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Review

Infection, immunity and the neuroendocrine response

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ABSTRACT

The Central Nervous (CNS) and Immune Systems (IS) are the two major adaptive systems which respond rapidly to numerous challenges that are able to compromise health. The defensive response strictly linking innate to acquired immunity, works continuously to limit pathogen invasion and damage. The efficiency of the innate response is crucial for survival and for an optimum priming of acquired immunity. During infection, the immune response is modulated by an integrated neuro-immune network which potentiates innate immunity, controls potential harmful effects and also addresses metabolic and nutritional modifications supporting immune function. In the last decade much knowledge has been gained on the molecular signals that orchestrate this integrated adaptive response, with focus on the systemic mediators which have a crucial role in driving and controlling an efficient protective response. These mediators are also able to signal alterations and control pathway dysfunctions which may be involved in the persistence and/or overexpression of inflammation that may lead to tissue damage and to a negative metabolic impact, causing retarded growth.

This review aims to describe some important signalling pathways which drive bidirectional communication between the Immune and Nervous Systems during infection. Particular emphasis is placed on pro-inflammatory cytokines, immunomodulator hormones such as Glucocorticoids (GCs), Growth hormone (GH), Insulin-like Growth Factor-1 (IGF-1), and Leptin, as well as nutritional factors such as Zinc (Zn).

Finally, the review includes up-to-date information on this neuroimmune cross-talk in domestic animals. Data in domestic animal species are still limited, but there are several exciting areas of research, like the potential interaction pathways between mediators (i.e. cytokine-HPA regulation, IL-6-GCS-Zn, cytokines-GH/IGF-1, IL-6-GH-Leptin and thymus activity) that are or could be promising topics of future research in veterinary medicine.
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Contents

1. Introduction . . . 142
2. General aspects on bidirectional cross-talk between the immune and neuroendocrine systems . . . 142
3. The integrated immune-neuroendocrine response during infection . . . 145
   3.1. Pathogen recognition and inflammatory/innate response activation . . . 145
   3.2. Acute phase reaction and neuroendocrine response . . . 145

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3.3. Cytokines, HPA activation and glucocorticoid release . . . 146
3.4. A key role for IL-6 . . . 149
3.5. Changes in the somatotropic hormones, efficiency of immune response and body growth. . . . 151
3.5.1. Immune challenge and GH/IGF-1 axis . . . 151
3.5.2. The role of somatotropic hormones in the immune response. . . . 152
3.5.3. Infection, immunity and growth. . . . 153
3.6. Adipokines and immunity: a role for leptin as a neuroendocrine link? . . . 154
4. Conclusions . . . 156
Acknowledgements . . . 157
References . . . 157

1. Introduction

The Central Nervous (CNS) and Immune Systems (IS) are the two major adaptive systems which respond rapidly to the numerous challenges that are able to compromise health.

It has been known for more than 70 years (Seyle, 1936, 1955) that an acute challenge, such as environmental stressors, tissue damage or infection, induces a stereotyped neuroendocrine response in humans and animals which results in physiological adaptation. On the other hand, inflammation/innate and acquired immunity, when efficiently activated against pathogens, provide an immediate and adaptive response with the clearance of pathogens and the development of immunological memory. The study of the communication between CNS and immune systems continued to show evidence and to define the many interactions that occur among the neural, neuroendocrine and immune systems by bidirectional routes (Nagy and Berczi, 1978; Besedovsky et al., 1981; McCann et al., 1994; Berczi et al., 1998).

Recently, extensive literature has provided more detailed information on the molecular signalling which links the two systems during the integrated response to an immune challenge: it is now known that this bidirectional cross-talk is based on the secretion of cytokines, hormones, neurotransmitters and neuropeptides (Sternberg, 2006; Mocchegiani et al., 2006; Kelley et al., 2007; Elenkov, 2008).

The recent advances in the understanding of the complex interplay between inflammatory signals and several hormonal axis has better defined this "two way street". The emerging concept is that a critical balance exists between hormones [Growth Hormone (GH), Prolactin (PRL), Glucocorticoids (GCs), catecolamin, insulin)] and pro-inflammatory cytokines [mainly Interleukin (IL)-1, IL-6 and Tumor Necrosis Factor (TNFα)] involving nervous, endocrine, immune organs (like the thymus) and so called "target" tissues (i.e. adipose and muscle tissue). This balance can influence the immune response and, consequently, the course of infection/severity of the disease as well as body growth, during inflammatory states. Data on the cellular and molecular aspects has characterized, the bidirectional interactions between hormone–hormone as well as cytokine–hormone at the receptor level. For example, PRL and GH counteract the catabolic and immunesuppressive functions of GCs and these impair the action of GH, PRL and IGF-1, GCs inhibits the pro-inflammatory cytokines and cytokines induces GCs, GH/IGF-1 and insulin resistance, etc. (Kelley et al., 2007).

This review aims at reviewing some important signalling pathways which drive bidirectional communication between the Immune and Nervous Systems during infection. Particular emphasis is placed on pro-inflammatory cytokines, several immunomodulator hormones such as Glucocorticoids, Growth hormone, Insulin-like Growth Factor-1, Leptin as well as nutritional factors, such as Zinc (Zn).

Finally, the review aims to report the current available data on this neuroimmune cross-talk in domestic animals. The intent is to report the data from field studies in domestic animals, mostly available for the GH/IGF-1 axis and leptin, but also to highlight the importance of this exciting research area in veterinary medicine, underscoring other important points and pathways of the neuroimmune cross-talk triggered by immune challenge. Indeed, many other interactions between protein hormones and cytokine [i.e., pro-inflammatory citokines-Hypothalamic–Pituitary–Adrenal (HPA) axis regulation, IL-6-GCs-Zn/immune response, IL-6-GH-Zn-Leptin and thymus activity), although mainly studied in mice and humans, could be transferred to domestic animals and represent promising topic of future research.

2. General aspects on bidirectional cross-talk between the immune and neuroendocrine systems

The NS can influence the immune system through two major pathways, the neuroendocrine axis and the autonomic nervous system (sympathetic and parasympathetic nerves). In humans and animals the stress adaptive response has substantial effects on both inflammatory and immune response by activating a neuroendocrine response based on:

(a) activation of the hypothalamic–pituitary–adrenal axis (HPA) with subsequent peripheral secretion of cortisol from adrenal glands;
(b) somatotropic axis activity;
(c) activation of Hypothalamic–Pituitary–Gonadal (HPG) and Hypothalamic–Pituitary–Thyroid systems (HPT) (Eskandari et al., 2003).

Neural pathways (sympathetic and parasympathetic innervation) also regulate the innate immune response at regional, local and systemic levels through neurotrasmitters

[(Cathecolamines, Acethylcholine) and neuropeptides, Vasoactive Intestinal Peptide (VIP), Substance P (SP), Calcitonin-gene related peptide (CRGP)] which have variable effect on immune cells activation and cytokine production (for a more detailed review the reader is referred to Sternberg, 2006 and Elenkov, 2008).

In turn, cytokines and chemokines produced both at peripheral inflammatory sites and/or locally in the CNS can modulate brain function and hormonal secretion by endocrine glands (Mastorakos et al., 1998; Turnbull and Rivier, 1999; Turrin and Rivest, 2004).

Many cytokines can be also secreted by cells of CNS system in several brain sites: Interferon (IFN)-α, IFN-γ, IL-1, IL-2, IL-6 and TNF-α have been shown to be produced in the CNS mainly by astrocytes and microglia. IL-1, IL-6, Transforming Growth Factor (TGF)-β, LIF (Leukaemia Inhibitor Factor), MIF (Macrophage Inhibitor Factor), IL-10, IL-18 can be produced by the hypothalamus and/or pituitary glands (Breder et al., 1988, 1993; McGeer and McGeer, 1995; Maier and Watkins, 1998; Kronfol and Remick, 2000; Petrovsky, 2001; Anisman and Merali, 2002; Silverman et al., 2005).

Pro-inflammatory and pro-immune cytokines are able to influence endocrine activity in the central nervous areas, in the thymus and pituitary and adrenal glands (Fig. 1).

They have been shown to stimulate or suppress the secretion of hormones at different levels of the CNS

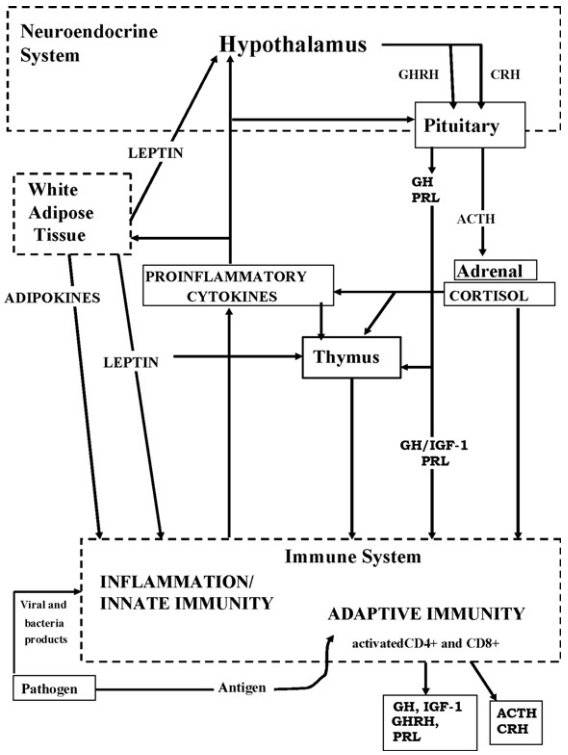

Fig. 1. Main organs and signalling pathways in bidirectional communication between Immune and Neuroendocrine Systems: pro-inflammatory cytokines, HPA and the somatotropic axis, thymus activity and adipose tissue hormones (see the text for explanation) (Webster and Sternberg, 2004; Mocchegiani et al., 2006; Sternberg, 2006; Gabler and Spurlock, 2008; Elenkov, 2008).

(Rothwell and Hopkins, 1995; Besedovsky and del Rey, 2000; Weigent and Blalock, 1999; Savino and Arzt, 1999; Petrovsky, 2001; Steinmann, 2004; Elenkov, 2008; Correa et al., 2007).

