ABSTRACT

This review highlights fundamental mechanisms of the stress response and important findings as to how the immune system is affected and affects, in turn, such a response. The crucial link between stress response and energy metabolism is dealt with as well. The effector mechanisms in the stress response are remarkably similar for both infectious and non–infectious stimuli, albeit differently modulated. "Psychosensitive stimuli/behavioural response" and "Antigenic stimuli/immune response" are indeed two subsystems of a unitary, integrated complex aimed at providing optimal conditions for the host’s survival and adaptation.

The interaction between the immune system and the stress/inflammation complex has led to the development of a diversified network of cytokines and chemokines in vertebrate animals. The cytokine response can be mounted in different forms and extent by the host after exposure to both infectious and non-infectious stimuli. In this conceptual framework, microbial infections are just one category of stressing agents, which modulate the cytokine response for a better performance of the innate and adaptive immune responses.

The response to infectious and non–infectious stress leads to a metabolic shift that enhances energy, amino acids and micronutrients consumption. The influence of each nutrient on different aspects of immune function is not easy to define, but it is becoming clear that many nutrients have defined roles in the immune response and, accordingly, their requirements are changed to support optimal immune function. Therefore, impairment of immune functions may arise from intakes of nutrients below or above these modified ranges of requirements.

Key words: Immune system, Stress, Cytokines, Nutrients.
da stress e metabolismo energetico. I meccanismi effettoriali nella risposta da stress sono assai simili nel caso di stimoli stressanti di natura infettiva e non infettiva, quantunque differentemente modulati. I circuiti “Stimoli psico-sensitivi/risposta comportamentale” e “Stimoli antigenici/ risposta immunitaria” sono sotto-sistemi di un unico complesso integrato di regolazione omeostatica, attivo a fornire condizioni ottimali per la sopravvivenza e l’adattamento dell’ospite all’ambiente. L’interazione tra il sistema immunitario ed il complesso stress/infiammazione ha portato nell’evoluzione filogenetica dei vertebrati allo sviluppo di una rete diversificata di citochine e chemochine. La risposta in citochine può manifestarsi in forme e gradi differenti dopo esposizione a stimoli infettivi e non infettivi. In questo ambito, le infezioni microbiche rappresentano semplicemente una categoria di eventi stressogeni che modulano la risposta in citochine verso una migliore funzionalità delle risposte immunitarie innata ed adattativa. La risposta a stimoli stressogeni (microbici e non) conduce ad una modifica del metabolismo che aumenta il consumo di energia, aminoacidi e micronutrienti. L’influsso di ciascun nutriente su diverse funzioni del sistema immunitario non è facile da definire; si stanno chiarendo tuttavia il ruolo di molti nutrienti nella risposta immunitaria ed i relativi mutamenti di fabbisogni, atti a supportare la risposta immunitaria in forma ottimale. Di conseguenza, una compromissione della risposta immunitaria può derivare da livelli di nutrienti al di sotto o al di sopra di questi fabbisogni modificati.

Parole chiave: Sistema immunitario, Stress, Citochine, Nutrienti.

