Infection and anorexia

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Whereas anorexia is a common behavioral response to infectious diseases, the reasons for and mechanisms behind this observation are still unknown. When it is considered on an evolutionary basis, the organism must have net benefits from anorexia.

The first response to infection is the development of acute phase response (APR). The APR is triggered by microbial products and characterized by production of several cytokines known to induce anorexia. Several microbial products and cytokines reduce food intake after parenteral administration, suggesting a role of these substances in the anorexia during infection. Locally released cytokines may inhibit feeding by activating peripheral sensory fibers directly or indirectly, and without a concomitant increase in circulating cytokines. However, the final center for appetite or eating is the central nervous system (CNS). Thus, these peripheral signals must reach and interact with brain regions that control appetite. In addition, a direct action of cytokines and microbial products on the CNS is presumably involved in the anorexia during infection.

Key words: *infection, anorexia.*

It is common knowledge that nutrient intake decreases during infectious diseases. Of the factors that may underlie the reduction in nutrient intake in patients with infection, anorexia is usually the most prominent. Anorexia is a common behavioral response to upper respiratory infections, and this response has entered the folklore as advice to "feed a cold and starve a fever". In association with fever, decreased food and water consumption are the most common signs of infection[1,2]. Whereas it is well known that infection decreases appetite, the reasons for and mechanisms behind this observation are still unknown. It is well accepted that protein-energy malnutrition is a common cause of immunodeficiency and results in an increased susceptibility to infections. However, most clinical observations show a paradoxically lower prevalence of infection in anorexia nervosa patients[3,4].

The decreased survival time and increased mortality that force-feeding causes in experimentally infected laboratory animals reflects the short-term beneficial effect of anorexia during infection. Murray and Murray[5] showed that gavage feeding increased the mortality and shortened survival time in mice acutely infected with Listeria monocytogenes. In another study[6], mice were infected with a normally lethal dose of the bacterium Listeria monocytogenes. Mice that had previously been starved for 72 hours had a 5% mortality rate compared to the death of 95% of fed mice, 24 hours' post-infection. Thus, these results convincingly show that eliminating food intake in response to bacterial (and other) infections has definite survival benefits for the host.

Despite being beneficial in the beginning, chronic anorexia compromises host defense, delays recovery, and is ultimately deleterious.

Acute Phase Response

The acute phase response (APR) is a general term for a variety of systemic host reactions to infectious agents, physical trauma, and later stages of neoplastic disease. The anorexia of infection is part of the host's APR, which is characterized by alterations in immune,

endocrine, metabolic, and neural functions (Table I)[2,7,8]. All of these responses are postulated to be of substantial benefit to the host. Experimentally, the APR is often produced by the infusion of pathogens, such as bacteria, viruses or fungi, which are detected as foreign by the host.

Table I. Examples of the Multiple Processes of the Acute Phase Response[2]

Metabolic Responses
Fever
Adipsia
Gastroparesis
Plasma trace metal alterations
Lipid metabolism
Immune Responses
Leukocytosis
Hematopoiesis
Altered activity of natural killer cells
Cytokine production and regulation
Synthesis of acute phase proteins
Behavioral Responses
Sleep alterations
Decreased social exploration
Anorexia
Hyperalgesia
Endocrine Responses
Hypothalamic-pituitary-adrenal activation
Hyperinsulinemia
Hypoglycemia
Other Neuronal Responses
Sympathetic activation

The APR is triggered by microbial products such as bacterial cell wall compounds (e.g., lipopolysaccharides [LPS] and muramyl dipeptide [MDP]), microbial nucleic acids (e.g., bacterial DNA and viral double-stranded RNA), and viral glycoproteins. A number of endogenous mediators (tumor necrosis factor-α [TNF-α], interleukin-1 (IL-1), IL-6, IL-8, interferon-α, and interferon-γ) are currently known to induce anorexia as well as other components of the APR[2,9].

In the 1980s, cachectin, supposed to mediate the wasting and hypertriacylglycerolemia, was isolated from experimental animals infected with Trypanosoma cruzi[10]. Subsequently, it has been found that DNA sequence of cachectin was identical to that coding for TNF[11] that had been previously isolated from the serum of animals injected with bacterial endotoxins and was able to produce necrosis of transplanted tumors in animals[12].

Cachectin reduces the activity of lipoprotein lipase (LPL) and produces anorexia, weight loss, and fever when injected into experimental animals[11], and provokes very similar metabolic and hemodynamic changes to those observed during bacterial sepsis that could be blocked by the use of specific antisera or monoclonal antibodies[13,14].