The main cytokines involved in IS-NS communication are IL-1, TNF-α, IL-2, IL-6, IFN-γ, IL-12 and IL-10 (Hughes et al., 1994; Lissoni et al., 1997; Smith et al., 1999; Turnbull and Rivier, 1999; Dantzer, 2004; Mocchegiani et al., 2006; Hopkins, 2007; Correa et al., 2007; Tu et al., 2007). Recent studies have emphasized an important role for chemokines in the regulation of neuroendocrine pathways during immune challenge and in pituitary hormone secretion (for review, see Callewaere et al., 2007).

During antigen-mediated activation CD4+ and CD8+ lymphocytes are also able to produce hormones like GH, PRL, Adrenocorticotropin Hormone (ACTH), Thyroid Stimulating Hormone (TSH) and gonadotropins (Mocchegiani et al., 2006) (Fig. 1).

In addition, a great deal of evidence *in vivo* and *in vitro* confirms the existence of a close relationship between thymus and neuroendocrine system (Fig. 1).

Hormones and neuropeptides modulate the thymic microenvironmental interactions, cytokine production and thymic endocrine activity, thus controlling intra-thymic T cell proliferation and apoptosis, as well as influencing T cell differentiation. Many hormones (GCs, GH, PRL, thyroid hormones) and neuropeptides are able to modulate thymic hormones, i.e. thymulin, secretion via thymic epithelial cells (TECs), probably acting on TEC-specific receptors. In turn, both TECs and thymocytes are able to secrete many neuroendocrine hormones (ACTH, GH, PRL, FSH, LH). Thymic hormones also modulate the production of hypothalamus/pituitary hormones and neuropeptides. Athymic nude mice display low levels of PRL, GH, Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH); in addition, thymulin exhibits an "in vitro" stimulatory effect on perfused rat pituitaries enhancing PRL, GH, TSH, and LH release (Savino and Dardenne, 2000; Mocchegiani et al., 2006).

It has become clear that nervous, immune and endocrine systems share in the production of the same proteins that are able to act as immunomodulator and metabolic regulators.

Several hormones and their receptors have been identified in immune tissues and it has been shown that they partecipate in the development, differentiation and regulation of the immune response. Among them, GCs, GH, IGF-1, leptin and Zn-thymulin, have been paid particularly attention for their effects on the immune response both *in vitro* and *in vivo* (Table 1).

The discovery of leptin in 1994, followed by many others adipokines, has identified the white adipose tissue (WAT) as a multifunctional endocrine organ producing a variety of pro-inflammatory and anti-inflammatory cytokines, mediators and hormones and with a relevant role in processes involved in energy balance regulation and metabolism. Other than specific proteins (such as leptin, adiponectin, resistin, vistatin, vasfin), the adipokine group includes classical cytokines (TNF-α, IL-6, IL-8), growth factors (TGF-β) and proteins involved in acute phase and stress responses (Serum amyloid A, haptoglobin, metal-

Table 1
Selected hormones and their modulatory activity on immune response (+: positive effect; −: negative effect).

Hormone	Effect on inflammation/immunity
GH	+ basal proliferation of lymphoid cells and maturation of bone marrow derived cells (Savino, 2007) + neutrophils differentiation (Savino, 2007) + production of pro-inflammatory cytokines: IL-1, IL-6 and TNF-α (Savino et al., 2003; Tsigos et al., 1997) + T-cells cytotoxic activity, NK-cells activity (Shimizu et al., 2005) + T-cells migration and adhesion (Savino and Dardenne, 2000) + release of Reactive Oxygen Species (ROS) from macrophages (Dekaris et al., 1998) + thymulin production (Savino et al., 2003)
GCs	− leukocyte trafficking (Pitzalis et al., 1997) − chemotaxis and migration of neutrophils and monocyte; circulating numbers of monocytes and monocyte (Webster et al., 2002) − inflammatory signaling pathway (NF-κB, AP-1) (Webster et al., 2002) − inhibition of DC differentiation and MHC expression (Woltman et al., 2002; Matyszak et al., 2000) − priming of the antigen specific response of CD8+ lymphocytes against viruses (Dobbs et al., 1993; Truckenmiller et al., 2006) − production of inflammatory mediators (COX-2, iNOS, A2 phospolipase, 15-lipoxigenase) and of pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IL-11, IL-12, GM-CSF, TNF-α, IFN-γ) (Webster et al., 2002) − proliferation and activity of cytotoxic T lymphocytes (Bonneau et al., 1998) + Th2 response: IL-4, IL-10 production, inhibition of IL-12 (Agarwal and Marshal, 2001; Webster et al., 2002; Elenkov and Chrousos, 1999) + thymocyte and lymphocyte apoptosis (Migliorati et al., 1994; Herold et al., 2006; Wang et al., 2006)
IGF-1	+ differentiation and proliferation of myeloid cells (Lin et al., 1997) + anti-apoptotic factor for myeloid lineage cells (innate immunity cells (Burgess et al., 2003; Clark, 1997)) + NK-cell activity (Kooijmann et al., 1996) + *in situ* production of TNF-α from activated macrophages (Renier et al., 1996) + proliferation of lymphocytes T/B in lymphoid organs (van Buul-Offers and Kooijmann, 1998) + differentiation of thymic T-cell progenitors (Gjerset et al., 1990) + differentiation of pro-B lymphocytes in the bone marrow (Funk et al., 1994)
Leptin	+ lymphopoiesis; survival of CD4+CD8+ and CD4+CD8- thymocytes (Lam and Lu, 2007) + NK differentiation, proliferation and activity (Tian et al., 2002) + polarization of Th1 response in effector cells; anergie and hyporesponsiveness in CD4+CD25+ T regulatory cells; proliferation of CD4+ CD25− T cells (De Rosa et al., 2007) + activities of monocyte (NO and cytokines production: TNF-α, IFN-γ) (Mancuso et al., 2004; Otero et al., 2006) + oxidative stress in endothelial cells (Bouloumie et al., 1999) + stimulation activity of neutrophils (Caldefie-Chezet et al., 2003) + survival, maturation and cytokine production of Dendritic Cells (DC) (Lam et al., 2006)
Zn-Thymulin	+ thymocyte differentiation + NK activity + IL-2 production by T-cells + T-cells cytotoxicity and suppressor function (Savino and Dardenne, 2000; Meazza et al., 2007; Prasad, 2008; Onodera et al., 1994; Molly and Marsh, 2003; Mocchegiani et al., 2006)

lothionein, plasminogen activator inhibitor-1) (Trayhurn and Wood, 2004; Fantuzzi, 2005).

Recent studies have emphasized these new functional aspects of both adipose and muscle tissue and their involvement as integral components of bidirectional communication between immune and endocrine systems. Adipocytes and myofibers have TLRs for innate pathogen recognition receptors and produce cytokine and immune modulators which may be able to regulate energy and protein metabolism as well as to exert effects on inflammatory and innate immune responses (Gabler and Spurlock, 2008; Quinn, 2008).

Adiponectin and leptin are two major adipokines involved in metabolic modulation and energy balance. The role of leptin in particular as an important link between nutritional and energy homeostasis during infection, and as an immunomodulator hormone (Matarese et al., 2005; Bernotiene et al., 2006; Otero et al., 2006) is being increasingly studied (Table 1).

Indeed, neuroendocrine regulatory factors play a major role in the development of the Immune System (IS) and in the functional activation and regulation of the immune response; conversely, the signals (cytokines/chemokines) from inflammatory/immune responses induce activation of a neuroendocrine response which controls and dampens inflammation, permitting the return to a homeostatic state and modulation of tissue metabolism which temporarily repartions nutrients and favours immune system activity rather than other functions (Mastorakos et al., 1998; Webster et al., 2002; Sternberg, 2006).

The increased understanding of neuroendocrine control of inflammation in man has provided important insights into the pathogenesis of some inflammatory/immune-mediated diseases, neuropsychiatric disorders such as major depression, and metabolic diseases (Schiepers et al., 2005; Elenkov, 2008).

Similarly, in animals, evidence suggests that the bidirectional communication between the immune and neuroendocrine systems could play a pivotal role both in metabolic, productive and behavioural homeostasis and in the efficiency of immune responses against infectious agents and hence in the maintenance of health (Berczi et al., 1998; Davis, 1998; Sartin et al., 1998; Haeryfar and Berczi, 2001). Certainly, despite increasing progress in animal immunology, there is still much to understand on how exogenous and/or endogenous factors (management

practices, environmental stressors, nutritional factors) can influence the development and the activation of immune responses in terms of functional efficiency. In intensive animal husbandry, neonates are highly sensitive to various stressors such as weaning, mixing, fighting for dominance and shipping, and stressors have been shown to negatively affect the development and efficiency of immunity, with an increased risk for infectious diseases (Hicks et al., 1998; Deguchi and Akuzawa, 1998; de Groot et al., 2001; Kanitz et al., 2002; Tuchscherer et al., 2002).

Indeed, the nervous system appears to be an integral partner of innate immunity in modulating and controlling the immediate, non-specific host response to pathogens (Sternberg, 2006). Thus, the evaluation of the efficiency and the role played by this intimate functional connection in response to infection appears crucial.

3. The integrated immune-neuroendocrine response during infection

3.1. Pathogen recognition and inflammatory/innate response activation

The immune system continuously works to limit pathogen invasion and tissue damage and to efficiently protect the organism against invaders. It is evident that immunity against pathogens is orchestrated by natural (innate) and acquired (adaptive) immunity which intimately interact with each other by close cooperation between their cellular components.

The innate response provides the first defensive line against pathogens because it can be activated immediately after infection. Early recognition of pathogens is the key event in the initiation of an innate immune response; innate immune cells are able to recognize pathogens by receptors that function as "danger signals" and activate an immediate and constant response. The pathogen recognition by innate immune cells occurs by means of Pattern Recognition Receptors (surface, humoral and cytoplasmatic PRRs) binding Pathogen Associated Molecular Pattern (PAMPs). A major pathway of pathogen recognition is based on the TOLL-like Receptors (TLRs) expression on the surface of innate and inflammatory cells [neutrophils, macrophages, endothelial cells, Natural Killer (NKs) cells, Dendritic Cells (DCs)]. Different bacterial molecules are recognized by TLRs, particularly by TLR2 (peptidoglycan and lipotheicoic acid), TLR5 (flagellin), TLR9 (bacterial CpG) and TLR11 (uropathogenic bacteria). In Gram-negative bacterial infections, lipopolysaccharide (LPS) is released during host-mediated bacteriolysis: LPS complexes with host LPS binding protein, and soluble CD14, or membrane-bound CD14 found on the surfaces of macrophages and dendritic cells. This complex is recognized by TLR4, present on the cell membrane. TLR4 ligation leads to the induction of the inflammatory response characterized by the release of the pro-inflammatory mediators IL-1β, IL-6, TNF-α and macrophage migration inhibitory factory (MIF). During viral infection a role for TLRs in triggering the adaptive response has been established after the discovery of specific TLRs responsive to viral molecules (nucleic acids and envelope proteins). Double-stranded RNA (dsRNA), a viral PAMP generated during virus replication, binds and activates TLR3 and TLR9 recognizes CpG motifs of viral DNA. Moreover, single-stranded viral RNA (ssRNA), genomic material from many different viruses, triggers the activation of TLR7 and TLR8 (for a more detailed review on TLR-mediated pathogen recognition the reader is referred to Werling et al., 2006; Werling and Coffey, 2007).

