean mass. Interestingly, ghrelin administration appears to improve skeletal muscle mitochondrial oxidative capacity independent of food intake [134], suggesting that ghrelin may have peripheral anti-

catabolic effects, or engage a presently unknown hypothalamic anti-catabolic pathway. When utilized in an experimental model of CHF, ghrelin treatment improves muscle mass [135] and overall lean mass [136]. These promising data have resulted in multiple clinical trials examining the efficacy of ghrelin in cachexia of multiple etiologies.

8 Current and future therapy for decreased appetite in chronic disease

Few therapeutic options exist currently for the treatment of anorexia in chronic disease. Progestational agents such as megestrol acetate have been effective in improving food intake, and produce significant weight gain. However, the weight gain associated with its use is mostly due to increased fat and water mass [137, 138]. Treatment with exogenous ghrelin and ghrelin analogs however, has been very successful in early clinical trials in patients suffering from cachexia resulting from several underlying disorders. In patients with CHF, ghrelin administration improved exercise capacity, and increased lean body mass and muscle strength [139]. Ghrelin also improves food intake, performance status, muscle strength, and lean mass in chronic obstructive pulmonary disease [140]. Early studies in cancer cachexia have been less compelling. A phase I study showed that ghrelin was well tolerated by cancer patients, but no differences were observed in nutritional intake or body weight [141], although food intake did trend toward improvement. Single injection of ghrelin into cachectic cancer [142] and renal failure [143] patients improved immediate post-injection food intake in both groups. Further studies are currently underway to study the efficacy of ghrelin treatment in larger groups of cachectic patients, with the hope of introducing ghrelin as a standard treatment option in cachexia.

9 Conclusions

The anorexia associated with chronic disease is a multifactorial process that is variable and likely dependent on the etiology of the underlying disease. Many inflammatory molecules appear to be sufficient to cause reduced food intake in animal models acutely, but sustained decreases in food intake as occur in cachectic patients may be driven by a specific subset of inflammatory mediators, or the combined action of multiple mediators acting simultaneously. While numerous brain regions are activated by inflammation, only a few neuronal subtypes have been identified that respond directly to inflammatory cytokines. Whether ARC POMC and AgRP neurons represent an integrator of inflammatory cytokine signaling, or other as yet unidenti-

fied neurons are also directly responsive to these cytokines remains to be elucidated. Regardless, agents targeting these neurons or their downstream receptor the MC4R have been remarkably effective in preclinical studies and early clinical trials. It is likely that the best outcomes for anorectic patients will be obtained by combination therapy targeting both inflammatory mediators and their neural targets.

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