While many aspects of the APR 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. The aim is to inhibit the proliferation and spread of the infectious agent.

Although short-term anorexia may be beneficial for the host, the results of long-term decrease in nutrient intake are wasting syndrome and cachexia, which enhances susceptibility to infections, exacerbates their harmful effects, and influences their outcome.

Why Does Infection Induce Anorexia?

When it is considered on an evolutionary basis, the organism must have net benefits from anorexia[15]. Anorexia may represent a behavioral adaptation that modulates the immune system to help combat bacterial infection, a trait that may have emerged during prehistoric times when bacterial pathogens posed a greater threat[16]. Anorexia may be an adaptive behavioral modifier that shifts T helper balance away from the T helper 2 bias and compromises the fight against bacterial pathogens[16].

If anorexia/cachexia were on the whole harmful, it would be incredible that over the course of several hundred million years, the effects of inflammatory cytokines on appetite regulatory centers would be retained.

The suppression of hunger eliminates the need to find food, thus saving energy and reducing the heat loss from the body that would be lost by convection. In addition, anorexia reduces the availability of food-derived micronutrients such as iron and zinc that are essential for the growth of pathogenic microorganisms and enhancement of immune function by enhancing monocyte and macrophage activity[2,15,17]. There is also evidence that anorexia protects the host by limiting the potentially detrimental metabolic effects of the APR[15]. Finally, anorexia leads to premature death of infected cells. This

conclusion was based on historical data from prisons and concentration camps, and with experimental animal data[18].

Apoptosis, or cell suicide, is becoming recognized as a useful defense against intracellular parasites, and nutrient restriction promotes apoptosis. Whether an infectious process is rapid or insidious, an appropriate defense is apoptosis of infected cells as early as possible. When nutritional resources are limited, tissues undergo atrophy via apoptosis and/or cell size reduction. Cells with limited proliferative capacity such as neurons and cardiac myocytes require especially strong inputs to undergo apoptosis[15]. It has been shown that functionally impaired cells preferentially undergo apoptosis and that this tendency is greatly increased during nutritional stress[19]. Another factor for a cell's decision to live or die is whether it has become infected[20]. It is of critical importance for infected cells to kill themselves rapidly before they can promote the spread of pathogens to other cells[21]. It is not surprising that intracellular pathogens (primarily viruses) have been found to make anti-apoptotic signals so that cell death is delayed until the pathogen is ready[15]. Cell death and subsequent phagocytosis of apoptotic cells represents an important regulatory mechanism that has been conserved through evolution[22].

How Does Infection Induce Anorexia?

Microbial products

Experimental work on the neurobiological basis of anorexia during infection has focused on the examination of neural, physiologic, and behavioral changes in rodent models after systemic administration of bacterial endotoxins and cytokines as potential mediators of the APR. Several microbial products and cytokines reduce food intake after parenteral administration, suggesting a role of these substances in the anorexia during infection.

Lipopolysaccharides (LPS) and MDP both reduce food intake after parenteral administration in animals. Appetite suppression following LPS usually appears four hours' post-administration, with the effect sometimes lasting up to 24 hours. The anorectic effect of peripherally administered LPS and MDP is primarily characterized by a reduction in meal number, with no significant effect on meal size, and does not depend on a concomitant inhibition of water intake or gastric emptying[23,24]. There is no obvious tolerance with repetitive injection of MDP or with continuous administration of LPS and MDP[25]. Peripherally ineffective LPS and MDP dosages reduce food intake after intraventricular infusion in rats, showing that LPS and MDP can act directly in the central nervous system (CNS) to inhibit feeding[26,27]. It is likely that microbial nucleic acids and viral glycoproteins also suppress feeding[17]. Viral dsRNA is released from dying, virus-infected cells and triggers the production and release of cytokines[17,28]. Viral glycoproteins are also potent inducers of the APR, which is relevant for retro- and DNA viruses that do not synthesize dsRNA[29].

Cytokines

New knowledge of the effects of cytokines in human beings now helps to explain some of the symptoms (e.g., fever, anorexia, malaise, chills, headache, and muscle aches and pains) of infectious diseases. Components of bacteria (both LPS and MDP) increase levels of several cytokines believed to mediate anorexia, including TNF-α, IL-1β[24,30] and interferons[31]. Peripherally administered cytokines, which inhibit feeding similar to LPS or MDP, usually reduce meal number and meal size[32,33] and do not inhibit water intake[34]. These discrepancies suggest that the interactions between bacterial products and cytokines are complex.