PAMP-TLR-mediated recognition activates the cell via TIR (Toll/IL-1 receptor domain) and sequentially the signal transduction and the nuclear translocation of NF-κB factor engages the gene transcription for many pro-inflammatory cytokines, chemokines, complement proteins, and adhesion molecules of innate response, driving the recruitment and the activation of inflammatory and immune cells. Cytokines and TLR-mediated cell activation also induce the expression of selectins, cytokine and chemokine receptors and integrins on the endothelial surface, orchestrating the recruitment of circulating leucocytes (neutrophils, monocytes and NK) and the activation of tissue stromal cells and tissue-resident innate cells such as immature DCs, macrophages, γ/δ lymphocytes and mast-cells (Della Chiesa et al., 2005).

Thus, the concerted action of epithelial, endothelial, inflammatory and innate cells expressing TRLs constitutes the first barrier against pathogens at sites of infection. After a natural recognition of pathogens, the most prominent pro-inflammatory cytokines (IFNα/β, IL-1, TNF-α, IL-6, IL-8, IL-15) released by activated tissue and inflammatory cells, upregulate aspecific effector mechanisms of defence. These locally produced cytokines trigger endothelial activation, chemokine expression and the recruitment of inflammatory cells, inducing macrophage activation and maturation of dendritic cells which, in turn, promote antigen presentation (Hoebe et al., 2004; Turrin and Rivest, 2004; Thacker, 2005; Corradi et al., 2007).

During infection, the upregulation of pro-inflammatory cytokines (mainly IL-1, TNF-α, IL-6, MIF) induces the Acute Phase Reaction (APR) characterized by fever, impairment of the level of consciousness, anorexia, hormonal changes and metabolic modifications such as protein catabolism, lypolisis and gluconeogenesis. Moreover, classical features of the APR include hypoferremia, hypozincaemia and hepatic production of Acute Phase Proteins (APPs) like metallotionein (MT) (Gruys et al., 2005). In this context, the interaction among pro-inflammatory cytokines, particularly IL-6, MT and Zinc can play an important role in influencing the inflammatory and innate immune response (Mocchegiani et al., 2007) (see Section 3.4) (Fig. 2).

The APR is an immediate response in which a drastic increase of the local and systemic natural defensive mechanisms provides rapid and efficient protection. To be beneficial, the APR must be acute, destroy the pathogen, limit and repair the damaged tissue within a short time, and drive a subsequent acquired immune response against the pathogen (Berczi et al., 1998; Haeryfar and Berczi, 2001).

3.2. Acute phase reaction and neuroendocrine response

For a successful resolution of infection, an efficient activation of innate/inflammatory and acquired immunity is required to block pathogen replication and invasion, as well as to operate the tissue clearance of pathogens and/or infected cells.

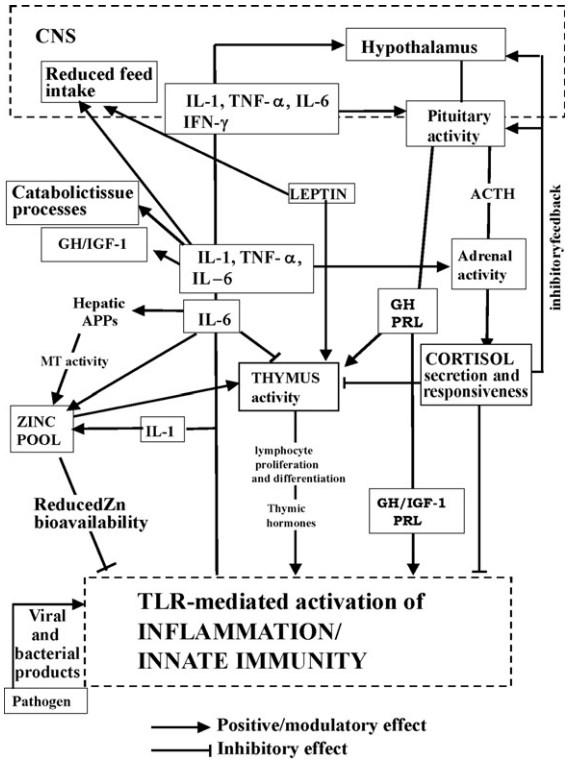

Fig. 2. Main immune and neuroendocrine signals during the APR (see text for explanation).

This adaptive response to pathogens appears to be dependent on the efficient interaction between the immune and neuroendocrine systems. During the APR, pro-inflammatory cytokines stimulate a neural and neuroendocrine response which amplifies the innate immunity, induces metabolic changes and controls inflammation to restore the homeostatic state (Fig. 2).

It is known that in many bacterial and viral infections, activation of the neuroenocrine axis occurs. Lypopolysaccharides (LPS), toxins, other components of bacteria and many viruses have been shown to induce changes on the HPA, HPG and HPT axes.

Indeed, cytokines produced in the central lymphoid organs and at the periphery have a pivotal role in orchestrating the neuroendocrine immune network during infection.

Pro-inflammatory cytokines and PAMPs can reach and affect the CNS by several mechanisms: (a) by passive diffusion into different areas where the blood–brain barrier (BBB) is absent or poorly developed, i.e. circumventricular sites, or by BBB breakdown due to a pathological condition; (b) by active transport across the BBB; (c) moreover, cytokines may also trigger pro-inflammatory signals in the brain through the interaction with receptors on BBB endothelial cells and the subsequent increased synthesis and release of second messengers (prostaglandins and nitric oxide) which can influence neuronal activity; (d) a pathway may also be mediated via the nervus vagus (Banks et al., 1995; Watkins et al., 1995; Merril and Murphy, 1997; Maier and Watkins, 1998; Turrin and Rivest, 2004; Correa et al., 2007).

The circumventricular organ (CVO) may be a key area of entry or action for many circulating inflammatory/immunogenic agents (PAMPs and LPS). In CVO, receptors for pro-inflammatory cytokines and TLRs (CD14, TLR2, TLR4, TLR9) are constitutively expressed. It may be also the site through which cytokines and pathogens can act upon the HPA axis by means of a structural connection between CVO organs and the CRH neurons of the hypothalamic paraventricular nucleus (PVN) (Bette et al., 2003; Turrin and Rivest, 2004; Chakravarty and Herkerenham, 2005; Kielian, 2006; Correa et al., 2007).

IL-1 has a direct effect on the HPA axis both at the hypothalamic and pituitary level, causing increased plasma concentrations of CRH, ACTH and cortisol (Sapolsky et al., 1987; Besedovsky and del Rey, 2000). IL-1 also stimulates release of GH, TSH, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) and inhibits PRL secretion from rat anterior pituitary cells (Beach et al., 1989; Xu et al., 1999; Mocchegiani et al., 2006).

The endocrine action of TNF-α is characterized by fever, hepatic synthesis of acute phase proteins and induction of catabolic processes (Hopkins, 2007) and ACTH, PRL and GH secretion during acute phase response (Berczi et al., 1998, 2000; Sartin et al., 1998). In the cow, contrary to man and rodents, recombinant bovine TNF-α induces considerable rises in plasma cortisol with a variable response in plasma ACTH, suggesting a possible direct action on adrenal glands (Soliman et al., 2004). Although this cytokine shows an inhibitory effect on cortisol secretion in adrenal cells *in vitro*, the positive effect of TNF-α *in vivo* may be different than that of intra-adrenal TNF-α as a result of integrated cytokine pathways targeting the gland (Judd et al., 2000; Silverman et al., 2005).

Studies *in vivo* have demonstrated a role of INF-γ in the neuroimmune circuit as a stimulating factor of the HPA axis, particularly ACTH secretion, and in the inhibition of GH and TSH production (Holsboer et al., 1988; Vankelecom et al., 1997; Weigent and Blalock, 1999). IFN-γ also upregulates the Glucocorticoid Receptor (GR) expression on macrophages, thus suggesting a control mechanism induced during immune activation (Salkowsky and Vogel, 1992). In the cow, the intravenous administration of INF-γ induces a dose-dependent rise in the plasma levels of both cortisol and ACTH indicating that the stimulatory effect on cortisol secretion is mediated by the CRH–ACTH axis (Soliman et al., 2004).

The potential pathways which mediate the effect of pro-inflammatory cytokines and/or LPS on the neuroendocrine system are still partially unknown for the somatotropic axis as well, and possible alternative mechanisms to intrahypothalamic pathways have been suggested, such as a direct action on pituitary (Daniel et al., 2002, 2005; Carroll, 2008).

3.3. Cytokines, HPA activation and glucocorticoid release

The activation of the HPA axis is one of the major neuroendocrine features of the APR. Pro-inflammatory cytokine (IL-1, TNF-α, IL-6) production during the APR is

controlled both by intrinsic anti-inflammatory mechanisms [i.e, IL-10, IL-1 receptor antagonist (IL-Ra) and TNFRs (soluble TNF receptors)] and by the stimulation of HPA and cortisol release. Moreover, strict regulation also occurs to prevent overactivation of inflammation and immune-mediated tissue damage (Sternberg, 2006). This is even more crucial in the presence of an overproduction of cytokines during inflammation/infection. It is likely that, if a counterbalance does not occur, some diseases (uncontrolled inflammation, catabolic disease, autoimmune phenomena, psychiatric disorders) may develop (Schiepers et al., 2005; Mocchegiani et al., 2006; Elenkov, 2008).

During the APR, while innate mechanisms of defence are strongly increased, the activation of the HPA axis exerts a negative modulation on adaptive immunity (Fig. 2).

