Nutrition, stress and immune activation

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Summary

The response to stress (physical, social or microbial) provokes an integrated reaction involving the immune system (via cytokines), the central nervous system (via nervous output) and the endocrine system (via hormones) each influencing and influenced by the other physiological responses to environmental change. In this context, the concept of a link between nutrition and immunity is readily appreciated, in that nutritional deficiencies may cause stress or may alter CNS output and thereby impact on immune function. However, this paper addresses some facets of nutrition-immune interactions which are less obvious. While the selective effects on immunity of individual components of the diet, and the effect on selective components of the immune system of nutrient imbalance, are addressed, the concept is proposed that changes in immune status have a feedback effect on nutrient intake and utilisation partitioning such that inappropriate immune activation has deleterious effects on growth and development. The potential mediators by which these effects occur are explored.

Introduction

The immune system consists of a set of specialised cells which have the capacity to recognise and respond to a foreign challenge, whether infectious or benign, by a set of effector reactions involving a myriad of humoral factors and cellular activities designed to inactivate and expel the challenge material. It is now widely accepted that this response forms part of an integrated homeostatic network, influencing and influenced by other physiological responses to environmental change (1). This network is regulated not only by the central nervous system, through direct innervation of effector sites or by neurotransmitter output, but also by soluble factors produced by both the endocrine system (hormones) and the immune system (cytokines and acute phase proteins).

Exposure to acute environmental stressors, such as temperature extremes, overcrowding, or disturbance to established social hierarchies, increases pituitary output of ACTH which activates the production from the adrenal cortex of corticosteroids which are powerfully immunosuppressive (2). Other pituitary hormones also have immunomodulatory effects - growth hormone release has been reported to promote lymphocyte activation (3); melanocyte stimulating hormone has anti-inflammatory effects (4); arginine vasopressin acts synergistically with ACTH to modulate immunosuppression (5); and prolactin is immunostimulatory and maintains immunological functions (6,7). On the other hand, immunologic stress by chronic exposure to invading microbes or microbial antigenic debris results in the production of inflammatory cytokines such as IL-1, IL-6 and TNF-a, as well as an array of acute phase proteins which, in addition to amplifying the immune response, have feedback effects on the CNS and metabolic pathways causing behavioural and metabolic changes. In addition to the cross-talk between the immune and endocrine responses, there is also a dense innervation of lymphoid compartments allowing changes in CNS output following environmental change to directly impact on immune function either by surface neurotransmitter receptors on immune cells (8,9) or there is even the potential for direct synapsing to occur between nerve terminals and immune cells (10).

Thus the integrated neuroendocrine-immune responses (Figure 1) to external challenges or stress encompass a complex series of host metabolic interactions. In this context, the concept of a link between nutrition and immunity is readily appreciated, in that nutritional deficiencies may cause stress or may alter CNS output and thereby impact on immune function. However, this paper will

address some facets of nutrition-immune interactions which are less obvious. The selective effects on immunity of individual components of the diet, and the effect on selective components of the immune system of nutrient imbalance, will be addressed. But more importantly this paper will focus on the concept that changes in immune status can have a feedback effect on nutrient intake and utilisation, leading to the proposition that inappropriate immune activation can have deleterious effects on growth and development, and will explore the potential mediators by which these effects occur.

