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Cytokines and the Anorexia of Infection: Potential Mechanisms and Treatments

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Anorexia during infection is thought to be mediated by immunoregulatory cytokines such as interleukins 1 and 6 and tumor necrosis factor. This article reviews the potential mechanisms of action by which these cytokines are thought to suppress food intake during infection and examines the proposition that blocking of cytokine activity might be one approach to improving food intake of the infected host.

Key words: *Animal models, interleukin-1alpha, interleukin-1beta, interleukin-6, tumor necrosis factor alpha, anorexia, infection, lipopolysaccharide*

Acute infectious illness precipitates a series of stereotypical responses regardless of the nature of the etiologic agent (Gabay and Kushner 1999; Long 1996). These responses include fever, anorexia, hypoferremia, gluconeogenesis, protein and fat catabolism, negative nitrogen balance, and increased hepatic synthesis of acute phase proteins such as C-reactive protein. While many aspects of the acute phase response to infection have been shown to be of adaptive value in host resistance to infection, the suppression of food intake during infection has long puzzled clinicians. It seems paradoxical that food intake should be suppressed at a time when metabolic rate can rise 10% to 13% for each degree centigrade rise in body temperature.

Maintaining optimum nutritional status of patients is an integral part of modern nursing practice (Rynbergen 1938; Verity 1996). Anorexia with infection is a problem frequently encountered by nurses due to the relatively high frequency of infection in acutely ill persons (Pittet and others 1999; Schumann 1996). Infection is also a frequent complication of chronic illness and, in some cases, preexisting malnutriton may contribute to the increased risk of acute infection (Giner and others 1996; Riquelme and others 1997). The combination of anorexia, hypermetabolism, lipolysis, and proteolysis produces the decline in nutritional status and body weight that is the hallmark of chronic infections (Arsenijevic and others 1997).

Because metabolic rate, oxygen consumption, and protein catabolism are elevated during infection (Arsenijevic and others 1997; Hill and others 1997; Ling and others 1997; Souba 1994), nursing interventions to increase the intake of high-calorie or high-protein foods would seem to be indicated (Lutz and Przytulski 1997, 452-70; Verity 1996). However, there are very few data that such interventions improve the nutritional status of infected patients (Moldawer and Copeland 1998). In contrast, protein/calorie supplementation may increase the metabolic stress of infection (Carlson 1997; Greig and others 1984). Murray and Murray (1979) found that gavage feeding increased the mortality and shortened survival time in mice acutely infected with *Listeria monocytogenes*, whereas Wing and Young (1980) reported that fasting reduced mortality of infected mice. Therefore, the etiology of appetite suppression during infection must be explored more fully before appropriate nursing intervention for this phenomenon can be prescribed.

Anorexia as Part of the Acute Phase Response to Infection

An experimental model frequently used to study the acute phase response to infection is to inject healthy animals with lipopolysaccharide (LPS), an immunogenic component of the cell wall of gram negative bac-

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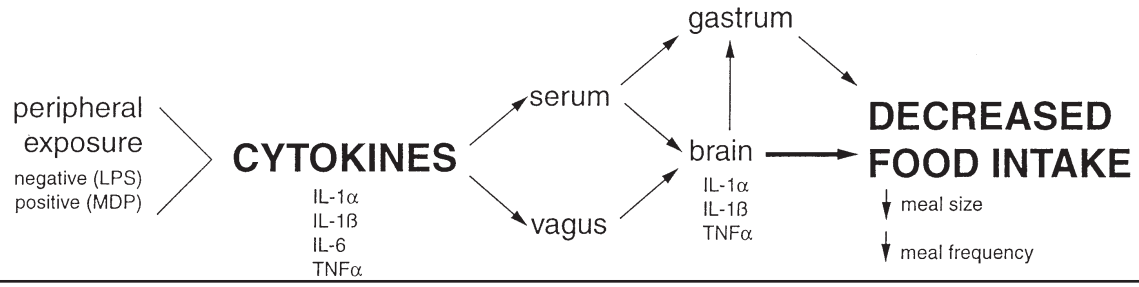

Figure 1. **Purported pathways by which cytokines (IL-1α, IL-1β, IL-6, TNFα) affect food intake during infection.**

teria (Langhans 1996) or muramyl dipeptide (MDP) from the cell wall of gram positive bacteria (Langhans and others 1990; Roth and others 1997; Gayle and others 1998; Biberstine and others 1996). Activated leukocytes exposed to bacteria or bacterial products such as LPS or MDP secrete immunoregulatory cytokines such as interleukins, interferons, and tumor necrosis factor (Chang and Bistrian 1998; Gabay and Kushner 1999). These cytokines act to amplify inflammatory and immune cell responses to infection, raise body temperature, and alter protein, lipid, and carbohydrate metabolism in the host during infection (Chang and Bistrian 1998; Elmquist and others 1997; Hill and others 1997; Ling and others 1997; Tompkins 1997).