Introduction

The stress response is a conserved, physiological coping reaction to adverse environmental conditions, as diverse as physical and/or psychological constraints, injuries, trauma, poor microclimate and others. In this respect, immune responses, stress and inflammation are an ancestral, overlapping set of responses aimed at the neutralization of stimuli perturbing body homeostasis (Ottaviani and Franceschi, 1998). The complex interaction between the immune system and the stress/inflammation complex has mainly developed in the phylogenetic evolution on the basis of a diversified system of cytokines and chemokines. Such complexity can be accounted for by the extreme variety of tasks to be performed and by the necessary fine-tuning of the relevant effector mechanisms. In particular, cytokines are the foundation in vertebrate animals of the complex cross-talk between brain and immune system. The two main circuits, “Psycho-sensitive stimuli/behavioural response” and “Antigenic stimuli/immune response,” are indeed subsystems of a unitary integrated complex aimed at providing optimal conditions for the survival and adaptation of the host. This can be adequately grasped bearing in mind the crucial role of pro-inflammatory cytokines in the induction of sickness behaviour (lethargy, anorexia, curtail of both social and reproductive activities), that is a clearly defined motivational status (Kelley et al., 2003). The host adopts different behavioural priorities to mount a well-organized, integrated response to microbial infections; interestingly, depression is likely to provide an important adaptive advantage to sick animals and anorexia is associated with a better chance for survival under such conditions. Owing to the above, it can be argued that the immune system and other homeostatic control systems share important regulatory factors, even though they formally perform diverse, apparently diverging physiological functions (Amadori, 2007). As a result, the canonical boundaries between immune and neuroendocrine control systems can no longer be recognized in a continuum of homeostatic circuits, in which a single recognized effector function is part of a wider strategy for better survival and adaptation. Such a strategy is based upon networks of multidirectional signalling and
feedback regulations effected by neuroendocrine - and immunocyte - derived mediators (Plytycz and Seljelid, 2002).

In general, the effector mechanisms in the stress response are remarkably similar for both infectious and non–infectious stimuli, albeit differently modulated. Thus, a pro-inflammatory cytokine like interleukin-1 (IL-1) induces activation of the hypothalamo-pituitary-adrenocortical (HPA) axis as well as stimulation of cerebral noradrenaline. The effects of IL-1 are remarkably similar to those observed following either LPS administration (reminiscent of infectious stress) or acute, non-infectious stressing events in laboratory animals, such as electric shock or restraint (Dunn et al., 1999). Likewise, the brain produces interferon-α (IFN-α) in response to non-inflammatory as well as inflammatory stress; the intracerebral injection of this cytokine may alter the brain activity to exert a feedback effect on the immune system (Hori et al., 1998). Therefore, a cytokine response can be mounted in different forms and extent by the host after exposure to both infectious and non-infectious stimuli. In this conceptual framework, microbial infections are just one category of stressing agents, which modulate the cytokine response for a better performance of the innate and adaptive immune responses.

How do cytokines work? Interesting inferences can be drawn from the in vitro dose/response curves of several cytokines which are often bell-shaped. Beyond a narrow concentration range in which the dose response is positive, the response can diminish or even reverse as in the change from stimulation to suppression of the primary antibody response to Sheep Red Blood Cells in interferon-α (IFN-α) treated mice (Nagao et al., 1998). Accordingly, IFN-α abides with the general rule of most cytokines: low dose priming, high dose suppression (Cummins et al., 2005). This crucial feature dictates the very outcome of cytokine secretion that can be dramatically different as a result of both timing and concentration in tissues and organs. Therefore, autocrine versus paracrine effector functions may prevail on the basis of the above parameters. In addition, overt hormone-like systemic activities are displayed in cases of major stressing events (infectious and non-infectious), whenever emergency control actions are badly needed. Thus, for example, peak plasma interleukin-6 (IL-6) concentrations precede the liver acute phase response in case of serious threats to the host such as tissue damage or bacterial infections (Murtaugh et al., 1996).

In this scenario, the immune system is affected by the stress response and, in turn, it affects the stress response on which the cytokine network can exert important regulatory functions.