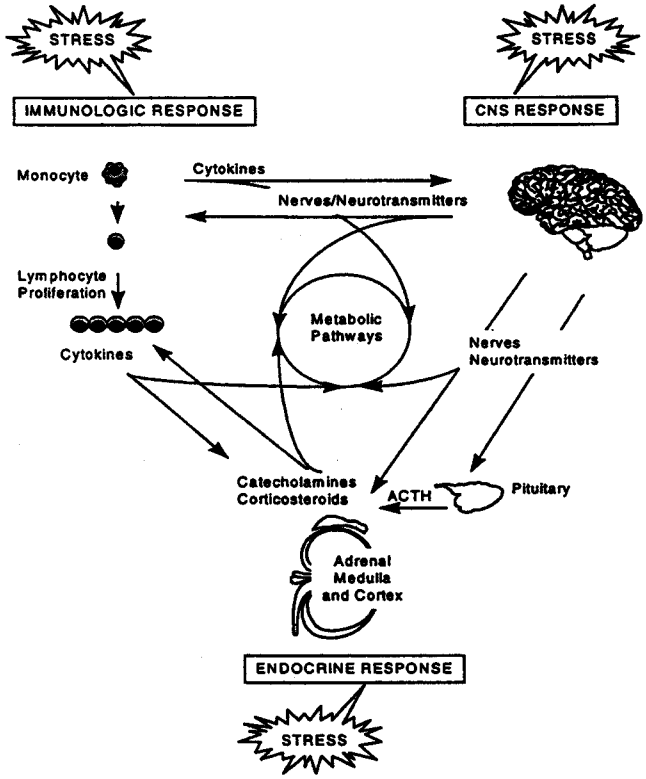

Figure 1.
The neuroendocrine-immune network. The response to stress (physical, social or microbial) provokes an integrated reaction involving the immune system (via cytokines), the central nervous system (via nervous output) and the endocrine system (via hormones) each of which influences the output of the other.

Dietary imbalance, deficiency, and immunity

The most obvious nutritional influences on immune function are those caused by malnutrition. Although mild malnutrition has little effect on immune competence in children (11), severe protein/calorie malnutrition causes pronounced suppression of immune activity (12,13), by activation of the pituitary adrenal axis (14), by direct effects on lymphocyte function and migration (15), and by central noradrenergic hyperactivity (16,17). These effects are particularly pronounced at mucosal sites. Young mice fed a protein-deficient diet for only 6-8 weeks display reduced local IgA responses in lacrimal glands, leading to an absence of local antibody in tears (18), a reduced local antibody response in the intestine due to induction of abnormal suppressor T cell activity (19) and impaired differentiation of IgA B cell precursors in gut associated lymphoid tissues (20).

Obesity is a condition associated with altered nutritional, metabolic, endocrine and psychological status and has an adverse effect on immunological function. Studies with genetically obese (ob/ob) mice show reductions in various aspects of cell-mediated immunity which do not appear to be due to inherent immune cell defects but rather result from changes in the physiological milieu in which they function (21). Less is known about immunocompetence of animals made obese through overfeeding. Dietary induced obesity usually results from the feeding of high-fat diets

and the immune status of the obese subject may reflect the duration of feeding and the type of fat fed. However, obese dogs are less resistant to infection than normally fed dogs (22) and weight reduction strategies for the treatment of obesity have also been shown to produce further alterations in immune responsiveness (21).

Selective deficiencies of dietary components also have immunosuppressive effects and excellent reviews have been published summarising the earlier literature on this subject (22,23). Vitamin A deficiency has been demonstrated to depress immune function (24,25), and vitamin A supplementation reduces childhood mortality to infectious disease (26), although in animal experiments it has been shown to increase IL-1 production following bacterial endotoxin challenge (27). As in severe malnutrition, vitamin A deficiency has its most pronounced effects on mucosal immunity, causing a decreased number of IgA antibody-producing cells in the gut, a selective increase in T suppressor cells and a decreased ability to control the localisation and systemic translocation of intestinal bacteria (28,29). Vitamin A deficiency also exacerbates the risk of HIV infection via breast milk (30), causes decreased bile transport of plasma IgA to the intestinal lumen (31) and impaired immunoblast localisation in the gut (15). In addition to absolute depression in immune responsiveness, hypovitaminosis A causes an imbalance in regulatory T cells with a relative decrease in the T helper:T suppressor cell ratio (26) and an imbalance in the production of cytokines, the immunoregulatory molecules of the immune system, leading to a bias towards T helper cell activities which downregulate antibody production and promote cell-mediated responses (29,32,33).

Vitamin E deficiency causes increased inflammation following endotoxin challenge, but in dairy cows vitamin E deficiency in association with selenium deficiency causes increased susceptibility to mastitis as a result of decreased neutrophil numbers and activity, which is reversed by vitamin E and selenium supplementation (34). Even in normal animals, vitamin E administration promotes neutrophil activity (35) and when given in association with vaccination results in increased antibody responses (36,37).

Trace minerals have also been shown to be important for immune function. Copper deficiency suppresses the response to endotoxin challenge (38), zinc deficiency results in decreased metallothionein synthesis following endotoxin challenge (39), iron exacerbates the inflammatory response in arthritic patients by increasing inflammatory cytokine production (40) and chromium ameliorates the suppressive effects of stress on the immune response (41).