Cytokine production in response to microbial products is activated through the surface protein CD14 and other binding sites including toll-like receptors[35-37]. The released cytokines stimulate non-specific and specific immune reactions and cause CNS-mediated effects and an activation of the hypothalamic-pituitary-adrenal axis[17]. They might inhibit feeding through neural and humoral pathways activated by their peripheral actions.

Several cytokines, including TNF-α, IL-1, IL-2, IL-6, IL-8, and interferons inhibit feeding after parenteral administration, suggesting a role of these substances in the anorexia during infection[38-40]. The first cytokine that was held responsible for causing anorexia was TNF. Further studies showed that the action of TNF can only be understood in the context of simultaneous presence of other cytokines[9]. More direct evidence is provided by the observations

that cachexia in experimental animal models can be mitigated by administration of specific antagonists of cytokines[9]. Indeed, a number of viruses can subvert the action of TNF-α (and other cytokines) through the production of soluble TNF receptors or by inhibiting TNF-induced apoptosis of the infected cell[41,42].

Interleukin-1 shares many of the characteristics of TNF and can also produce anorexia, hyper triacylglycerolemia, and stimulate hepatic fatty acid synthesis[43,44]. In addition, IL-1 reduces LPL activity and produces lipolysis[43,45]. IL-1β is the best known member of this cytokine family that may act in the brain, where it has also been shown to mediate LPS-induced fever and anorexia[46]. Also, IL-1β-converting enzyme-deficient mice resist the anorectic effect of intra cerebroventricularly, but not intraperitoneally, administered LPS, suggesting that IL-1β is crucial for the anorexia in response to central but not peripheral LPS administration[47]. IFN-γ knockout mice are also insensitive to the anorectic effect of LPS, suggesting that IFN-γ is necessary for the suppression of feeding by LPS[48].

Whereas chronic peripheral administration of IL-1 and TNF-α is normally accompanied by tolerance of their anorectic effects[49], continuous central administration or repetitive intraperitoneal injections of IL-1β, given when the anorectic effect of the previous injection has subsided, does not cause tolerance[50,51]. This effect is interesting because cytokines may be released in a cyclic fashion during several diseases.

Additionally, IL-6, IL-8, interferons and several other cytokines may contribute to reduced food intake during infection[52-54]. Another mediator responsible from anorexia is leptin. Microbial products and cytokines dose-dependently increase leptin expression in adipose tissue, which is closely related to reduced food intake[55,56]. However, the action of leptin on appetite suppression and fever are dependent on brain IL-1β[30]. Taken together, these data suggest that leptin is not necessary for anorexia during infection, but may contribute in several ways; further studies are necessary to critically examine these interactions[17]. It has also been shown that α-melanocyte-stimulating hormone, stimulated by LPS, may enhance the anorexia during infection[57].

Cytokines modulate gastric motility and emptying that can inhibit feeding. Prostaglandins (PG), and especially PGE2, play an important role as secondary mediators of gastric function and feeding behavior. 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[11]. Cytokines may also induce the release of hormones that are physiologic satiety signals including cholecystokinin, glucagon, insulin, and leptin (Fig. 1)[58].

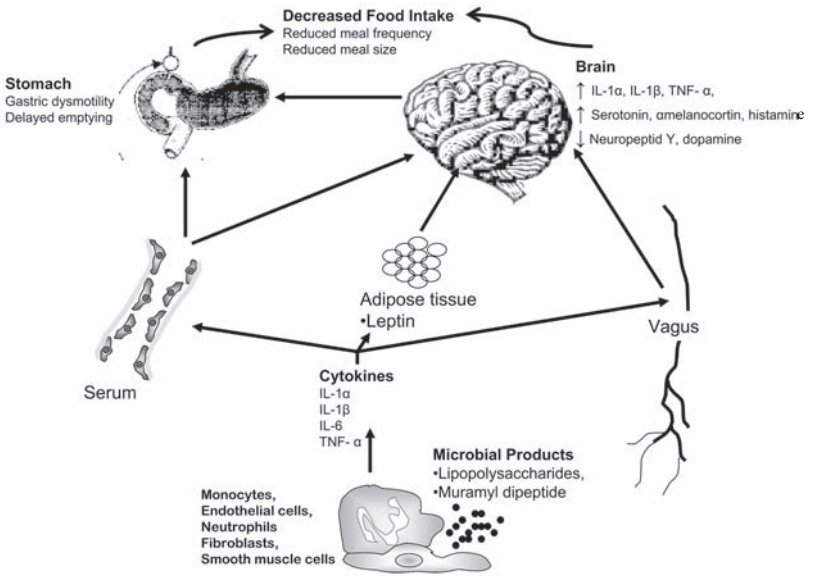

Fig. 1. Pathways in the anorexia during infection.