The immune system affects the inflammation/stress response

The inflammatory response is started by the host to achieve better fitness in managing adverse environmental conditions (infectious or non-infectious) and then curtailed to avoid major tissue damage. According to the danger theory (Matzinger, 2002), the usual limits of the inflammatory response can only be trespassed in case of major infectious threats, the priority being the survival of the host. Thus, strict control over start and extent of the inflammatory response is mandatory for a successful outcome of the coping reaction. Pro-inflammatory cytokines of the immune system such as Tumor Necrosis Factor (TNF)-α, IL-1 and IL-6 play a pivotal role in mounting and directing the inflammatory response. At the same time, the immune system displays important regulatory functions which start at very beginning of the inflammatory response:
• the early development of CD4+/CD25^{high} T regulatory (Treg) lymphocytes, which prevent a harmful progression of the inflammatory response in organs during e.g. viral infections. Subsequent IFN-\(\alpha\), IL-10 and IL-15 responses in tissues are usually the foundation of this Treg-mediated control action (Durbin et al., 2000);
• the harnessing of pro-inflammatory cytokines by means of an array of humoral and cell-mediated control mechanisms (TNF-\(\alpha\) soluble receptors, IL-1 decoy receptor, IL-1 receptor antagonist) (Kumar, 2003);
• the local and systemic IFN-\(\alpha\) response, which is likely to prevent a lethal septic shock at the onset of bacterial infections, as shown e.g. in the Schwartzman's reaction model (Billiau, 1988). It also exerts a potent anti-inflammatory control activity in the late stages of microbial infections and, probably, in the framework of its physiological release under healthy conditions (Bocci et al., 1985). The control action is based on the transcriptional control of genes coding for inflammatory cytokines, pathogen-associated molecular pattern (PAMP) receptors (CD14) and, possibly, other undetected structures (Amadori, 2007).

The immune system is affected by the stress response

According to the school of thought concerned with biological functioning, welfare is meant as the state of an individual as regards its attempts to cope with the environment. Whenever animals are forced to deal with severe, prolonged coping reactions with a considerable energy expense, welfare suffers and a serious depression of the immune system results as one of the negative outcomes. In this scenario, clinical immunology tests (complement, lysozyme, serum bactericidal activity) reveal a substantial decrease in the ability of the immune system to deal with environmental pathogens, which paves the way to opportunistic microbial infections (Amadori, 1997). Interestingly, the above functions relate to the innate immune system, which does not have memory and acts irrespective of antigenic specificities by recognition of conserved microbial PAMPs. A defective innate immune response forces the host to a wider use of the adaptive immune response (antibody and cytotoxic T lymphocytes), which is by far more demanding in terms of energy expense. In turn, the efficiency of the adaptive immune response is also poor under conditions of chronic stress. The dramatic failure of potent Foot-and-Mouth Disease vaccines in Holstein cattle reared under hot climate conditions in Saudi Arabia is a very convincing demonstration of this tenet (Woolhouse et al., 1996). Which rationale, which explanation in terms of phylogenetic evolution can be proposed for immunosuppression under stress conditions? It is worth dissecting this issue in models of acute versus chronic stress. Acute stressing events well beneath the host’s threshold for coping are not dangerous and often conducive to useful learning experiences: free-range male animals involved e.g. in voluntary mating activities show a stress response which is obviously of no concern! Interestingly, transient acute stresses may be associated with a better immune response; such events may even be thought of as nature’s adjuvant under field conditions (Dhabhar and Viswanathan, 2005). Surely, this is not true of long-distance journeys of calves and pigs, which show, in fact, distinct signs of serious inflammatory reactions and immunosuppression, usually peaking at day 4-5 after transportation. The frequent detection of a serum IFN-\(\alpha\) respon-
Immune System Response to Stress Factors

It is well established (Artursson et al., 1989) that stress can affect the immune system. In farm animals, chronic stress is a major concern, as it can have both positive and negative effects on immune function, depending on the duration and intensity of the stress. Chronic stress can lead to changes in the immune system that are detrimental to overall health.

Chronic stress in farm animals can derive from a variety of conditions, including:
- Climate and microclimate conditions (temperature, humidity, draught, etc.);
- Microbial infectious pressure;
- Pain, fear, inability to perform a defined repertoire;
- Barren environment, boredom;
- Inadequate diet;
- Metabolic stress for both milk and meat production.