There is convincing evidence that cytokines also mediate the behavioral aspects of the acute phase response, including anorexia (see reviews by Dantzer and others 1998; Johnson 1998; Plata-Salamán 1998a, 1998b). These observations led several authors to propose that anticytokine approaches might abate the weight loss and nutritional decline that occurs with acute infection (Haslett 1998; Johnson 1998; Moldawer and Copeland 1998; Plata-Salamán 1995; Souba 1994; Zheng and others 1995). Such approaches might be particularly helpful in preventing the nutritional decline of chronic infections like HIV. The purpose of the present article is to examine this proposal in the context of what is known about how cytokines act to reduce food intake during infection. The physiological pathways involved in cytokine-induced anorexia are represented in Figure 1.

Although multiple cytokines have been shown to suppress food intake, this review will be limited to the effects of interleukin-1 alpha (IL-1α), IL-1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNFα), which have been more extensively studied than other cytokines, for example, interferon gamma or IL-8 (Plata-Salamán 1998a, 1998b; Chang and Bistrian 1998). This review will also be limited to studies in which the effects of these cytokines can be compared to the effects of LPS as a model of the acute phase response to infection. Although there are limitations to the use of an animal model for understanding human ingestive behavior, the rat and mouse have been extensively used as an animal model in both feeding and cytokine research (Gallaher 1992; Plata-Salamán 1998a; Langhans 1996).

Cytokines as Mediators of Anorexia during Infection

Injection of healthy animals with LPS produces the signs and symptoms of the acute phase response to infection, including anorexia and increased plasma levels of TNF, IL-6, and IL-1 (Faggioni and others 1995; Fantuzzi and others 1996). Injection of IL-1α, IL-1β, IL-6, or TNFα will reduce food intake in healthy animals (McCarthy in press; Plata-Salamán 1998b). Injection of LPS in C3H/HeJ mice, a strain that is resistant to LPS, does not suppress food intake or elevate plasma levels of IL-1β. However, food intake is suppressed when these mice are injected with IL-1β (Segretti and others 1997). Thus, cytokine production is associated with the suppression of food intake following injection of LPS.

Research to determine which cytokines are important in the suppression of food intake during infection has revealed a complex network of cytokines that have overlapping effects on food intake. For example, the anorexigenic effects of LPS can be blocked partially

by pretreatment with antisera to IL-6 or TNFα (Strassman and others 1993) or with an IL-1 receptor antagonist (IRAP) (Swiergiel and others 1997). It should be noted that injection of an antibody or receptor blocker for any one cytokine does not return food intake of LPS-injected animals to control levels, but only improves food intake compared to animals injected with LPS alone. Thus, no one cytokine explains in full the anorexigenic effect of LPS. Cytokines may also have synergistic effects on food intake; combined injection of IL-1β and TNFα produces a greater suppression of food intake than that seen with injection of the same dose of IL-1β alone (Yang and others 1994; van der Meer and others 1995).

Studies using animals made tolerant to LPS, IL-1β, or TNFα by repeated injections suggest that TNFα may play a more important role in LPS-induced anorexia than IL-1β. LPS-tolerant animals will develop anorexia when injected with TNFα, whereas TNF-tolerant animals do not develop anorexia when injected with LPS (Porter, Arnold, and others 1998). In contrast, IL-1-tolerant animals do reduce their food intake when injected with LPS (Langhans and others 1993). Thus, responsiveness to IL-1β is not necessary for the suppression of food intake following injection of LPS.