GCs from the HPA axis and noradrenalin from the sympathetic/adrenomedulallary system appear to be the prominent mediators driving this "immunoconversion". Altered levels of GCs and TNF-α and a reduced response to GH and PRL are consistent with transitory thymic apoptosis and adaptive immune suppression which is considered to be important in controlling potential autoimmune responses during inflammation (Haeryfar and Berczi, 2001).

However, hormones released by the pituitary and adrenal glands must also control pro-inflammatory cytokines; high plasmatic glucocorticoid levels suppress a further release of pro-inflammatory cytokines (Fig. 2).

Despite recent studies suggesting that GCs may stimulate inflammation in some circumstances such as during the early phase of acute stress (Sorrells and Sapolsky, 2007), activation of the HPA axis is still considered the main physiological feedback loop of inflammation and the anti-inflammatory effects of GCs inhibit the production and activity of pro-inflammatory and pro-immune cytokines (Table 1).

GCs are able to inhibit the NF-kB pathway, IL-12 and IFN-γ synthesis, while they upregulate IL-10, IL-4 and TGF-β secretion; thus, during an immune-inflammatory response, HPA axis activation, with increased levels of GCs, provokes a Th2 shift, thus controlling an excessive Th1 response (Vivero-Paredes et al., 2006; Pace et al., 2007; Elenkov, 2008). This negative feedback loop serves as a major regulatory mechanism to prevent tissue damage by inflammatory over-activation (Fig. 2). GCs play a fundamental role in controlling and restraining innate/inflammatory and neuroendocrine responses primed against a variety of challenges including pathogen infection (Chrousos, 1995; Sternberg, 2006; Calcagni and Elenkov, 2006).

If glucocorticoids have a central role in the control of the local and systemic inflammatory response during and after pathogen challenge and in the prevention of excessive inflammation, it is thus not surprising that a failure in GCs production or tissue resistance to the inhibitory effects of GCs may result in uncontrolled inflammation and potential damage. Chronic inflammation, inflammatory tissue damage in infection, autoimmunity are characterized by a dysregulation of the pro-/anti-inflammatory and Th1/Th2 cytokine balance (Sternberg, 2006). In humans, this mechanism appears to be involved in the pathogenesis of some diseases such as Rheumatoid Arthritis, cardiovascular disease, diabetes, cancer, and depression (Calcagni and Elenkov, 2006; Pace et al., 2007).

Experimental evidence has confirmed that, depending on the pathogen, dose and species, the suppression of HPA activation by different mechanisms, results in an increase of immune/inflammatory reactivity and of the severity of infection (Bailey et al., 2003; Webster and Sternberg, 2004).

Adrenal release of GC is thought to depend mainly on HPA axis activation with increased levels of ACTH which itself triggered by CRH release from hypothalamus.

As mentioned above, alternative pathways for adrenal glucorticoid regulation have been reported, such as altered sensitivity of adrenal to ACTH and ACTH-independent stimuli (e.g. neuropeptides, endotoxin, immune cytokines and adipocyte-derived adipokines). Thus, several possible mechanisms can contribute to the dissociation of ACTH and cortisol levels observed in a wide variety of diseases including inflammation and sepsis. Several preclinical and clinical studies have suggested that further evaluation of the clinical significance of non-ACTH-driven glucorticoid release during clinical illness could be of great interest (Bornstein et al., 2008; Webster and Sternberg, 2004).

Moreover, not only the activity but also the cortisol levels of HPA axis are important in controlling immune activation. Recent evidence suggests that the reactivity of specific immune cells to GCs, which depends on the number of Glucocorticoids Receptors (GRs) and/or the expression of intracellular signalling, is also fundamental (Heijnen, 2007). Several studies have shown that inflammation itself may contribute to altered glucocorticoid sensitivity: bacterial and viral products and some cytokine signalling pathways can interact with the GR signaling pathway and thereby alter glucocorticoid action (Elenkov and Chrousos, 1999; Webster and Sternberg, 2004; Pace et al., 2007).

Thus, a dysregulation of HPA axis characterized by altered ACTH and GC secretion and/or reduced GC responsiveness or increased tissue GC resistance can increase the susceptibility to infection and the risk of mortality from septic shock (Sternberg, 2006) [Fig. 3(e)].

Recent studies have described the value of HPA hormone changes as prognostic indicators and predictors of survival in critically ill animals.

In one study, septic foals had significantly higher mean ACTH, cortisol, and ACTH/cortisol ratio than normal foals and the mean ACTH/cortisol ratio (A/C) was significantly higher in the septic, non-surviving foals as compared to the septic survivors. These results indicate that the severity of sepsis and survival appear to be associated with increased ACTH/cortisol ratios highlighting a dysfunction of the HPA axis (Gold et al., 2007a).

Castagnetti et al., 2008 reported that, in critically ill neonatal foals, ACTH plasmatic levels and A/C values were higher in septic non-surviving foals than in survivors, confirming that the A/C ratio may be more indicative of the functionality of HPA axis than the absolute value of each hormone.

In another study, vasopressin (AVP), ACTH and cortisol were higher in septic foals and increased plasma and ACTH concentrations were associated with mortality. Several

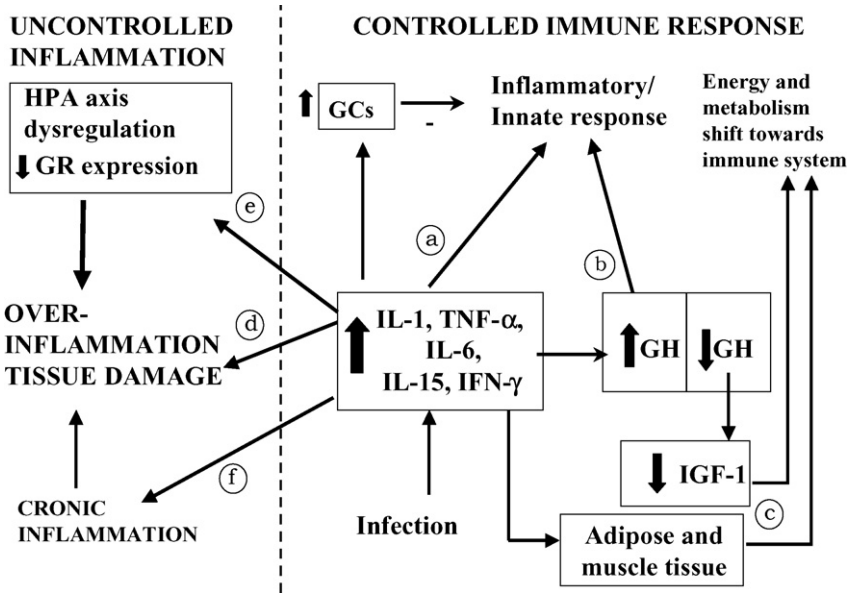

Fig. 3. Possible pathways involved in controlled immune response or in uncontrolled inflammation: the central role of pro-inflammatory cytokine levels and glucocorticoids. (a) IL-1, TNF-α and IL-6 production sustains an early and efficient inflammatory/innate response which limits and destroys the pathogen and primes acquired immunity; glucocorticoids (GCs) control the local and systemic inflammatory response preventing damage by excessive inflammation; (b) uncoupled regulatory linkage between GH and IGF-1 during infection: increased levels of GH could be considered as a compensatory attempt to sustain innate immunity and counteract excessive GC activity; (c) reduced GH and IGF-1 activity drives metabolic and nutritional modifications towards supporting the immune function; cytokine production in adipose and muscle tissue can favour energy partitioning; (d) uncontrolled high levels of pro-inflammatory cytokines, IL-1, TNF-α particularly IL-6, cause inflammatory tissue damage concomitantly with (e) HPA axis dysregulation, altered levels of ACTH and/or GCs and reduced GCs Receptor (GR) expression; (f) persistent levels of IL-6 mediate chronic inflammation (Calcagni and Elenkov, 2006; Heemsherk et al., 2001; Sternberg, 2006; Heijnen, 2007; Pace et al., 2007; Elenkov, 2008; Webster et al., 2002; Webster and Sternberg, 2004; Gabay, 2006; Gabler and Spurlock, 2008; Quinn, 2008).

septic foals had increased AVP:ACTH and ACTH:cortisol ratios, which indicated relative adenohypophyseal and adrenal insufficiency. The results in foals differ from those in humans where septic patients often have low ACTH and cortisol levels and this may reflect species-related differences or could depend on age and on duration and severity of illness. Only in some critically foals, low or normal levels, associated with marked increase of ACTH, could suggest relative adrenal insufficiency (RAI) (Hurcombe et al., 2008).

All these studies, however, have concluded that additional research is needed to define relative adrenal insufficiency in sepsis, in order to justify specific treatment protocols.

Septic dogs, on the other hand, show results similar to that seen in septic humans. Low delta-cortisol values following adrenocorticotropic hormone administration was associated with systemic hypotension and decreased survival, indicating that RAI occurs in some septic dogs and is a marker of more severe illness (Burkitt et al., 2007).

Indeed, it is generally assumed that in severe sepsis a largely unopposed pro-inflammatory response results in increased organ injury and mortality and that serum levels of TNF-α, IL-1β correlate with the severity of sepsis (Martin et al., 1997; Meduri et al., 1995).

However, it has become clear that any single circulating mediator cannot be predictive of severity of infection, which likely depends on the balance between pro-inflammatory and anti-inflammatory mediators.

Recent studies have reported that timing and intensity of a predominant anti-inflammatory response [IL-10, IL-1Ra (IL-1 receptor antagonist) and TNFRs (soluble TNF receptor) levels] can also be an important predictive condition of mortality. An intense anti-inflammatory response is able to induce immunesuppression [Fig. 4(e)] leading to an increased risk of bacterial overinfection (Ashare et al., 2005). Non-surviving septic foals also have a significantly greater increase of IL-10 gene expression compared to survivors (Pusterla et al., 2006).

MIF is a fundamental pro-inflammatory cytokine produced by mononuclear and T cells and is also constitutively expressed by endocrine cells such as pituitary cells (Bernaghen et al., 1993). MIF is considered a major mediator of septic shock in murine models of infection and is involved in the pathogenesis of some inflammatory diseases (Sashinami et al., 2006). During gram-negative sepsis in humans, MIF is markedly and persistently upregulated together with overriden levels of GCs (Emonts et al., 2007).

Current data would thus indicate that a severe imbalance between pro-inflammatory (i.e. MIF, TNF-α, IL-6) and anti-inflammatory (GCs, IL-10) responses exists in sepsis and can influence the severity of the disease.