It can be argued that the high energy demand for coping under these conditions forces animals to re-define their metabolic priorities to the detriment of the immune response. This is clearly shown by the leptin model: under chronic stress induced by starvation, leptin is shut off by adipocytes, which leads to serious defects of immune effector functions (Sánchez-Margalet et al., 2003). Secondary antibody responses and immunological memory may be energetically costly (Martin et al., 2007) and therefore down-regulated during food restriction. In addition, a conflict often arises in farm animals between immune response and performance under conditions of high infectious pressure. The M. hyopneumoniae model in pigs is a very convincing example of this crucial link (Pointon et al., 1985). A similar conflict can be envisaged as regards energy expense for milk production and immune effector functions in the early lactation period of high yield dairy cows.

The interaction between the immune and the neuroendocrine systems is bidirectional, as exemplified by the action/response pattern of glucocorticoids.

Environmental and metabolic stress enhances the secretion of glucocorticoids; their anti-inflammatory activity is related to the down-regulation of IFN-γ and pro-inflammatory cytokines such as IL-1, IL-2, IL-3, GM-CSF, TNF-α, IL-6 and IL-8. However, the effect of glucocorticoids is not unidirectional, since they also stimulate MIF, a proinflammatory cytokine (Fingerle-Rowson et al., 2003).

Infection, injury or inflammation activate the production of regulatory cytokines, which stimulate the release of circulating glucocorticoids from the pituitary-adrenal axis (Charmandari et al., 2005). Cytokines with known neuroendocrine effects are IFNs, that enhance steroidogenesis, IL-1, IL-2, IL-6 that increase blood concentration of ACTH and glucocorticoids (Petrovsky, 2001); in particular IL-1 is a potent secretagogue of ACTH in sheep (Kemppainen and Behrend, 1998). The immune response to an antigen leads to the differentiation of native T helper (Th) cells to Th0 and, then, Th1 or Th2. Cytokines produced by Th1 cells stimulate the immune response and Th1 cell proliferation, inhibiting the production of cytokines secreted by Th2 and viceversa. Th1 cytokines (IFN-γ, TNF-α and IL-2) generate a considerable proinflammatory response, often associated to tissue damage, whilst those arising from Th2 (IL-4, IL-5, IL-10) show helper functions for B lymphocytes, enhancing the production of IgM, IgE and distinct subclasses of IgG antibody. Cortisol concentrations that inhibit IL-2 production lead to an increase in IL-4, which drives the differentiation of Th0 lymphocytes to the Th2 subpopulation, with a concomitant increase of immunoglobulins. Furthermore, the effect of corticosteroids can vary with...
respect to blood concentration so that, for instance, when cortisol output is high the immune system secretes pro-inflammatory cytokines: IL-6 in cattle (Judd and MacLeod, 1992; Shuster et al., 1993) and pigs (Wang et al., 2006), and IL-8, IL-18, IL-1β in humans (Enwonwu et al., 2005).

The modification of immune response related to an increase of blood cortisol can be investigated in vivo using the anterior pituitary hormone, adrenocorticotropic hormone (ACTH), or hypothalamic corticotrophin-releasing hormone (CRH). Heifers injected with ACTH twice a day (100 U) for 5 days in a row had concentrations of plasma cortisol ten-fold higher than the basal value. The ACTH challenge enhanced the mRNA expression of pro-inflammatory cytokines (IL-2, IL-6, TNF-α, IFN-γ) in blood leukocytes (Figure 1). However, in another study, ACTH administration to calves twice daily for 2 days caused a lower increase in plasma cortisol, that inhibited the in vitro lymphocyte proliferative response and IL-2 production (Blecha and Backer, 1986). These apparently contradictory results would indicate that the effect of stress on the immune system is either suppressive or stimulatory, as a result of factors such as duration and intensity of stressors, basal animal health status, and also the markers of immune response measured.

Animal species exhibit different sensitivity to glucocorticoids that can be related to mutations and splice variants in the glucocorticoid receptor (GR). In particular, the N-terminal region of this nuclear receptor is involved in the transactivation of downstream genes, and mutations in this domain decrease the transcriptional activity without affecting ligand affinity. This is considered the reason for individual variations, cortisol resistance and different regulatory functions of cortisol (Stolte et al., 2006).