This conclusion has been supported by data from studies using animals genetically altered so they are missing the gene (gene knockouts) needed to synthesize the IL-1 receptor. Injection of LPS in IL-1 receptor knockout mice will decrease food intake to levels seen following injection of LPS in the wild-type genetically unaltered mice (Leon and others 1996). Similar data have been obtained using IL-1β knockout mice (Fantuzzi and others 1996) and IL-1β converting enzyme (ICE) knockouts (Burgess and others 1998). In the IL-1β knockout mice, injection of LPS was still accompanied by increased serum levels of IL-1α, TNFα, and IL-6. Taken together, these data strongly suggest that IL-1β is not essential for the suppression of food intake following injection of LPS, or that the anorexigenic effect of LPS can be fulfilled by other cytokines that have similar effects on food intake (Fantuzzi and Dinarello 1996). These data are summarized in Table 1.

The functional redundancy of cytokines in mediating LPS-induced anorexia has also been demonstrated in experiments using IL-6 knockout mice. Injection of LPS reduced food intake as it did in wild-type controls (Fattori and others 1994). However, plasma levels of TNFα were higher in the IL-6 knockout mice than in the wild-type mice (Fattori and others 1994; Kozak and others 1998). These data suggest that IL-6 is not essential for suppression of food intake following injection with LPS, or that increased synthesis of TNFα compensates for the absence of IL-6. Thus, the development of anticytokine interventions to improve the nutritional status of the infected host must await clearer definition of which cytokines to target.

Table 1. Effects of LPS or Cytokines on Food Intake of Rats and Mice

	LPS	TNF	IL-1	IL-6
Healthy animals	↓	↓	↓	↓
LPS tolerant	NE	↓	↓	NT
IL-1 knockouts	↓			
IL-6 knockouts	↓			
Leptin deficient	↓			

NOTE: NE = no effect; NT = not tested.

Potential Mechanisms by Which Cytokines Affect Food Intake

Another tack in the development of anticytokine interventions might be to target the mechanism of action by which cytokines suppress food intake. The regulation of food intake is a complex process, involving multiple types of afferent signals that arise with the ingestion, absorption, or subsequent metabolism of nutrients. These signals are integrated at the level of the hypothalamus (see reviews by Bernardis and Bellinger 1996; Blundell and Halford 1994; Levine and Billington 1997; Rowland and others 1996) and result in efferent signals that alter nutrient intake and/or energy expenditure (Levine and Billington 1997). Cytokines have been shown to alter the nature or activity of afferent signals as well as the synthesis or release of several neurotransmitters that are involved in the modulation of feeding behavior (Feleder and others 1998; Gayle and others 1997; van der Meer and others 1995; Yang and others 1999). As shown in Figure 1, bacterial products or cytokines could affect food intake at several physiological levels (Weingarten 1996; Johnson

1998), resulting in reduced meal size or meal frequency (Plata-Salamán 1994). Understanding these endogenous interactions may produce strategies for improving food intake during infection (Bessesen and Faggioni 1998).

Fever

The ingestion, digestion, and assimilation of nutrients produce heat, and Brobeck (1948) postulated that the postprandial rise in total body heat content contributes to the sense of satiety. Therefore, it is possible that fever is a factor in the reduction of food intake during infection. This hypothesis seems all the more plausible since injection of LPS, IL-1α, IL-1β, TNFα, or IL-6 induces both fever and anorexia (Elmquist and others 1997; Kluger and others 1998). However, fever can occur without anorexia (McCarthy and others 1986) and anorexia can occur during infection without fever (Larson and others 1996). It is possible to reduce fever in animals injected with LPS without improving their food intake (Huang and others 1999; McCarthy and others 1984). Thus, fever per se does not explain the suppression of food intake during infection.

Gastric Stasis

Gastric distention and the rate of gastric emptying are known to influence meal size and the interval between meals. It has been proposed that gastric stasis, which often accompanies fever, contributes to the anorexia of infection (van Miert and van Duin 1998). Injection of LPS delays gastric emptying, as does IL-1α (McCarthy and Daun 1992; Daun and McCarthy 1993), IL-1β (Sütõ and others 1996; Coimbra and Plourde 1996), and IL-6 (McCarthy in press) in a dose-dependent fashion. These data are summarized in Table 2. In vitro, IL-1α, IL-1β, and TNFα induced relaxation of gastric muscle strips in a dose-dependent fashion, whereas IL-6 or LPS did not alter contraction of the gastric muscle strips (Montuschi and others 1993; Montuschi and others 1994). These authors concluded that, in vivo, the effects of LPS on gastric motility are mediated by IL-1α, IL-1β and TNF, which act directly to reduce contraction of stomach muscle. This conclusion is supported by the demonstration of IL-1β receptors on rat stomach (Mugridge and others 1991).