Site of Action

Microbial products are mainly released and cytokines are produced in the periphery during most infections. Locally released cytokines may inhibit feeding by activating peripheral sensory fibers directly or indirectly, and without a concomitant increase in circulating cytokines[46]. Sub-diaphragmatic vagal afferents in rats appear to be responsive to peripheral IL-1β because intravenous administration of IL-1β increased multiunit activity in gastric and hepatic branch vagal afferent fibers[59]. Visceral afferent nerves are not necessary for the anorectic effects of intraperitoneally injected LPS, MDP, and IL-1β. This conclusion does not exclude the possibility that afferent neural signals play some as yet unidentified role in the anorexia during infection[17].

Although peripheral and brain mechanisms are involved in cytokine-induced anorexia, the net behavioral response results from signaling to a final pathway for appetite or eating control that depends on brain mechanisms (i.e., conscious and decision-making processes)[24,58]. Thus, these peripheral signals must reach and interact with brain regions that control appetite. The hypothalamic feeding-associated sites are targets for cytokine action. In addition, a direct action of cytokines and microbial products on the CNS is presumably involved in the anorexia during infection. Intracerebroventricular administration of cytokines and bacterial products at doses that yield pathophysiologically relevant concentrations in the cerebrospinal fluid reduces food intake[26,40]. Brain administration of a cytokine requires 500- to 1000-fold lower doses to induce anorexia compared with the doses required when using various peripheral routes of administration[40,58].

Vagal afferents have been implicated in the anorexia during infection because subdiaphragmatic vagotomy attenuated intraperitoneally administered LPS and IL-1β-induced suppression of instrumental responses to obtain food in mice[60]. Subdiaphragmatic vagotomy, however, did not block the effects of subcutaneously or intravenously administered IL-1β, and systemic capsaicin pretreatment failed to block the effects of intraperitoneally administered IL-1β and LPS on food-motivated behavior[33].

The effects of peripherally and centrally administered cytokines and bacterial products on anorexia are different. Intraperitoneally administered bacterial products (LPS and MDP) selectively reduce meal frequency[23]. While intraperitoneally injected IL-1β and TNF-α affect meal size and meal frequency[32,34,49], in tracerebroventricularly administered cytokines primarily reduce meal size[27]. Tolerance to centrally and peripherally administered LPS and cytokines is also different[25,49-51]. IL-1 receptor antibodies administered intracerebr oventricularly inhibit the anorectic effect of intracerebroventricularly injected LPS, but not that of intraperitoneal LPS injection[61]. Likewise, the anorectic effect of intra cerebroventricularly, but not intraperitoneally, injected LPS is blunted in IL-1β converting enzyme-deficient mice[47]. These findings indicate that IL-1β is necessary for the effect of centrally but not peripherally administered LPS. Finally, it has been shown that the central anorectic effect of LPS does not depend on TNF-α mediated pathways[62,63].

Once released extracellularly from macrophages and monocytes, IL-1 and TNF are transported into the circulation. However, due to these cytokines being large hydrophilic peptides, they are regarded as not having the ability to cross the blood brain barrier (BBB). Cytokines can reach CNS cytokine receptors through active or passive transport mechanisms (retrograde axonal cytokine transport and peripheral-to-brain communication via afferent neural-fiber signaling)[57], through circumventricular organs (which lack a BBB)[64], or they can act through receptors on endothelial cells of the brain vasculature and stimulate the release of subsequent mediators such as eicosanoids[65] and PG production via the enzyme cyclooxygenase 2 (COX-2)[66]. BBB may also regulate the passage of cytokines into the CNS because bacterial products and cytokines may increase BBB permeability[67,68]. De novo CNS cytokine synthesis may also occur in response to peripheral infections, but its role in the accompanying anorexia is still open to discussion[17,58].