Dietary lipids may influence the nature of an immune response by affecting cytokine and acute phase protein production and altering membrane fluidity. For instance rats fed coconut oil have a reduced acute phase protein response to endotoxin challenge, especially with respect to eicosanoids, relative to rats fed corn oil (42). In humans, fish oil supplementation produces a similar effect (43). Fish oils have been effectively used to limit inflammatory responses in rheumatoid arthritis (44), in burn injury (45) and toxic shock due to caecal perforation (46).

Amino acids modulate the immune response in many different ways. Dietary deficiencies of arginine, lysine, tryptophan, phenylalanine, leucine, isoleucine, methionine and cysteine impact negatively on the immune system (23,47). Nevertheless, it is unclear whether inflammatory states, which produce profound alterations in tissue protein metabolism (see below) might change the requirements for amino acids (48). However, it appears that metallothionein synthesis is particularly sensitive to the availability of cysteine and glycine, and that cysteine is particularly important for hepatic protein synthesis during inflammation (48) along with phenylalanine, tryptophan and tyrosine for acute-phase protein synthesis (49). Dietary availability of arginine and its precursor, glutamine, are also important as arginine is a substrate for nitric oxide synthesis (50) a potentially critical factor in the regulation of macrophage activity (51).

Immune activation, nutrient requirements and utilisation partitioning

While nutritional deficiencies and imbalances lead to immune dysfunction, it is becoming increasingly clear that chronic immune activation and stress can combine to alter the requirements for dietary nutrients (52). Early growth failure and short stature in humans are not always due to nutritional deficiencies as recurrent respiratory and gastrointestinal tract infections also produce these effects (53). In a study of children in Guatemala living under conditions of poor sanitation and hygiene, 34% of subjects, although apparently healthy, had elevated white cell counts and erythrocyte sedimentation rates (54) and in limited epidemiological studies prophylactic use of antibiotics in subjects exposed to poor environments resulted in improved weight gain compared to controls with the same dietary intake (55). Indeed Black (53) has explored the proposition that controlling childhood diseases may reduce the level of malnutrition on a global scale, although concedes that this may not be as cost effective as direct nutritional intervention. Similarly, in intensive animal production systems it is an established management principle that even in the absence of infectious disease outbreaks, animals grow faster if antibiotics are added as a feed supplement (56), and this growth permitting effect has been attributed to the reduction in immunologic stress by antibiotic treatment (57).

In studies with chickens, administration of bacterial endotoxin or polydextrins caused a large increase in acute phase protein production from the liver and a cessation of ovulation and a decrease in egg protein synthesis (58), as well as a significant reduction in weight gain. Decreased feed intake accounted for about 70% of the decreased growth rate, the remainder being due to reduced feed conversion efficiency due to metabolic inefficiencies caused by the immune response (59). Although endotoxin administration decreased growth and feed consumption at low energy densities, when the dietary energy density was increased above 13.4 kJ/g using cornstarch, but not corn oil, the growth depressing effect of immunogens was eliminated, but persistent alterations in carcass composition occurred (60). In particular, immunologically stressed chicks had a greater proportion of gain in visceral organs and less in the carcass, regardless of the nutrient density of the diet.

Thus the effect of microbial load together with other environmental stressors such as ambient, nutritional, or psychological factors, combine to provoke an integrated homeostatic response, described by Elsasser (61) as an 'endocrine-immune gradient', the sum of homeostatic responses to all environmental stressors involving the endocrine, immune and central nervous systems (Figure 2). Elevation in the gradient leads not only to growth retardation, but qualitative changes in nutrient partitioning. Under optimal conditions, the nutrient input into muscle development of growing animals exceeds that for fat deposition, but as energy intake increases and exceeds the requirement for protein synthesis, fat deposition increases disproportionately to lean tissue deposition (57). However, the point at which switchover from muscle to fat deposition occurs is reduced in the face of a high endocrine-immune gradient. This redistribution of resources within the body in response to changes in the gradient explain the large differences observed in traits such as fatness, feed conversion efficiency and protein accretion in animals of the same genotype maintained on a similar diet, but which have been exposed to an environment with different levels of microbial contamination (62). Even in humans both physiological and psychological stress have been linked to fatness (63), although changes in eating patterns and nutritional intake in these subjects accounts for a significant part of the effect.

The repartitioning of nutrients in the face of immunologic stress has been shown to be mediated by a combination of cytokines and acute phase proteins. The so-called 'acute phase response' following infection or antigenic challenge is the immunological component of the homeostatic response to infection, tissue injury or other immunological disturbance and is characterised by the production of IL-1, IL-6, TNF-α and interferons (Table 1 and Figure 3).