Table 2. Effect of LPS or Cytokines on Gastric Function

	Gastric Contraction in vitro	Gastric Emptying in vivo
LPS	NE	↓
IL-1α	↓[a]	↓[b]
IL-1β	↓[a]	↓[b]
IL-6	NE	↓
TNF	↓[a]	?

NOTE: NE = No effect; ? = contradictory data.
a. Dose dependent.
b. Reduced by PG inhibitors.

Others have shown that pretreatment of animals with IRAP will block the development of gastric stasis in animals injected with IL-1β (Sütõ and others 1996; Coimbra and Plourde 1996).

Although gastric stasis frequently occurs with fever and anorexia, delayed gastric emptying may not play an important role in the suppression of food intake during infection. IL-1α and IL-6 can be given at doses that reduce food intake without inducing detectable changes in gastric emptying (McCarthy and Daun 1992; Daun and McCarthy 1993, McCarthy in press). There are conflicting data as to whether TNFα delays gastric emptying, which may reflect differences in the doses injected (McCarthy in press; Patton and others 1987). To date, no one has determined whether administration of agents that increase gastric motility will increase food intake during the acute phase response to infection.

Prostaglandin E2

Prostaglandins (PG), and especially PGE2, play an important role as secondary mediators of gastric function and feeding behavior (Fargeas and others 1984). Exposure to IL-1β, TNF, or LPS will increase the synthesis and release of PGE2 in multiple cell types, and injection of PGE2 will reduce food intake and gastric motility (Stein and others 1994). These findings led to the hypothesis that inhibitors of PG synthesis might be useful in reversing the anorexia of infection (Uehara and others 1990). Pretreatment of animals with ibuprofen or indomethacin, which inhibit PG synthesis, partially blocks the anorexigenic effects of IL-1α

(McCarthy and Daun 1992), IL-1β (Langhans and others 1993; Shimizu and others 1991; Uehara and others 1990), or TNF (McCarthy in press; Mahoney and Tisdale 1989). Pretreatment with ibuprofen or indomethacin will also improve gastric emptying in animals injected with IL-1α (McCarthy and Daun 1992) or IL-1β (Sütõ and others 1996). However, pretreatment with ibuprofen or indomethacin does not improve food intake or gastric emptying in animals injected with LPS or IL-6 (Langhans and others 1993; McCarthy in press). Thus, cytokines mediate LPS-induced anorexia with overlapping, but not identical mechanisms of action; some are PG-dependent, and others are PG-independent. The differential use of PG pathways by different cytokines limits the clinical utility of inhibitors of PG synthesis to improve food intake during infection.

Cholecystokinin

Another approach to unraveling the complex relationship between immunoregulatory cytokines and food intake is to examine the effect of cytokines on other peptides involved in the regulation of food intake or meal size. Cholecystokinin (CCK) is a hormone that is released from the small intestine with feeding. It acts to slow gastric emptying and cause cessation of feeding. Injection of IL-1β (Kurosawa and others 1997) or IL-1α (Daun and McCarthy 1993) will increase plasma levels of CCK. Pretreatment with a CCK-A receptor antagonist will partially block the development of gastric stasis and anorexia in animals injected with IL-1α (Daun and McCarthy 1993). The effects of IL-1β are also partially blocked by a CCK-A receptor antagonist (Kurosawa and others 1997), whereas others have reported that IL-1β potentiates the anorexigenic effect of CCK (Bucinskaite and others 1997). Thus, the interaction of IL-1α/IL-1β and CCK may be a potential target for improving food intake during infection.

Leptin

Another hormone important in the regulation of food intake is leptin. It is released from adipocytes with feeding and acts at the level of the brain to reduce food intake, probably via suppression of neuropeptide Y (NPY), a neuropeptide that stimulates food intake (Wolf 1997). Injection of LPS, IL-1β, or TNFα increases plasma leptin levels and increases mRNA for leptin synthesis in adipocytes (Sarraf and others 1997; Berkowitz and others 1998). However, injection of LPS in leptin-deficient mice (ob/ob) suppresses food intake without inducing an elevation in serum leptin levels; injection of LPS in leptin receptor–deficient mice (db/db) also suppresses food intake (Faggioni and others 1997). Similarly, injection of LPS in IL-1β knockout mice suppresses food intake (Fantuzzi and others 1996) without a concomitant rise in plasma leptin levels (Faggioni and others 1998). These data suggest that neither IL-1β or leptin is essential for the suppression of food intake following injection of LPS. Thus, blocking leptin may not yield the desired results of increasing food intake during infection.