Conversely, conditions characterized by chronicly high levels of GCs can affect the susceptibility to those infections normally controlled by Th1-mediated immunity by altering the Th1/Th2 balance. Excessive and prolonged production of cytokines like IL-1 and TNF-α can induce increased activation

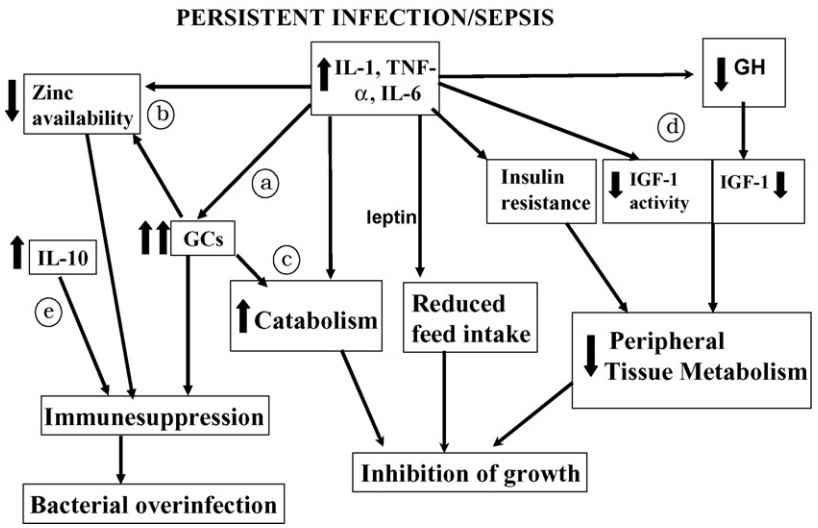

Fig. 4. Possible pathways contributing to immunosuppression and catabolic state in persistent infection and sepsis. (a) Excessive and chronic production of cytokines induces overactivation of HPA; (b) persistent levels of IL-6 and of GCs induce immunosuppressive effects by impairing Th1 immunity and zinc bioavailability; (c) High GCs and pro-inflammatory cytokines exert tissue catabolic effect; (d) pro-inflammatory cytokine levels lead to muscle and liver GH resistance and the inhibition of IGF-1 activity (see the text); (e) high levels of anti-inflammatory mediators such as IL-10 contributes to immunesuppression with an increased risk of bacterial overinfection. (Spurlock, 1997; Briard et al., 2000; Heemskerk et al., 1999; Frost and Lang, 2004; Ashare et al., 2005; Mocchegiani et al., 2006, 2007; Cooney and Shumate, 2006).

of the HPA axis with subsequent immune-suppression (Calcagni and Elenkov, 2006; Correa et al., 2007). This has been shown to occur in the presence of chronic bacterial and viral infections, and is mediated by upregulation of GC receptors (GR) (Webster and Sternberg, 2004).

Thus, the severity of infection depends on a complex interaction between activating and controlling pathways. These include the status of activation and/or dysregulation of the HPA axis, tissue sensitivity, response and direct effect of pathogen on GR and the level and persistence of pro-inflammatory cytokines [Fig. 3(d and e)]. In this context, IL-6 seems to play a pivotal role.

3.4. A key role for IL-6

In inflammation, IL-6 has a major effect on the hepatic synthesis of Acute Phase Proteins (APPs) and is also critical in controlling the extent of acute local and systemic inflammation, particularly in decreasing the level of pro-inflammatory cytokines by exerting a protective effect against potential damage and favouring anti-inflammatory activity. IL-6 not only elicits the APR but also promotes acquired cell-mediated and humoral response such as B-cell differentiation, immunoglobulin production and T cell activation (Thacker, 2005; Maggio et al., 2006). Furthermore, evidence has suggested that IL-6 stimulates the development of Th2 cells (Rincon et al., 1997). It has been demonstrated that IL-6 shifts the Th1/Th2 balance of an immune response towards Th2 in two independent ways, by promoting early IL-4 expression and by rendering CD4 T cells unresponsive to IFNγ signals, inducing the expression of Silencer of Cytokine Signaling (SOCS)1 (Dienz and Rincon, 2009).

Several studies have demonstrated that IL-6 acts as an effective pyrogen and as a circulating mediator of HPA activation influencing each level of the axis (Hopkins, 2007). IL-6 receptors have been detected in the brain and in the pituitary and adrenal glands. IL-6 stimulates CRH production by the hypothalamus and induces ACTH, PRL, GH secretion by the pituitary gland.

It also directly stimulates the release of glucocorticoids from the adrenal cortex with ACTH as a permissive factor for this activity. Indeed, as IL-6 increases ACTH stimulation of the adrenal cortex, higher levels IL-6 may be associated with higher levels of cortisol in response to ACTH (Savino and Arzt, 1999; Savino and Dardenne, 2000; Barney et al., 2000; Silverman et al., 2004; Zarković et al., 2008). The direct effect of IL-6 on adrenal function is probably most important during chronic conditions (Judd et al., 2000).

From studies of a murine model of infection, the efficiency of the HPA axis response depends on IL-6 and is crucial for protection against TNFα-mediated mortality (Ruzek et al., 1999); moreover, an IL-6 and ACTH-independent immune-adrenal pathway has been identified to explain the dissociation of ACTH and corticosterone levels (Silverman et al., 2004). During protozoan or viral infection, high serum levels of IL-6 and glucocorticoids may be associated with low or normal levels of ACTH (Silverman et al., 2004; Corrêa-de-Santana et al., 2006). In fact, there is evidence that, when a sustained glucocorticoid response is needed to control the inflammation, a CRH-independent alternative pathway can occur through direct action of IL-6 on adrenal glands. This dissociation between high cortisol and low corticotropin hormone levels may occur in chronic inflammation or sepsis (Judd et al., 2000; Vermes and Beishuizen, 2001; Silverman et al., 2004, 2005).

Taken together, these results suggest that IL-6/HPA axis may respond differently during acute or chronic inflammation (Mastorakos and Ilias, 2006). Chronic overproduction of IL-6 and related HPA axis dysregulation, has been

considered an important pathway affecting health status during chronic inflammation, chronic stress, aging and metabolic disease (Maggio et al., 2006; Gabay, 2006).

Thus, IL-6 shows contrasting activities in acute or chronic inflammation. During acute inflammation IL-6 mediates the APR (Gruys et al., 2005) and modulates the over-activity of inflammation. Conversely, persistent levels of IL-6 induce transition to chronic inflammation, where it has a damaging effect by promoting the recruitment, proliferation and survival of monocyte/macrophage cells at the site of injury (Gabay, 2006) [Fig. 3(f)].

Several studies have emphasized the role of IL-6 as a marker of viral and bacterial infection in pigs (Fossum, 1998; Van Reeth, 2002; Thacker, 2005).

During experimental infection with *A. pleuropneumoniae*, IL-1 and IL-6, but not TNF, are rapidly and dramatically increased in the bronchoalveolar lavage (BAL) fluid of the lung within 24 h of infection. The increased levels of IL-1 might increase the severity of disease, and elevated IL-6 levels are consistent with an acute phase response (Murtaugh et al., 1996) coinciding with fever and respiratory symptoms. Thus, while the presence of IL-6 in serum seems to be restricted to the acute phase of infection, the persistent levels of this cytokine can be a valuable tool as markers for ongoing (subclinical) infections (Fossum, 1998).

In a porcine model of acute respiratory syndrome by PRCV (Porcine Respiratory Coronavirus), long-term treatment with dexamethasone may increase the viral replication by inhibiting innate cells and early cytokine response. This may be followed later by high levels of IL-6 in serum and BAL fluid, consistent with inflammatory-mediated lung damage; in this scenario IL-6 may play a role in sustaining inflammation and immunosuppression, together with high levels of corticosteroids (Zhang et al., 2008).

Moreover, Brockmeier et al. (2008) have demonstrated that pigs coinfected with PRCV and *Bordetella bronchiseptica* showed greater and more sustained expression of cytokines, particularly IL-6 and monocyte chemotactic protein-1 (MCP-1), which may partially explain the increased severity of pneumonia.

Rau et al. (2007) measured IL-6 plasma levels in dogs with naturally occurring systemic inflammatory response syndrome (SIRS) and sepsis. Higher plasma IL-6 levels on the day of admission were significantly correlated with a more severe degree of disease, increased mortality rate, and earlier fatality. The Authors concluded that plasma IL-6 concentration is predictive of outcome in canine SIRS and sepsis and may be a valuable laboratory parameter for assessing critically ill dogs.

Concentrations of TNF-α and IL-6 may also be promising markers for the identification of periparturient sows with subclinical coliform mastitis (Zhu et al., 2004).

Results from a study of a murine model of sepsis, induced by cecal ligation and puncture (CLP), showed that sepsis moves through different stages, a early phase of increased inflammation in which dying mice have high levels of IL-6 and a late phase in which the response is variable. During the chronic phase of sepsis some mice die with evidence of immune suppression (increased bacterial growth and low levels of IL-6) while other mice die with signs of immune-stimulation (high levels of IL-6 and bacterial growth) (Xhiao et al., 2006).

In septic foals, Gold et al. (2007b) demonstrated an upregulation of TLR4 and IL-4 gene expression in Peripheral Blood Mononuclear Cells (PBMC) and no significant changes in IL-1β, IL-8, IL-6 and IFN-γ at the time of admission; however a strong increase of IL-6 was observed in foals which died. The authors highlighted that, despite the presence of sepsis and the upregulation of TLR4, gene expression of IFN-γ was not upregulated. Despite the limited number of non-surviving foals, the authors concluded that increased IL-6 expression should be evaluated further as a potential marker for poor prognosis.

Zinc plays an intriguing role in the GC–cytokine interaction during infection, due to strong interrelation between pro-inflammatory cytokines (IL-1, TNF-α and IL-6) and zinc status (Mocchegiani et al., 2006, 2007). Hypozincemia is frequent in acute and chronic inflammatory and infectious diseases. During the APR, hypozincemia is mainly due to a redistribution of zinc among various tissue, particularly the liver, and is associated with an increase in the hepatic zinc pool. IL-1, and particularly IL-6, has been shown to enhance both the induction of metallotionein (MT)-bound zinc and zinc transporter gene expression (Liuzzi et al., 2005).