**Nutrition and immunity**

Animals exposed to acute or chronic stress respond by activating the neuroendocrine and immune systems (Blecha and Backer, 1986; Murata et al., 1987). The cortisol HPA-associated release, together with catecholamin secretion, leads to nutrient mobilisation from tissues, especially from skeletal muscle (Klasing et al., 1987). The interactions between stress response and metabolic functions are shown in Figure 2 (Charmandari et al., 2005). Stress conditions and infections are often associated to body weight losses due to the increased requirements of specific nutrients (Elsasser et al., 2001). The priority for nutrients utilisation in domestic animals under normal conditions is for tissues with the highest metabolic rate, such as brain and CNS, followed by bone and muscle, whereas tissues with lower metabolism, such as fat, receive lesser priority. During pregnancy, foetus and placenta have the same priority as brain and CNS, as shown in Figure 3 (Hammond, 1944). The reverse priority is observed during starvation or conditions that raise nutrient demands above the intakes. In this case, fat reserves are preferentially exploited to provide metabolic fuel, and skeletal muscles to provide amino acids and glutamine (Elsasser et al., 2001).

Some examples, reported below, highlight the role of nutrition in preserving the integrity of the immune system or facing infectious challenges.

During infection and sepsis, the demand for glutamine to support monocyte and macrophage functions dramatically increases. Under these conditions, glutamine is used as a carbon source by immune cells for proliferation whilst glucose is diverted to other tissues, more dependent on it as energy fuel (Newsholme and Calder, 1997). Glutamine is a conditional essential amino acid, that
Figure 1. Effect of ACTH administration to heifers on plasma cortisol and mRNA expression of IL-2, IL-6, IFN-γ, TNF-α in leukocytes (experimental data obtained by Stefanon, Sgorlon, Farinacci, Colitti and Gaspardo).

Heifers were injected with ACTH (100 U; n=5) twice daily for 5 days. Plasma cortisol concentration (A) and leukocytes mRNA expression of interferon-γ (IFN-γ), interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) (B) were significantly (P<0.05) increased after 5 days of ACTH injection.
Figure 2. Schematic representation of the interactions between the stress system and metabolic functions (adapted from Charmandari et al., 2005).

Glucocorticoids antagonize the actions of growth hormone, GH, and sex steroids on fat tissue catabolism (lipolysis), and muscle and bone anabolism. Chronic stress is associated with increased visceral adiposity, decreased lean body (bone and muscle) mass and suppressed osteoblastic activity. This phenotype is observed in patients with Cushing’s syndrome and with metabolic syndromes, such as visceral obesity, insulin resistance, hypertension, and sleep apnea. Many of them display increased HPA axis activity and demonstrate similar clinical and biochemical signs. SMS: somatostatin. GnRH: gonadotropin-releasing hormone.

Glutamine is stored for about 60% in skeletal muscle and it is also involved in nucleic acid, amino sugars and protein synthesis, regulation of acid/base balance, protein, carbohydrate and fat metabolisms. It is also a precursor of neurotransmitters and obligates fuel for cell proliferation. Immunocompetent cells require glutamine for the synthesis and release of IL-1, IL-6 and TNF-α, as hepatic cells do for the production of acute-phase proteins. The interorgan flow of glutamine (GLN) dramatically changes from healthy to septic states, when an increase in skeletal muscle breakdown is observed (Karin-ch et al., 2001). The site of GLN uptake in healthy animals is the small intestine and the release is provided mainly by muscle and lung. During sepsis the liver becomes the major organ of GLN uptake and skeletal muscle serves as exporter.

Another dietary amino acid related to immune functions is arginine, an essential amino acid in ruminants that is involved in protein and urea synthesis and ATP generation. Arginine is also required for nitric oxide production, a potent immunoregulatory mediator, and it is the precursor of polyamines that have a key role in DNA replication,
regulation of cell cycle and division. In humans and laboratory animals, arginine was shown to increase lymphocyte proliferation, NK cell activity and macrophage cytotoxicity (Evoy et al., 1998).