The observation that plasma leptin did not rise after injection of LPS in IL-1β knockout mice suggested that IL-1β is essential for the release of leptin following injection of LPS. Others reported that injection of leptin in IL-1 receptor knockout mice does not reduce food intake, and pretreatment of normal animals with IRAP will inhibit the anorexigenic effect of leptin (Luheshi and others 1999). These data suggest that IL-1β is necessary for the anorexigenic effect of leptin. However, the 2 peptides act via different mechanisms to reduce food intake. Pretreatment of rats with indomethacin will partially block the anorexigenic effects of IL-1β (Uehara and others 1990) but does not block the anorexigenic effect of leptin (Luheshi and others 1999).

Interventions to block leptin as a secondary mediator of anorexia during infection could also prove detrimental to the infected host. The toxic effects of LPS are exaggerated in leptin-deficient mice, and pretreatment with exogenous leptin protects the leptin-deficient mice from the toxic effects of LPS (Faggioni and others 1999). Similarly, the toxic effects of TNFα are exaggerated in leptin-deficient as well as leptin receptor–deficient mice and treatment with exogenous leptin protects the leptin-deficient mice from the toxic effects of TNFα (Takahashi and others 1999). Thus, interactions between cytokines and leptin may extend

beyond the suppression of food intake during infection.

Peripheral versus Central Effects of Cytokines on Food Intake

Given the importance of the brain in the regulation of food intake (Bernardis and Bellinger 1996; Blundell and Halford 1994; Rowland and others 1996), it comes as no surprise that intracranial (IC) injection of LPS, IL-1α, IL-1β, or TNFα will reduce food intake (Fantino and Wieteska 1993; Kent and others 1994; Plata-Salamán and Borkoski 1993). The brain is also capable of making cytokines in response to peripheral or central injection of LPS (Woodroofe 1995). Peripheral injection of LPS results in increased brain levels of mRNA for synthesis of IL-1β and TNFα (Gatti and Bartfai 1993; Laye and others 1994). When LPS or MDP is injected IC, there are increased brain levels of IL-1β and TNFα (Faggioni and others 1995) and mRNA for synthesis of IL-1β and TNFα (Gayle and others 1998; Ilyin and others 1998).

IL-1β

Subsequent work with gene knockouts or receptor-blocking molecules has demonstrated that IL-1β is more important as a mediator of LPS-induced anorexia in the central nervous system than it is in peripheral compartments (Dantzer and others 1998). As previously discussed, intraperitoneal (IP) injection of LPS suppresses food intake in IL-1β knockout mice, probably due to the concomitant release of IL-6 and TNFα that have overlapping suppressive effects on food intake (Fantuzzi and others 1996). Similarly, IP injection of LPS in ICE gene knockout mice suppresses food intake whereas IC injection of LPS does not (Burgess and others 1998). Thus, in the brain, IL-1β may be essential for the reduction in food intake seen after IC injection of LPS.

Whether injected IP or IC, the anorexigenic effects of IL-1β are mediated primarily at the level of the brain. As shown in Table 3, the anorexigenic effects of IL-1β injected IP are blocked by IRAP IP and are partially blocked by IRAP IC (Kent and others 1992; Swiergiel and others 1997). If IL-1β is injected IC, IRAP IC completely blocks its anorexigenic effect (Plata-Salamán and French-Mullen 1992) whereas IP injections of IRAP do not (Kent and others 1992). Similar data were obtained using an antisense nucleotide to derail synthesis of the IL-1 receptor (Sonti and others 1997). Pretreatment with the antisense nucleotide injected IC, but not IP, blocked the anorexigenic effect of IC-injected IL-1β. Taken together, these data clearly demonstrate that IL-1β suppresses food intake via a receptor-mediated direct action in the central nervous system.