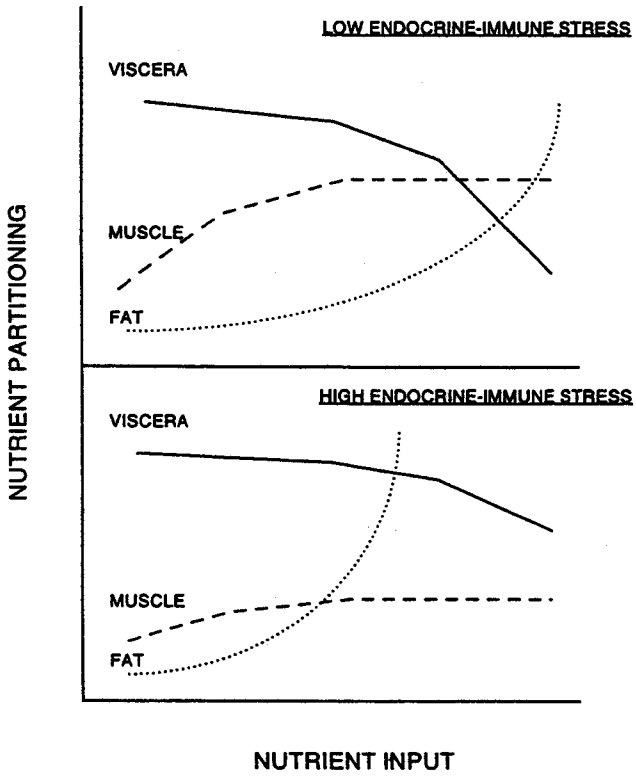

Figure 2. The relationship between nutrient input and utilisation partitioning under high and low endocrine-immune stress. With low endocrine-immune stress protein accretion is more efficient with muscle development having preference over fat deposition; with high endocrine-immune stress relatively more nutrient utilisation is channelled toward fat deposition.

Many of these cytokines produce CNS-mediated effects on behaviour - for instance IL-1 induces fever (64), reduces social exploration and appetite (65), and impairs spatial navigation learning (66); IL-6 is somnogenic (67) and induces lethargy, depression, anorexia and fever (68,69); interferons produce fever, lethargy, anorexia, vomiting and general malaise (70). Indeed the neurological side-effects following administration of cytokines limit their potential use for therapeutic purposes (71). It is not surprising therefore that associated with immune challenge are classical symptoms of illness which form part of the essential response to achieve homeostasis, a response which has been termed 'sickness behaviour' (65).

The cytokine mediation of the effects of immune challenge is supported by the observation that feeding antibiotics to chickens in an environment with heavy microbial contamination decreases the amount of circulating IL-1 to levels more similar to those of birds raised in a clean environment (57). In addition to the behavioural effects of inflammatory cytokine production, manifested as inappetance and reduced feed intake, there are direct effects on metabolism causing redirection of nutrients away from normal metabolism to support the host defence responses, such that the use of amino acids for muscle protein accretion is diverted by deamination for use as an energy source (72). Thus cytokine release as part of the adaptive response to microbial challenge results in muscle catabolism to supply amino acids for acute phase protein synthesis, as a gluconeogenic substrate and to satisfy the increased demand for protein synthesis by leukocyte proliferation and antibody synthesis (73). However, the amino acid composition of muscle tissue is different from the composition of proteins synthesised in response to immune activation following infection or trauma. The net loss of body nitrogen that accompanies this process derives from the oxidation of mobilised amino acids that remain after the synthesis of acute-phase proteins has been satisfied (49).

Table 1. Overlapping roles of leukocytic cytokines in the regulaton of metabolism[1] (adapted from Klasing and Johnstone (80)).