There are also several central neurochemicals involved in the normal control of feeding, such as serotonin, dopamine, histamine, corticotropin releasing factor, neuropeptide Y, and a melanocyte-stimulating hormone. Reciprocal, synergistic, and antagonistic interactions between various pleiotropic cytokines, and between cytokines and neurochemicals, form

a complex network that mediates the anorexia during infection[17]. Cytokines act in a cascade pattern, that is, a cytokine can induce the production and release of other cytokines, including in the CNS, and cytokine– cytokine interactions induce anorexia with additive or synergistic activities[40,58,69].

The PGs activate neurons producing serotonin[70], a known anorexigenic transmitter[71,72], which in turn has recently been shown to stimulate melanocortin signaling[73]. Thus, the signaling cascade set off by pathogenic bacteria ultimately results in activation of the central anorexigenic system. Change of CNS concentrations of dopamine, serotonin and histamine during infections may also contribute to the development of anorexia[17].

Intracerebroventricularly injected neuropeptide Y (NPY), synthesis of which can be reduced by intracerebroventricularly infused IL-1β[69], can prevent or reverse intracerebroventricular IL-1β- and IFN-α-induced anorexia[74,75].

Treatment

As the anorexia of infection is initially beneficial for the host, sick individuals should not be forced to eat unless in poor condition. Nutritional support is usually recommended in patients who do not resume sufficient oral intake within 7 to 10 days after disease onset[76].

Although attempts to block the anorexia during disease by targeting specific cytokines have yielded mixed results, cytokine-induced anorexia can be blocked with the appropriate receptor antagonists, monoclonal antibodies, and other cytokine inhibitors supporting specificity of cytokine action on feeding[77,78]. The difficulties in determining the right time of application and the appropriate dosage of a potential cytokine antagonist probably also contribute to some of the negative results.

Pentoxifylline, which is a cytokine inhibitor (in particular TNF-α), has been used successfully in the treatment of acute and chronic infection-induced anorexia[31]. Substances that block common key steps in cytokine synthesis or cytokine action, or inhibitors of eicosanoid synthesis, are more promising than attempts to antagonize specific cytokines. Indomethacin (a prostaglandin synthesis inhibitor), ibuprofen or paracetamol have been used to abolish the anorectic effect of IL-1[2]. It has also been shown that COX-2 inhibition during LPS-induced inflammation results in preserved food intake and maintenance of body weight, whereas COX-1 inhibition results in augmented and prolonged weight loss[79].

Targeting the neurochemical mediation of the anorexia during infection may even be more efficient. Future studies should research these neurochemical mechanisms and the cytokine actions at the BBB[17].

Conclusion

The mechanisms of the anorexia during infection are not yet fully understood, but are presumably based on interactions between various pleiotropic cytokines as well as between cytokines and other humoral mediators of the effects of microbial products. Present data suggest that the anorexia of infection is ultimately due to a modulation of central neurochemical mechanisms that control normal eating. Peripherally produced cytokines modulate these neurochemical mechanisms through a direct action on the brain and perhaps through pathways activated by their peripheral actions. The exact contributions of these mechanisms to the anorexia during infection need to be established.

REFERENCES

1. Eccles R. Understanding the symptoms of the common cold and influenza. Lancet Infect Dis 2005; 5: 718-725.
2. Exton MS. Infection-induced anorexia: active host defence strategy. Appetite 1997; 29: 369-383.
3. Bowers TK, Eckert E. Leukopenia in anorexia nervosa: lack of increased risk of infections. Arch Intern Med 1978; 138: 1520-1523.
4. Marcus A. The immune system in eating disorders: an overview. Nutrition 1997; 13: 853-862.
5. Murray MJ, Murray AB. Anorexia of infection as a mechanism of host defense. Am J Clin Nutr 1979; 32: 593-596.
6. Wing EJ, Young JB. Acute starvation protects mice against Listeria monocytogenes. Infect Immun 1980; 28: 771-776.
7. Brady LS, Lynn AB, Herkenham M, et al. Systemic interleukin-1 induces early and late patterns of c-fos mRNA expression in brain. J Neurosci 1994; 14: 4951-4964.
8. Hart BL. Biological basis of the behavior of sick animals. Neurosci Biobehav Rev 1988; 12: 123-127.
9. Matthys P, Billiau A. Cytokines and cachexia. Nutrition 1997; 13: 763-770.