Table 3. Effects of Central versus Peripheral IRAP on IL-1β-Induced Anorexia

	IRAP IP	IRAP IC
IL-1β ip	Completely blocked	Partially blocked
IL-1β ic	Not blocked	Completely blocked

IRAP = IL-1 receptor antagonist; IP = intraperitoneal; IC = intracranial.

Like anorexia, gastric stasis can be induced by IC, IP, or intravenous (IV) injection of IL-1β (Sütõ and others 1994), and the gastric stasis induced by IV injection of IL-1β can be blocked by IC or IV injection of IRAP (Sütõ and others 1996; Coimbra and Plourde 1996). Thus, gastric stasis following injection of IL-1β is also centrally mediated through IL-1β receptors. However, the role of PG in mediating the effect of IC versus IP injection of IL-1β on food intake and gastric stasis may differ. Indomethacin injected IP will partially block the gastric effects of IV- or IC-injected IL-1β (Sütõ and others 1994; Sütõ and others 1996). Similarly, the anorexigenic effects of IC-injected IL-1β are partially blocked by IP, but not IC, injection of ibuprofen (Shimizu and others 1991). Thus, PG synthesis may play an important role in mediating the peripheral, but not the central, effects of IL-1β on food intake and gastric stasis.

Leptin

IL-1β also appears to be important in mediating the anorexigenic effects of leptin at the level of the brain. Central injection of IRAP will inhibit the reduction in food intake seen after IC or IP injection of leptin

(Luheshi and others 1999). Neither IC nor IP injection of leptin suppresses food intake in IL-1 receptor knockout mice (Luheshi and others 1999). These data indicate that the effects of leptin in the brain are also mediated by IL-1β.

Leptin is thought to suppress food intake by suppressing expression or activity of NPY in the brain (Wolf 1997). Central injection of NPY will block the anorexic effect of IL-1β if injected concomitantly with IL-1β, or reverse the anorexia if injected after IL-1β (Sonti and others 1996). Others have suggested that IL-1β could block the release of NPY in the brain (McCarthy and others 1995) or decrease mRNA for NPY synthesis in the brain (Gayle and others 1997). To date, no one has examined if interventions to increase NPY activity increase food intake during the acute phase response to infection.

Connecting the Peripheral and Central Effects of Cytokines

One question being hotly debated in the literature is how LPS or cytokines present in the periphery might exert their anorexigenic effects at the level of the brain. One theory is that circulating (humoral) LPS or cytokines enter the brain in areas where the blood brain barrier is more permeable (Blatteis and Sehic 1997; Elmquist and others 1997). There is evidence that IL-1α, IL-1β, IL-6, TNFα, and leptin enter the brain via a carrier-mediated transport mechanism within the vascular endothelium of the brain (Banks and others 1995; Banks and others 1996). Alternatively, it has been suggested that circulating LPS or cytokines stimulate production of cytokines or PG by meningeal macrophages or perivascular microglia, which could lead to the synthesis and release of cytokines in the brain (Elmquist and others 1997; van Dam and others 1992).

Vagal Connections

The 2nd theory is that the vagus nerve serves as the connecting signal between the brain and periphery (Maier and others 1998). There is evidence that IV administration of IL-1β increases mass activity of the gastric vagal afferent nerve (Bucinskaite and others 1997; Kurosawa and others 1997). It has also been demonstrated that neurons in an area of the brain stem that serves as a relay between sensory information from the vagus nerve and the central autonomic nervous system, the nucleus of the solitary tract (NTS), express IL-1 receptors. Intravenous administration of IL-1β activates these sensory neurons, and the activation was matched by an increase in discharge activity of gastric vagal afferent nerve (Ek and others 1998). The increased activity of the gastric afferent vagal nerve could be partially blocked by pretreatment with indomethacin, an inhibitor of PG synthesis. This finding is congruent with previous reports that pretreatment with ibuprofen and indomethacin partially improves food intake and gastric emptying in animals injected with IL-1α or IL-1β (McCarthy and Daun 1992; Uehara and others 1990). It would be interesting to examine the direct effects of TNFα and IL-6 on vagal afferent nerve activity given that these 2 cytokines appear to have less of an effect on gastric motility than does IL-1α/IL-1β (McCarthy in press).