Other nutrients known to interfere with the immune response are some antioxidant compounds, as α-tocopherol (Meydani and Tengerdy, 1993) and dehydroascorbate (Lehr et al., 1997); also glutathione, an antioxidant tripeptide consisting of glycine, cysteine and glutamate, has been shown to enhance the activity of cytotoxic T cells and lymphocyte proliferation. Different classes of herb phytochemicals can modulate the immune response, and the effect is not necessarily related to antioxidant properties. Such effects of phytochemicals are due to several action mechanisms, such as modulation of enzyme activities, modulation of gene expression and antioxidant activities. In a recent study, the effects of two patent-protected plant extracts, rich in polyphenols, on the activity of ovine neutrophils (Farinacci et al., 2007) indicated a dose-dependent decrease or increase in superoxide production, a marker of neutrophil ‘respiratory burst’, for the two extracts (Figure 4). Furthermore, Ginseng possesses both immunostimulant and immunosuppressant activities, which accounts for the term ‘adaptogenic’ herb; its immunostimulant activities to polysaccharide fractions, whereas its immunosuppressant activities to be attributed to ginsenosides (Haddad et al., 2005).

Nutrients can indirectly affect immune functions through endocrine modulation. Undernutrition is known to suppress insulin-like growth factor (IGF-I) and to enhance growth factor (GH) secretion in animals (Ketelslegers et al., 1995; Breir, 1999), thus diverting energy from growth to survival, affecting apoptosis and functions of blood polymorpho-

Figure 3. Prioritization of nutrient utilization by different tissues in the animal body, based on their metabolic rate (adapted from Hammond, 1944).
nucleated cells. The physiological interactions between nutrition, endocrine adaptive response and immune system, include not only the somatotrophic axis (IGF-I, GH), but also the lactotrophic (prolactin, PRL) and thyreotropic ones (Kelley et al., 2007).

An example of naturally occurring effect of nutrition on the immune response is the high yielding dairy cow around parturition. During the transition period, such cows experience metabolic and oxidative stress related to the profound modification of dry matter intake and nutrient demands. The demand for specific nutrients rises and the required dietary modifications can affect circulating insulin and IGF-I levels (Andersen et al., 2004). In addition, a marked change also occurs in the levels of various systemic and local hormones related to the end of pregnancy and the beginning of milk secretion (Vangroenweghe et al., 2005), such as IGF-I, GH, prolactin and thyroxine.

It should be stressed that different components of the immune system probably do not show the same dose-response relationship (Yaqoob and Calder, 2003). For several nutrients, dietary intake above recommendations is required to enhance immune functions, but for others excess intake can impair the immune response. This latter condition might, in part, reflect the negative interaction among nutrients, as in the case of excess (n3) PUFA and α-tocopherol requirements (McGuire et al., 1997).

Conclusions

Studies regarding the biology of stress and immune response highlight the complex interaction between the immune and

Figure 4. Effect of two patent-protected plant extracts (C1 and C2) on PMA-induced neutrophil superoxide production (Farinacci et al., 2007).

Superoxide production was measured by cytochrome c reduction assay on neutrophils pretreated with increasing doses of extract (0, 6.67, 20, 60, 180 mg/ml); original data were converted to percentage values relative to control cells. Values are mean (n=3) and vertical lines sd. For concentration response studies, the percentage values were regressed against the natural logarithm of extract concentration (Ln dose). C1 and C2 inhibited or increased, respectively, significantly (P<0.01) the superoxide production of neutrophils in a dose-dependent manner.
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Recent evidence confirms the direct and hormone-mediated roles of nutrients in the regulation of immune functions. In this respect, the involvement of cellular and intermediate metabolism in the immune response deserves further investigation. The definition of nutrient requirements to prevent and to cope with infectious and non-infectious stress, as well as to ameliorate animal welfare, will require a systems biology approach involving multidisciplinary research. This review will hopefully prompt a re-appraisal of some crucial issues and help define research priorities in this fascinating, somehow elusive field of investigation.

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