10. Beutler B, Cerami A. Cachectin and tumor necrosis factor as two sides of the same biological coin. Nature 1986; 320: 584-588.
11. Tracey KJ, Lowry SF, Cerami A. Cachectin: a hormone that triggers acute shock and chronic cachexia. J Infect Dis 1988; 157: 413-420.
12. Old LJ. Tumor necrosis factor (TNF). Science 1985; 230: 630-632.
13. Beutler B, Milsark IW, Cerami AC. Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effects of endotoxin. Science 1985; 229: 869-871.
14. Tracey KJ, Hesse DG, Manogue KR, et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteremia. Nature 1987; 330: 662-664.
15. LeGrand EK. Why infection-induced anorexia? The case for enhanced apoptosis of infected cells. Med Hypotheses 2000; 54: 597–602.
16. Bazar KA, Yun AJ, Lee PY. ''Starve a fever and feed a cold'': feeding and anorexia may be adaptive behavioral modulators of autonomic and T helper balance. Med Hypotheses 2005; 64: 1080-1084.
17. Langhans W. Anorexia of infection: current prospects. Nutrition 2000; 16: 996-1005.
18. Murray J, Murray A, Murray N. Anorexia: sentinel of host defense? Perspect Biol Med 1978; 22: 134-142.
19. Grasl-Kraupp B, Bursch W, Ruttkay-Nedecky B, Wagner A, Lauer B, Schulte-Hermann R. Food restriction eliminates preneoplastic cells through apoptosis and antagonizes carcinogenesis in rat liver. Proc Natl Acad Sci USA 1994; 91: 9995-9999.
20. Williams GT. Programmed cell death: a fundamental protective response to pathogens. Trends Microbiol 1994; 2: 463-464.
21. Legrand EK. Implications of early apoptosis of infected cells as an important host defense. Med Hypotheses 2000; 54: 597-602.
22. Giles KM, Hart SP, Haslett C, Rossi AG, Dransfield I. An appetite for apoptotic cells? Controversies and challenges. Br J Haematol 2000; 109: 1-12.
23. Langhans W. Bacterial products and the control of ingestive behavior: clinical implications. Nutrition 1996; 12: 303-315.
24. Schwartz GJ. Neural–immune gut–brain communication in the anorexia of disease. Nutrition 2002; 18: 528-533.
25. Kent S, Bret-Dibat JL, Kelley KW, Dantzer R. Mechanisms of sickness-induced decreases in food-motivated behavior. Neurosci Biobehav Rev 1996; 20: 171-175.
26. Gayle D, Ilyin SE, Flynn MC, Plata-Salaman CR. Lipopolysaccharide (LPS)-, and muramyl dipeptide (MDP)-induced anorexia during refeeding following acute fasting: characterization of brain cytokine and neuropeptide systems mRNAs. Brain Res 1998; 795: 77-86.
27. Plata-Salaman CR, Borkoski JP. Centrally administered bacterial lipopolysaccharide depresses feeding in rats. Pharmacol Biochem Behav 1993; 46: 787-791.
28. Majde JA, Guha-Thakurta N, Chen Z, Bredow S, Krueger JM. Spontaneous release of stable viral double-stranded RNA into the extracellular medium by influenza virus-infected MDCK epithelial cells: implications for the viral acute phase response. Arch Virol 1998; 143: 2371-2380.
29. Ankel H, Westra DF, Welling WS, Lebon P. Induction of interferon-alpha by glycoprotein D of herpes simplex virus: a possible role of chemokine receptors. Virology 1998; 251: 317-326.
30. Sachot C, Poole S, Luheshi GN. Circulating leptin mediates lipopolysaccharide-induced anorexia and fever in rats. J Physiol 2004; 561: 263-272.
31. Broberger C. Brain regulation of food intake and appetite: molecules and networks. J Int Med 2005; 258: 301-327.
32. Debonis D, Meguid MM, Laviano A, Yang ZJ, Gleason JR. Temporal changes in meal number and meal size relationship in response to rHu IL-1 alpha. Neuroreport 1995; 6: 752-756.
33. Bret-Dibat JL, Creminon C, Couraud JY, et al. Systemic capsaicin pretreatment fails to block the decrease in food-motivated behavior induced by lipopolysaccharide and interleukin-1 beta. Brain Res Bull 1997; 42: 443-449.
34. Langhans W, Balkowski G, Savoldelli D. Further characterization of the feeding responses to interleukin-1 and tumor necrosis factor. In: Lehnert H, Murison R, Weiner H, Hellhammer D, Beyer J (eds). Endocrine and Nutritional Control of Basic Biological Functions. Seattle: Hogrefe & Huber; 1992: 135.
35. Malhotra R, Bird MI. L-selectin: a novel receptor for lipopolysaccharide and its potential role in bacterial sepsis. Bioessays 1997; 19: 919-923.
36. Rietschel ET, Schletter J, Weidemann B, et al. Lipopolysaccharide and peptidoglycan: CD14-dependent bacterial inducers of inflammation. Microb Drug Resist 1998; 4: 37-44.
37. Yang RB, Mark MR, Gray A, et al. Toll-like receptor-2 mediates lipopolysaccharide-induced cellular signalling. Nature 1998; 395: 284-288.
38. Plata-Salaman CR. Anorexia during acute and chronic disease. Nutrition 1996; 2: 69-78.
39. Langhans W, Hrupka B. Interleukins and tumor necrosis factor as inhibitors of food intake. Neuropeptides 1999; 33: 415-424.
40. Sonti G, Ilyin SE, Plata-Salaman CR. Anorexia induced by cytokine interactions at pathophysiological concentrations. Am J Physiol 1996; 270: R1394-1402.
41. Spriggs MK. One step ahead of the game: viral immunomodulatory molecules. Annu Rev Immunol 1996; 14: 101-130.
42. Ploegh HL. Viral strategies of immune evasion. Science 1998; 280: 248–253.
43. Feingold KR, Soued M, Serio MK, et al. Multiple cytokines stimulate hepatic lipid synthesis in vivo. Endocrinology 1989; 125: 267-274.
44. Hellerstein MK, Meydani SN, Meydani M, Wu K, Dinarello CA. Interleukin-1 induced anorexia in the rat. Influence of prostaglandins. J Clin Invest 1989; 84: 228-235.