One group of investigators has shown that the anorexigenic effects of IP-injected LPS or IL-1β are reduced when the vagus nerve is severed below the level of the diaphragm (Bret-Dibat and others 1995). In contrast, another group of investigators has shown that selective severing of the afferent branches of the vagus nerve below the level of the diaphragm does not prevent the anorectic effects of IP-injected IL-1β or LPS (Schwartz and others 1997). These authors argue that the humoral effects of cytokines are more important than vagal effects in activating brain mechanisms that suppress food intake during infection. This argument does not explain the observation that following IP injection of LPS in vagotomized animals, there is no increase in brain levels of IL-1β mRNA in spite of elevated plasma IL-1β (Laye and others 1995). Similarly, vagotomy blocked the increase in brain IL-1β mRNA but did not affect IL-1β mRNA levels in the liver (Hansen and others 1998). These data argue that the vagus nerve is important in transmitting cytokine signals to the brain.

Another argument put forth to support the role of the vagus nerve in cytokine-to-brain communication is the suggestion that higher doses of IL-1β may be needed to induce anorexia in vagotomized animals

than in intact animals (Bluthé and others 1996). These authors argue that the higher dose injected IP might exceed the ability of the liver, which is richly enervated by the vagus nerve, to clear IL-1β from the portal circulation as it is absorbed. Thus, LPS or cytokines exiting the portal circulation (humoral) could exert anorexigenic effect elsewhere in the body, for example, the brain or other branches of the vagus nerve (Maier and others 1998). However, others have shown that severing of the hepatic branches of the vagal nerve does not alter the anorectic effect of IP-injected LPS or IL-1β (Porter, Hrupka, and others 1998) or of IV-infused IL-1α (Laviano and others 1995). Although these data suggest that LPS, IL-1β, or IL-1α do not act primarily at the level of the liver to suppress food intake, these data do not rule out a contribution of other afferent branches of the vagus nerve in mediating anorexia during infection. These data bring us back to the question of vagal versus humoral communication between the immune system and the brain. As shown in Figure 1, a combination of communication routes is a more likely explanation. This again makes it difficult to know how to target the effects of cytokines to improve food intake during infection.

Conclusions

Given the correlation between malnutrition and poor clinical outcomes in acutely ill persons (Giner and others 1996; Verity 1996), inhibition of cytokine activity may be one approach to improving the nutritional status of infected patients (Souba 1994; Haslett 1998). However, the role of cytokines in the anorexia of infection is complex, with overlapping and synergistic effects on food intake and factors known to affect food intake. Thus, anticytokine approaches to improving the nutritional intake of infected patients must await clearer definition of which cytokines or secondary mediators to target.

This line of investigation also is confounded by evidence that the relative importance of any one cytokine is not the same in the peripheral and central compartments. Work with leptin, NPY, and other peptides and neurotransmitters (Feleder and others 1998; Yang and others 1999) suggests that multiple parallel central pathways are involved in the regulation of food intake (Levine and Billington 1997) and may be engaged by cytokines (Plata-Salamán 1998a; Weingarten 1996). It is tempting to speculate that the overlap and divergence of cytokine effects on food intake may allow for fine tuning of the host response to infection in light of the nature of the infectious agent (Gayle and others 1998) or the prior nutritional status of the host (Plata-Salamán and others 1997; Souba 1994). Intuitively, this may explain in part why obese mice, which are leptin deficient (ob/ob), or obese rats, which are leptin receptor deficient (fa/fa), demonstrate greater suppression in food intake than their lean litter mates when injected with LPS (Faggioni and others 1997) or IL-1β (Plata-Salamán and others 1997).

Because cytokines mediate many aspects of the acute phase response to infection, caution must be taken not to cancel out the positive, adaptive aspects of cytokine activity. For example, mortality following infection with *Listeria monocytogenes* is increased in IL-6 knockout mice (Kopf and others 1994) and TNF receptor knockout mice (Rothe and others 1993). In contrast, susceptibility to *Listeria monocytogenes* is not different in IL-1β knockout mice compared to their wild-type controls (Zheng and others 1995).

Most important, we need evidence that feeding alters the course of infection or improves nutritional status during infection (Moldawer and Copeland 1998). At this point, we do not know if the suppression in food intake plays an adaptive role in host recovery from infection (Gabay and Kushner 1999; Hart 1988; Long 1996; Murray and Murray 1979; Wing and Young 1980). Questions about which cytokine or cytokine effect to manipulate to improve food intake during infection may be premature without answers to this more basic question.

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