Metallotioneins (MTs) have a crucial role in regulating zinc homeostasis due to their high affinity for zinc. An important function of MTs is the release of zinc in response to oxidative/nitrosative stress in order to up-regulate zinc-dependent antioxidant enzymes. During acute inflammation, MTs act as protective agents preventing zinc deficiency and as chemotactic factors that govern the trafficking of leucocytes to the site of inflammation.

Heightened levels of metallothionein, associated with high IL-6 and low zinc release by MT, have been observed in diseases characterized by chronic inflammation, stress and in syndromes of accelerated ageing in man. Thus, under conditions of chronic inflammation, MT over-expression may reduce zinc availability, causing impaired innate immune responses and down-regulation of anti-oxidant activity. Furthermore, high levels of MTs alter chemotactic response of leucocytes, which in turn may alter the outcome of inflammation, causing tissue damage (Mocchegiani et al., 2007; Mazzatti et al., 2008).

It has also been reported that during infection, high levels of GCs, along with high levels of IL-1 and IL-6, are associated with consistent zinc loss in urine and faeces, with subsequent impairment of innate immunity. Taking into account that Zn is important for innate immunity, Zn deficiency associated with stress and high levels of GCs, cause a decrease in the resistance to infection [Fig. 4(b)] and a continuous imbalance of Th1/Th2 paradigm. Thymic functions are influenced by zinc bioavailability because zinc is required to instigate the biological activity of thymulin which promotes T cell function and affects T lymphocyte differentiation. Zinc deficiency causes hypoplasia of primary and secondary lymphoid organs (thymus, spleen, lymphnodes, and Payer's patches), a decreased number of total T-lymphocytes, impaired T-helper and T-suppressor function, reduced NK cell activity, an imbalance

of the Th1/Th2 with major production and release of Th2 cytokines (IL-6) and subsequent low resistance to infections (Shankar and Prasad, 1998; Mocchegiani et al., 1998b, 2000, 2006).

Even though one study has evaluated its effect on body growth and intestinal efficiency (Hedemann et al., 2006), few studies have been performed on the effect of zinc on immune responses in pathological conditions in domestic animals. Zinc deficiency and decreased thymic endocrine activity were observed in piglets fed from sows exposed to aflatoxins AFB1 and AFG1 as compared with healthy control piglets. The lymphocytes mitogen responsiveness (PHA) was decreased and thymic cortical lymphocyte depletion was also present. These results suggest that the thymic defect, followed by impaired peripheral immune efficiency, may have largely depended on low peripheral zinc (Mocchegiani et al., 1998a).

In calves fed milk supplemented with zinc, higher IgG and IgM responses were observed, suggesting a stronger humoral immune response, probably as a result of the beneficial effect of zinc on the interaction between T helper cells and B cells (Prasad and Kundu, 1995).

Other studies reported that, in contrast to findings in laboratory animals, marginal Zn deficiency does not appear to impair antibody production or lymphocyte responsiveness to mitogen stimulation in ruminants (Spears, 2000; Spears and Kegley, 2002). A suggested hypothesis is that the dietary requirements of trace minerals to optimize immune function may be higher than the requirements for growth (van Heugten et al., 2003).

These results confirm that further studies on the effect of zinc-deficiency on immune functions in persistent inflammatory states and infection, and on the potential therapeutic role of zinc supplementation in these conditions, are needed.

3.5. Changes in the somatotropic hormones, efficiency of immune response and body growth

3.5.1. Immune challenge and GH/IGF-1 axis

It is well known that infection-mediated inflammation and the APR are associated with a complex hormonal response involving the somatotropic axis. Evidence has shown that during the immune response to infection, the GH/IGF-1 axis has a prominent regulatory role.

In understanding GH activity, it must be remembered that GH has two distinct effects: a direct effect resulting from GH binding to its receptor on target cells and an indirect effect mediated primarily by IGF-I. Thus there exists a normal regulatory link between GH and IGF-1, that may be uncoupled during immune challenge.

In rodents and in livestock (pigs, sheep and cattle), most experimental studies have been conducted using lypopolisaccharide (LPS) as an inducer of immune challenge and as mediator of acute septic shock. Less is known about somatotropic axis alteration during natural infection in animals. Moreover, neither *in vivo* or *in vitro* studies have clearly established the mechanisms by which LPS induces changes in GH and IGF-1 in domestic animals. Following endotoxin challenge, changes in GH concentrations appear to be species-specific. Interestingly, uncoupling of the GH/IGF-I axis has been reported in sheep and in pig, but not in cattle (for review see Daniel et al., 2002; Carroll, 2008).

During infection or injection of LPS in cattle, a reduction of plasmatic GH is observed and appears to be mediated by TNF-α while in rats this inhibitory effect is mediated by IL-1α (Sartin et al., 1998).

Conversely, in sheep, administration of endotoxin (LPS) stimulates GH plasmatic levels with a moderate decrease in IGF-1 (Coleman et al., 1993; Briard et al., 1998, 2000). The increased circulating levels of GH after LPS treatment appeared to be mediated by IL-1β and TNF-α through a peripheral mechanism involving a direct action at the pituitary. It is also possible that LPS acts directly on pituitary cells, as suggested by the presence of CD14 on GH-positive somatotropes (Daniel et al., 2005).

In pigs, LPS challenge is characterized by high levels of GH with a loss in pulse activity, and by low IGF-I levels due to reduced pulsatile fractions of GH; the nonpulsatile fraction, however, remains high (Havener et al., 1997). The positive correlation found between the pulsatile fraction of GH and circulating IGF-I and IGFBP3 levels, indicates that the loss of pulsatility is important in maintaining GH mediators (IGF-I and IGFBP3) at low levels (Van den Berghe, 1999). Wright et al. (2000) found that LPS treatment in barrows induced an increase of cortisol and TNF-α associated with an increase of overall GH concentration and a reduction in circulating IGF-1.

The data on changes in the GH-IGF-1 axis during natural infection are controversial and depend on the type of infection. In fact, poorly growing piglets (Saleri et al., 2001) and pigs with enteric infections (Jenkins et al., 2004) show low levels of circulating IGF-1 and IGFBP3, whereas levels of IGFBP1, -2, and -4 are high in an acute parasitic infection (Prickett et al., 1992).

The study of growth and IGF-1 status in growing pigs persistently infected with porcine reproductive and respiratory syndrome virus (PRRSV) and *Mycoplasma hyopneumoniae*, showed a reduction in serum IGF-1 concentration despite similar levels of feed intake and average daily gain compared to non-infected pigs (Roberts and Almond, 2003).

Balay et al. (2000) studied active infection with *Salmonella thypimurium* in pigs and reported a reduction of IGF-1 plasmatic level without changes in GH and pro-inflammatory cytokine serum levels. This appeared in contrast with the previous results reported by Wright et al. (2000) after LPS treatment alone and the authors concluded that some infections may produce profound changes in the somatotropic axis in absence of significant increase of systemic pro-inflammatory cytokines. This result has been lately confirmed by Fraser et al. (2007) during repeated exposure of weaned pigs to *Salmonella choleraesuis.*

Indeed, several studies suggest that the normal regulatory link between GH and IGF-1 is uncoupled during an immune challenge. Increased GH levels are not associated with a corresponding increase in IGF-1, which in turn decreases with a state of GH resistance (Figs. 3 and 4). After an immune challenge, the increased level of GH could only partially be explained by a reduced feedback of

IGF-1. One possible explanation of this uncoupling could be that the increase in GH acts as a counterbalance to reduce the negative metabolic changes occuring in persistent infection, but its effect is limited by the impaired activity of IGF-1. Conversely, considering that extrametabolic effects of GH have an important impact on immune function, it can be hypothesized that the rise in GH during infection may be an attempt to improve innate [Fig. 3(b)] and cell-mediated immune activity directly and/or, indirectly by counteracting increased levels of GCs (Bottasso et al., 2007).

3.5.2. The role of somatotropic hormones in the immune response

Different studies have shown that the GH–IGF-I complex modulates the immune system to a varied extent, influencing both humoral and cellular functions (review by Heemskerk et al., 1999; Dorshkind and Horseman, 2000).

Furthermore, there is also data supporting the idea that GH and PRL are able to counteract the suppressive activity of GCs (Kelley et al., 2007). In the last decade, experimental molecular studies have provided additional data on bidirectional communication between the immune system and the somatotropic axis. Evidence highlights a positive effect on thymus activity (Dorshkind and Horseman, 2000; Savino and Dardenne, 2000; Mocchegiani et al., 2006; Savino et al., 2007) and many studies have demonstrated that GH, PRL and GH-related molecules can have beneficial effects on the immune system by acting via SOCS proteins (Redelman et al., 2008).

Communication pathways among somatotropic hormones and the immune system have been documented in a variety of domestic animals. GH and IGF-1 have been identified in immune tissues and it has been shown that they partecipate in the development, differentiation and regulation of the immune response.

Particularly, GH and PRL play a role as immunoregulator hormones in embryonic development, maturation and immunocompetence (Berczi et al., 1998; Davis, 1998). The identification of GH receptors on pig lymphocytes confirms a direct role of this hormone in immune system development and as an immunomodulator in the acute phase and in the innate immune response (Matteri and Carroll, 1997; Matteri et al., 1998; Wright et al., 2000; Haeryfar and Berczi, 2001).

Borghetti et al. (2006a) showed some important correlations between hormones (GH, PRL and cortisol) and the development of immune system in the first weeks of life in pigs.

In agreement with Matteri and Carroll (1997) plasma GH levels are high in newborn piglets, with constant decreases thereafter, reaching normal values in the post-weaning period. The high levels of GH at birth might be explained in relation to an early capacity of pigs to activate an inflammatory and innate response. Indeed, GH is able to increase IL-6, IL-2 and GM-CSF expression in the thymus (Savino et al., 2003) and in turn, IL-6 may regulate GH secretion (Tsigos et al., 1997). Since a paracrine influence exists between GH and IL-6 and TNF-α, GH could be fundamental in increasing the levels of these cytokines for a prompt imprinting of innate response to pathogens. These aspects could play a key role as, unlike other species, neonatal piglets produce pro-inflammatory cytokines (IL-1, TNF-α, IL-6) early in life (Matteri and Carroll, 1997; Schwager and Schulze, 1997).

Furthermore, plasma GH, PRL and cortisol levels are inversely correlated with some T cell subset numbers during the pre-weaning period, with more significant inverse correlations for the cortisol. These findings suggest the potential role of cortisol in the immunodepressive effect on immune cells, largely due to the stress condition present during delivery; on the other hand, they pinpoint the relevant role played by high GH and PRL levels during the pre-weaning period in counteracting a cortisol-mediated negative effect on intrathymic lymphocyte production and in preventing a subsequent negative influence on immune development (Borghetti et al., 2006a).