Response	Cytokines responsible
General	
decreased voluntary food intake	IL-1, TNF
increased resting enegy expenditure	IL-1, TNF
increased body temperature	IL-1, IL-6
Glucose metabolism	
increased glucose oxidation	IL-1, TNF
increased gluconeogenesis	IL-1
Lipid metabolism	
decreased lipoprotein lipase activity	IL-1, TNF
increased lipolysis in adipocytes	IL-1, TNF
increased hepatic triglyceride synthesis	TNF
Protein metabolism	
increased acute phase protein synthesis	IL-1, TNF, IL-6
increased muscle protein degradation	IL-1
Mineral metabolism	
increased metallothionein synthesis	IL-6
increased hepatic ceruloplasmin synthesis	IL-1, IL-6
Hormone release	
increased corticosteroid release	IL-1, IL-6
decreased thyroxin release	IL-1
increased insulin and glucagon release	IL-1, TNF

[1]Abbreviations: Il-1:Interleukin-1; TNF: tumor necrosis factor; IL-6: interleukin-6

The effects of microbial load on nutrient utilisation can be exacerbated by other concurrent stressors (74). The increase in glucocorticoid secretion during stress stimulates the utilisation of gluconeogenic precursors in the liver in association with its triggering of amino acid release from muscle. It has also been demonstrated that TNF-α can synergise with corticosteroids to increase muscle proteolysis (75).

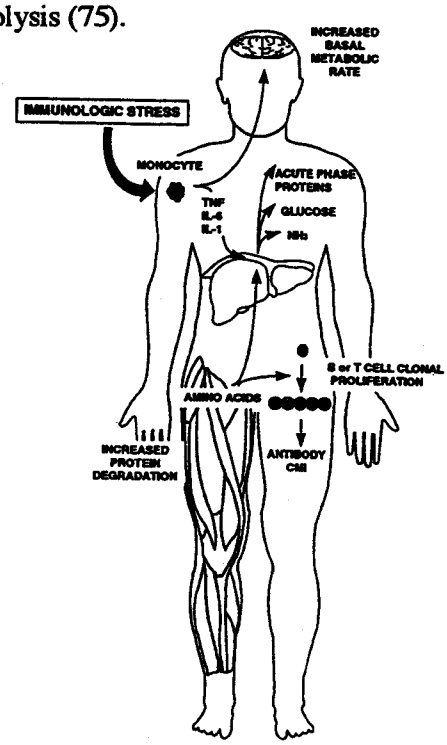

Figure 3. Metabolic effects of immunologic stress. Chronic immune activation causes inflammatory cytokine production which increases metabolic rate, promotes hepatic acture phase protein output and maintains antibody and cell mediated immune responses. The increased requirement for protein synthesis results in protein degradation and increase energy requirements. (Adapted from reference (72)).

Differences in growth patterns and body composition in response to environmental stressors (72) and differences in disease susceptibility in humans and other species (76) may well be explained on the basis of genetically determined variation in the integrated homeostatic response, reflected in the relative slope of the endocrine-immune gradients.

Amelioration of stress?

The new understanding now emerging regarding the integration of endocrine and immune responses to environmental stressors suggests opportunities for intervention by nutritional strategies or by manipulating hormone and/or cytokine responses. An ability to identify diet-dependent from diet-independent effects on growth will enable new nutritional strategies to be introduced (77). For instance, the effect of increasing dietary energy density on reducing the metabolic effects of immunologic stress was discussed previously (60). Therapeutic hormonal manipulation is common in humans to manage maladaptive endocrine responses to environmental change, but modification of these responses by pharmacological methods in animals grown for human consumption has met with intense consumer resistance. A novel alternative approach has been developed using vaccination techniques to achieve the same result. If appropriate vaccine formulations are used it is possible to achieve sufficient levels of anti-hormone antibodies, or antibodies to hormone receptors which block hormone action, to intercept signal transduction via the pituitary-adrenal axis. Immunisation against ACTH in a number of farm animal species has not only resulted in improved weight gain, and feed conversion efficiency, but improved carcass quality by reducing fat deposition (78).

There is currently great interest in manipulating cytokine profiles to optimise immune responses in both quantitative and qualitative terms. The use of anti-cytokine antibodies or gene therapy approaches for controlling in vivo cytokine production are now common laboratory procedures (79) and their routine therapeutic application in both man and animals is an imminent possibility for managing clinical disease. But these approaches may also prove to be useful to control the adverse effects of a maladaptive cytokine response to 'immunologic stress', a proposition currently under investigation in this laboratory.

Thus in animal production where economic reality is forcing increased dependency on intensive production systems (eg. in chicken, pig and feedlot cattle production), optimising feed conversion efficiency and carcass quality will depend increasingly on managing the endocrine-immune gradient. In human terms, the effect on growth and development of poor sanitation in developing countries, and the cost to effective immunity of exposure to the chronic, and often inescapable, emotional and physical stresses of modern developed societies, may need to be counterbalanced by similar strategies.

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