45. Grunfeld C, Feingold KR. Metabolic disturbances and wasting in the acquired immunodeficiency syndrome. N Engl J Med 1992; 327: 329-337.

46. Miller AJ, Hopkins SJ, Luheshi GN. Sites of action of IL-1 in the development of fever and cytokine responses to tissue inflammation in the rat. Br J Pharmacol 1997; 20: 274-279.

47. Burgess W, Gheusi G, Yao JH, et al. Interleukin-1 beta-converting enzyme deficient mice resist central but not systemic endotoxin-induced anorexia. Am J Physiol 1998; 274: R1829-1833.

48. Arsenijevic D, Garcia I, Vesin C, et al. Differential roles of tumor necrosis factor-alpha and interferon-gamma in mouse hypermetabolic and anorectic responses induced by LPS. Eur Cytokine Netw 2000; 11: 662-668.

49. Langhans W, Savoldelli D, Weingarten S. Comparison of the feeding responses to bacterial lipopolysaccharide and interleukin-1 beta. Physiol Behav 1993; 53: 643-649.

50. Weingarten S, Savoldelli D, Langhans W. Enhancement or loss of the hypophagic effect of interleukin-1 upon chronic administration. Physiol Behav 1992; 52: 831-837.

51. Finck BN, Johnson RW. Anorexia, weight loss and increased plasma interleukin-6 caused by chronic intracerebroventricular infusion of interleukin-1 beta in the rat. Brain Res 1997; 761: 333-337.

52. van Lettow M, van der Meer JW, West CE, van Crevel R, Semba RD. Interleukin-6 and human immunodeficiency virus load, but not plasma leptin concentration, predict anorexia and wasting in adults with pulmonary tuberculosis in Malawi. J Clin Endocrinol Metab 2005; 90: 4771-4776.

53. Plata-Salaman CR. Cytokines and feeding. Int J Obes Relat Metab Disord 2001; 25(Suppl): S48-52.

54. Arsenijevic D, Girardier L, Seydoux J, Chang HR, Dulloo AG. Altered energy balance and cytokine gene expression in a murine model of chronic infection with Toxoplasma gondii. Am J Physiol 1997; 272: E908-917.

55. Grunfeld C, Zhao C, Fuller J, et al. Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters - a role for leptin in the anorexia of infection. J Clin Invest 1996; 97: 2152-2157.

56. Sarraf P, Frederich RC, Turner EM, et al. Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. J Exp Med 1997; 85: 71-75.

57. Huang QH, Hruby VJ, Tatro JB. Role of central melanocortins in endotoxin induced anorexia. Am J Physiol 1999; 276: R864-871.

58. Plata-Salaman CR. Central nervous system mechanisms contributing to the cachexia–anorexia syndrome. Nutrition 2000; 6: 1009-1012.