Similarly to piglets, high levels of GH are present in human at birth, together with high cortisol concentrations; there is then a decrease which is positively correlated to active thymulin (Meazza et al., 2007). Moreover, growth hormone-deficient children showed alterations in the pro-inflammatory cytokine-induced immune response, and GH treatment was able to improve immunological function (Pagani et al., 2005).

In vitro studies have reported that GH deficiency impairs NK activity (Mocchegiani et al., 1998b) and IGF-1 stimulates both NK function and production of ROS and cytokines by macrophages. IGF-1 appears to be particularly crucial for the paracrine and autocrine regulation of innate and acquired immunity by acting on NK cells, and on T and B lymphocytes. IGF-1 can regulate acquired immunity, mainly by stimulating lymphopoiesis in primary and secondary lymphoid organs and increasing responsiveness to antigen-mediated activation (Heemskerk et al., 1999).

In this context, the thymus plays a central role in bidirectional communication between neuroendocrine and immune systems during infection.

Animal studies have shown that treatment with GH increased thymulin serum levels as well as IL-6 production (Goya et al., 1992). GH exerts pleiotropic effects on thymus activity, enhancing thymocyte proliferation, thymocyte traffic in and out of the thymus, cytokines and thymulin production (Savino et al., 2003; Mocchegiani et al., 2006). GH is able to restore the zinc pool by improved intestinal absorption and, in turn, zinc and thymulin can enhance NK cell cytotoxicity, by regulating the receptor expression for IFN-γ and IL-2 (Onodera et al., 1994; Marsh et al., 2001; Merlino and Marsh, 2001; Molly and Marsh, 2003).

It is likely that these effects of GH are mediated, at least in part, by IGF-1 (Timsit et al., 1992). There is also evidence for a prolactin (PRL)-thymulin axis. TEC possess PRL receptors and PRL can stimulate thymulin synthesis and secretion both *in vitro* and *in vivo*. When GH is bound to zinc ions, it can bind to PRL receptors. There is a complex, positive interrelationship between GH, PRL, IGF-1 and, in this context, zinc bioavailability plays a pivotal role in the direct and indirect (via PRL o IGF-1) action of GH on thymus functions (Mocchegiani et al., 2006).

On the contrary, GCs induce apoptosis in immature thymocytes, NK cells, and cytotoxic T-lymphocytes

(Migliorati et al., 1994; Herold et al., 2006, Wang et al., 2006). Zinc and thymulin can protect thymocytes from apoptosis) induced by both GCs and TNF-α (Haeryfar and Berczi, 2001; Shankar and Prasad, 1998; Mocchegiani et al., 2004, 2006; Saitoh et al., 2004).

Severe cortical thymocyte apoptosis is a common feature in a variety of acute viral, bacterial and parasitic infections. The exact pathways leading to thymocyte death are not completely understood and may depend on the severity of infection (Savino, 2006). High serum levels of glucocorticoids, a typical event occuring in the host response to infections, have been considered a major pathway triggering thymocyte apoptosis (Herold et al., 2006). The apoptosis phenomenon triggered by TNFα may be also involved in thymocyte death during infection and the depletion of thymic lymphocytes may result from a direct action of pathogens reaching the thymic parenchyma (Goncalves da Costa et al., 1991). In any case, a transient or long-term decrease in the serum levels of thymulin plays an important role (Savino, 2006).

Given the strong correlation between GH and thymic function, thymocyte maturation and differentiation, GH could have a role during acute and chronic infections (Savino, 2007).

However, *in vivo* clinical trials in man and lab animals aimed at evaluating the effect of GH supplementation on the immune response during critical illness and sepsis, have reported contrasting results. If some *in vivo* studies have shown beneficial effects of GH and IGF-1 treatment on the immune response during bacterial challenge (Heemskerk et al., 1999; Ashare et al., 2008), others have described increased mortality in critically ill patients (Takala et al., 1999). Recently, no effect on immune response during an experimental model of sepsis was shown (Schmitz et al., 2008) after GH treatment. One possible explanation for a lack of effect GH on immune function in sepsis may be tissue resistance to GH, which could impede a direct activity of GH on lymphoid cells (Schmitz et al., 2008). Further studies on GH administration in severe infection are clearly needed.

In domestic livestock, some studies have been conducted to evaluate *in vivo* the changes of GH/IGF-1 as well as the effect of GH on immune response during antigen exposure and natural infection.

Elsasser et al. first described the link between pro-inflammatory cytokines and the somatotropic axis in cattle (Elsasser and Rumsey, 1986; Elsasser et al., 1988, 1991). These studies showed in particular that GH can modulate immune function and promote anabolic activity. Subsequent research by the same group focused on the effect of exogenous GH treatment on the immune response. These studies demonstrated that GH treatment was able to significantly decrease TNF-α concentration and hepatic content of TNF receptors after endotoxin challenge in calves, suggesting a modulatory role of GH on TNF-α activity (Elsasser et al., 1998). Conversely, in other studies on calves with protozoal infections, GH treatment did not affect infection-induced reduction of IGF-1 concentration (Sartin et al., 1998).

GH plasma concentrations in calves are high during the first week of life and then decrease during the following five weeks. One study showed that *E. coli* infection in the early postnatal period is charaterized by an increase in GH concentration, before diarrhea is observed, suggesting that GH increase may represent the organism's defense response to infection. Therefore, in addition to its role as a regulator of growth and immune function, it could play an important role in intestinal healing (Bruckmann et al., 2000).

Field studies in neonatal piglets have shown that GH plasma levels increase occur after pre-weaning vaccination, in association with increased levels of cortisol after weaning. Increased plasmatic levels of GH could be interpreted as a reactive response to the antigenic stimulus, as well as a counteractive response to increasing cortisol related to weaning-mediated stress (Borghetti et al., 2006b). Furthermore, unpublished results from our laboratory show that an increase of GH plasmatic levels is associated with increased levels of IL-6 in vaccinated pigs and not in unvaccinated pigs when naturally exposed to PRRSV field strain, suggesting that this could have a positive influence on the innate immune response and the consequent clinical protection observed in vaccinated animals compared to unvaccinated pigs.

Brown et al. (2004) evaluated the effects of plasmid-mediated GHRH treatment on immune function and on the morbidity and mortality in heifers; treated animals had significantly increased numbers of $CD2^{+}\alpha\beta$ T-cells, $CD25^{+}CD4^{+}$ cells, and $CD4^{+}CD45R^{+}$ cells compared to untreated animals. These increases were maintained long-term after treatment and were correlated with plasmid expression. At 300 days post-GHRH therapy, $CD45R^{+}/CD45R0^{-}$ naïve lymphocytes and NK cells were significantly increased. These changes in lymphocytes subpopulations were associated with improved health status and body condition scores, reduced hoof pathology and decreased mortality in treated heifers.

Recently, Thacker et al. (2006) have shown that plasmid-mediated GHRH supplementation before vaccination may enhance protection against *Mycoplasma hyopneumoniae* pneumonia and reduce the clinical outcome of the disease.

Taken together, all current experimental data suggest that, during an immune challenge, pro-inflammatory cytokines orchestrate a complex neuroendocrine homeostatic response that (Fig. 3): (i) controls the potentially harmful effect of inflammation; (ii) can modulate the innate immune response and influence its efficiency; (iii) drives metabolic and nutritional modifications towards favouring immune function at the expense of other tissues.

This integrated neuroimmune adaptive response directs and sustains the components of the immune system in inhibiting and destroying invading pathogens, and diverts nutrients to support these efforts.

3.5.3. Infection, immunity and growth

Much evidence currently suggests that during infection the neuroimmune cross-talk response can also strongly influence growth efficiency (Colditz, 2002).

Neuroendocrine and clinical changes occurring during the APR, such as fever and metabolic changes, initially support an efficient innate immune response; they can,

however, become detrimental over time, thus negatively influencing food intake and the energy balance and causing a drastic increase in tissue catabolism and nutrient utilization and loss.

Indeed, in addition to the increased nutrient requirements for the immune system, during the period of immune activation, complex interactions between cytokines, glucocorticoids and somatotropic hormones results in altered metabolism and decreased propensity for growth (Fig. 4).

Changes in the GH/IGF-1 axis during immune challenge have been studied as an important pathway for the impact of immunity on body growth in domestic livestock (Carroll, 2008).

An alteration of the GH-IGF-1 axis can affect both immune and metabolic responses, thus contributing, along with pro-inflammatory cytokines, to a state of hypercatabolism (Mizock, 1995; Cooney et al., 1997; Chang and Bistrian, 1998).

Prolonged activation of the HPA axis during infection leads to somatotropic axis suppression mediated by an increase of GCs and pro-inflammatory cytokine levels leading to liver GH resistance, and by an inhibition of IGF-1 activity on target tissue (Baxter, 2001; Yumet et al., 2002; Charmandari et al., 2005; Cooney and Shumate, 2006) (Fig. 4).

Endotoxin induces a state of resistance to GH which is associated with altered bioavailability and/or IGF-1 activity (Briard et al., 2000). It is thought that these hormonal changes, together with high levels of GCs and cytokines, lead to a catabolic state characterized by insulin resistance, neogluconeogenesis, lipolysis and muscle proteolysis.

Although IL-1β has been shown to enhance GC secretion which induces GH resistance, both a direct inhibition of tissue GH receptor expression and alterations of IGF-1 binding proteins (IGFBPs) [Fig. 4(d)] provide a better explanation for a direct effect of pro-inflammatory cytokines in causing a catabolic state during sepsis. Changes in plasmatic and tissue levels of IGFBPs have been described during endotoxemia, infection and following the administration of pro-inflammatory cytokines. Increased levels of IGFBP-1 appear particularly associated with the catabolic state (Fan et al., 1995a,b; Wolf et al., 1996; Lang et al., 1996; Kelley et al., 1996).

Moreover, food intake efficiency, energy balance, tissue metabolism and immune activation are all interrelated and likely depend also on central leptin–cytokine interactions.

In vivo experimental studies have highlighted a role for leptin as a circulating mediator which contributes to the loss-of-appetite effect of LPS (Fig. 2), through an increase in IL-1β in the hypothalamus (Luheshi et al., 1999; Sachot et al., 2004). A reduced production of ghrelin has also been described as a possible mechanism of LPS/cytokine-induced inhibition of food intake (Basa et al., 2003).