59. Kurosawa M, Uvnas-Moberg K, Miyasaka K, Lundeberg T. Interleukin-1 increases activity of the gastric vagal afferent nerve partly via stimulation of type A CCK receptor in anesthetized rats. J Auton Nerv Syst 1997; 62: 72-78.

60. Bret-Dibat JL, Bluthe RM, Kent S, Kelley KW, Dantzer R. Lipopolysaccharide and interleukin-1 depress food-motivated behavior in mice by a vagal-mediated mechanism. Brain Behav Immun 1995; 9: 242-246.

61. Bluthe RM, Dantzer R, Kelley KW. Effects of interleukin-1 receptor antagonist on the behavioral effects of lipopolysaccharide in rat. Brain Res 1992; 573: 318-320.

62. Hrupka B, Porter M, Langhans W. Central and peripheral interactions of lipopolysaccharide and tumor necrosis factor. Appetite 1998; 31: 277 (Abstract).

63. Porter MH, Arnold M, Langhans W. TNF-alpha tolerance blocks LPS-induced hypophagia but LPS tolerance fails to prevent TNF-alpha-induced hypophagia. Am J Physiol 1998; 274: R741-745.

64. Ota K, Katafuchi T, Takaki A, Hori T. AV3V neurons that send axons to hypothalamic nuclei respond to the systemic injection of IL-1beta. Am J Physiol 1997; 272: R532-540.

65. Licinio J, Wong ML. Pathways and mechanisms for cytokine signaling of the central nervous system. J Clin Invest 1997; 100: 2941-2947.

66. Cao C, Matsumura K, Yamagata K, Watanabe Y. Induction by lipopolysaccharide of cyclooxygenase-2 mRNA in rat brain; its possible role in the febrile response. Brain Res 1995; 697: 187-196.

67. Banks WA. Physiology and pathology of the blood–brain barrier: implications for microbial pathogenesis, drug delivery and neurodegenerative disorders. J Neurovirol 1999; 5: 538-555.

68. de Vries HE, Blom-Roosemalen MC, van Oosten M, et al. The influence of cytokines on the integrity of the blood– brain barrier in vitro. J Neuroimmunol 1996; 64: 37-43.

69. Gayle D, Ilyin SE, Plata-Salaman CR. Central nervous system IL-1 beta system and neuropeptide Y mRNAs during IL-1 beta-induced anorexia in rats. Brain Res Bull 1997; 44: 311-317.

70. von Meyenburg C, Langhans W, Hrupka BJ. Evidence for a role of the 5-HT2C receptor in central lipopolysaccharide-, interleukin-1 beta-, and leptin-induced anorexia. Pharmacol Biochem Behav 2003; 74: 1025-1031.

71. Waldbillig RJ, Bartness TJ, Stanley BG. Increased food intake, body weight, and adiposity in rats after regional neurochemical depletion of serotonin. J Comp Physiol Psychol 1981; 95: 391-405.

72. Nonogaki K, Strack AM, Dallman MF, Tecott LH. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT2C receptor gene. Nat Med 1998; 4: 152-156.

73. Heisler LK, Cowley MA, Tecott LH, et al. Activation of central melanocortin pathways by fenfluramine. Science 2002; 297: 609-611.

74. Sonti G, Ilyin SE, Plata-Salaman CR. Neuropeptide Y blocks and reverses interleukin-1 beta-induced anorexia in rats. Peptides 1996; 7: 517-520.

75. Turrin NP, Flynn MC, Plata-Salaman CR. Neuropeptide Y counteracts interferon-alpha-induced anorexia. Neuroimmunomodulation 1999; 6: 361-366.

76. Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. Am J Clin Nutr 1997; 66: 683-706.

77. Plata-Salaman CR, French-Mullen JM. Intracerebroventricular administration of a specific IL-1 receptor antagonist blocks food and water intake suppression induced by interleukin-1b. Physiol Behav 1992; 51: 277-279.

78. Plata-Salaman CR, Sonti G, Borkoski JP, Wilson CD, French-Mullen JM. Anorexia induced by chronic central administration of cytokines at estimated pathophysiological concentrations. Physiol Behav 1996; 60: 867-875.

79. Johnson PM, Vogt SK, Burney MW, Muglia LJ. COX-2 inhibition attenuates anorexia during systemic inflammation without impairing cytokine production. Am J Physiol Endocrinol Metab 2002; 282: E650-656.