Several pro-inflammatory cytokines produced during APR, such as IL-1α/β, IL-2, TNF-α, IL-6, IL-8, IL-18, have been implicated in the inhibition of food intake involving complex neurotrasmitter and neuropeptide systems (Langhans, 2007). TNF-α is one of the major mediators of the catabolic and anorexigenic effects during severe inflammation/infection (Figs. 2 and 4). It has been suggested that these effects are mainly dependent on central signaling, particularly in the hypothalamus, where the cytokine is able to modulate the signals from leptin and insulin in a dose-dependent way, leading to defective control of feeding (Romanatto et al., 2007). Similarly to other inflammatory cytokines and leptin, IL-18 shares the characteristics of an endogenous anorectic adipocytokine which has a physiological role in energy homeostasis by suppressing food intake and feed efficiency (Zorrilla et al., 2007).

However, tissue wasting can occur during chronic inflammation and sepsis/endotoxemia, and this muscle protein and lipid mobilization and loss is a complex event which cannot be accounted for only by anorexia and reduced food intake.

Indeed, as previously mentioned, the catabolic effect of pro-inflammatory cytokines, glucocorticoids and alteration of GH/IGF-1 response is likely fundamental (Spurlock, 1997; Frost and Lang, 2004; Cooney and Shumate, 2006). Immunological challenge and the consequent increase of cytokines (TNF-α and IL-6) and cortisol are involved in reduction of feed intake, skeletal muscle degradation and inhibition of growth (Webel et al., 1997; Wright et al., 2000). It is likely that clinical and subclinical infections impair the effectiveness of growth in livestock because the target tissues, such as liver and skeletal muscle, become GH-resistant. Therefore, loss of anabolic stimuli together with the catabolic effect of pro-inflammatory cytokines drives the metabolic balance of skeletal muscle towards a net loss of mass and function.

A common result of an altered hormone-cytokine ratio is that the biological effects of hormones are impaired by pro-inflammatory cytokines causing endocrine resistance: the role of pro-inflammatory cytokines, such as IL-1β, TNF-α and IL-6, in inducing resistance to IGF-1, GH, glucocorticoids, cathecolamines has recently been underlined (Pace et al., 2007; Kelley et al., 2007; Heijnen, 2007).

Furthermore, inflammation has been proposed to be very important for the development of insulin resistance (Festa et al., 2000) and metabolic syndrome: the link may be a cytokine-mediated acute response from the innate immune system. IL-6 is the primary trigger of C-reactive protein synthesis and plays an important role in the regulation of glucose and lipid metabolism (Lau et al., 2005). A recent study by Ingelsson et al. (2008), confirms the strong correlation between insulin resistance and C-reactive protein, which predicts the development of diabetes and metabolic syndrome. In particular, chronic elevation of IL-6 plasma levels could have a pivotal role in systemic insulin resistance, especially in liver and adipose tissue (Antuna-Puete et al., 2008). TNF-α is also involved in insulin resistance through alteration of insulin receptor structure (Hotamisligil et al., 1993).

3.6. Adipokines and immunity: a role for leptin as a neuroendocrine link?

Leptin has emerged as a neuroendocrine signal (Fig. 1) that is able to inform the immune system of current energy availability, both as glucose and lipid deposits (WAT)

(Demas, 2004). Recently, studies showing increased leptin production during infection and inflammation and dysregulated immune response in leptin signaling-deficient mice have provided strong evidence for the involvement of leptin in immune responses (Otero et al., 2006; Lam and Lu, 2007).

Different inflammatory stimuli (LPS, IL-1, TNF-α) regulate the expression of leptin in adipose tissue as well as its circulating level (Faggioni et al., 2001). Indeed, leptin is produced by inflammatory-regulatory cells and regulates several cytokine secretion patterns; in turn IL-1, IL-6, TNF-α LPS can increase circulating leptin.

Studies suggest a role for leptin in orchestrating the inflammatory response, in the development, activation and cytotoxicity of NK cells and also in the survival, maturation and cytokine production of dendritic cells (Table 1).

In innate immunity, leptin can modulate the overproduction of pro-inflammatory cytokines, thus protecting against susceptibility to LPS/sepsis, while it mainly has a pro-inflammatory activity during the adaptive immune response (Bernotiene et al., 2006).

On the contrary, there is evidence that chronic inflammation may lower plasma leptin concentrations. Chronic leptin deficiency impairs the control of inflammation with an increased sensitivity to inflammatory stimuli such as LPS and TNF-α and leptin-deficient mice have greater mortality when challenged with a pathogen (Mancuso et al., 2002).

On the other hand, experimental studies have demonstrated that leptin can modulate the Th1/Th2 cytokines and the activity of CD4+CD25+ regulatory T cells and CD4+CD25$^-$ effector T cells differently (Table 1); in leptin deficiency a switch to Th2 lymphocytes occurs, with consequent resistance to inflammation (Bernotiene et al., 2006; Otero et al., 2006; De Rosa et al., 2007).

Another important field of study concerns the interaction between leptin and cytokines in thymus activity and functions (Fig. 2).

IL-6, LIF and Oncostatin M appear to be thymosuppressive and are able to induce an acute loss of thymocytes, as observed in LPS-induced thymus atrophy. This thymosuppressive action probably reflects both systemic and intrathymic mechanisms involving epithelial thymic cells and corticosteroid production (Sempowski et al., 2000). Considering that IL-6 also has a positive endogenous effect on thymocyte proliferation at physiological concentrations, its thymosuppressive action could be dependent on higher concentrations present in some inflammatory conditions, like with endogenous GCs in the thymus (Gruyer and Sempowski, 2008).

In contrast, leptin has been suggested to exert protection against acute thymus atrophy induced by LPS (Hick et al., 2006). The exact mechanism may depend on systemic inhibition of GCs as well as increased levels of cytokines after LPS challenge, but could be due to a direct effect on thymocytes, causing the inhibition of dexamethasone-induced apoptosis (Howard et al., 1999).

Leptin is also able to improve insulin sensitivity, but the effect of leptin deficiency on insulin resistance remains unclear and probably depends on the quantity of adipose tissue, which influences leptin levels or leptin resistance (Antuna-Puete et al., 2008).

Limited information is available on the effects of leptin on immune function and on energy balance in livestock.

In cows, leptin induces Peripheral Blood Mononuclear Cells (PBMC) proliferation and pro-inflammatory cytokine expression (IL-12 and IL-18) and secretion (IL-1β and TNF-α) in isolated monocytes/macrophages (Ahmed et al., 2007). Leptin treatment in pigs has no effect on the proliferation of PBMC or on cytokine mRNA expression (Weber and Spurlock, 2004).

Soliman et al. (2002) showed that in sheep and cows, endotoxemia does not affect serum leptin levels, although it increases insulin and glucose, important stimulators of leptin secretion in rodents and humans.

However, Valderrábano et al. (2006) observed that fat mass stored by ewes in early pregnancy is associated with the expression of immunity against gastrointestinal nematode infection around parturition; this difference in the immune response appeared to be associated with serum leptin levels, suggesting that leptin may be a link between nutritional status and the immune mechanisms involved.

Spurlock et al. (1998) emphasized that in pigs, challenged with LPS and treated with GH, the changes in IGF-1 are independent of serum GH and the adipose leptin mRNA expression is not affected by LPS challenge.

Leininger et al. (2000), reported that acute endotoxemia following LPS treatment decreases circulating insulin, glucose and IGF-1 levels as well as leptin gene expression in adipose tissue, indicating that leptin appears more closely related to energy homeostasis than cytokine profiles.

Prolonged leptin administration does not influence circulating GH concentrations. It does, however, act directly on hepatocytes to suppress IGF-1 secretion, and influences liver IGF-1 mRNA abundance and circulating IGF-1 concentrations in an apparent dose-sensitive manner (Ajuwon et al., 2003).

Weber and Spurlock (2004) found that leptin modifies antibody isotype profiles consistent with a cellular immune response, but does not influence other immune parameters in pigs and concluded that the relevance of leptin in pigs may be related largely to its role in metabolism regulation and food intake, rather than influencing cellular and molecular immune pathways.

The interaction between leptin, inflammation and immune response is likely very complex *in vivo,* considering that other important neuroendocrine and metabolic modifications (cortisol, glicemia, changes in GH and thyroid hormones) associated with changes in leptin can indirectly influence the immune response (Otero et al., 2006).

Adiponectin has also been reported to play a role in the bidirectional communication between the immune system and adipose tissue, integrating inflammatory and metabolic pathways (for a more detailed review the reader is referred to Gabler and Spurlock, 2008).

In porcine macrophages and THP-1 monocytes, adiponectin antagonizes the activation of NF-κB transcription factor and the expression of inflammatory cytokines like

IL-6, but induces the expression of IL-10, an anti-inflammatory cytokine (Wulster-Radcliffe et al., 2004). Moreover, in the adipocyte, adiponectin may be a regulator of inflammation via its suppression of the NF-κB activation and upregulation of peroxisome proliferator-activated receptor (PPAR)γ2 after LPS treatment (Ajuwon and Spurlock, 2005). A wide range of circulating adiponectin multimers has been identified (Fruebis et al., 2001; Kobayashi et al., 2004). Several studies have shown that different adiponectin isoforms are able to induce common responses (i.e. increase of apoptosis, activation of AMPK, reduction of scravenger receptor expression), but also induce isoform-specific responses (pro-inflammatory or anti-inflammatory) (Neumeier et al., 2006). Recently, two isomers of the adiponectin receptor have been found (Yamauchi et al., 2003) that appear to play different roles in glucose and lipid metabolism (Bjursell et al., 2007).

The mobilization of energy and amino acids from adipose tissue and the growth deficiency observed during immune challenge suggests a pivotal role for adiponectin, particularly in the pig where adipocytes are the only source of this adipokine (Ding et al., 2004; Jacobi et al., 2004).

A similar emerging role has been suggested for IL-15 in muscle metabolism. IL-15, a cytokine involved mainly in NK cell proliferation and activation, is highly expressed in skeletal muscle. Il-15 has been studied in muscle metabolism in rats and it has been shown that this cytokine exercises a protective role against muscle wasting in this model (Carbò et al., 2000). These results suggest that IL-15 may protect muscle in pathological conditions (like cancer, stress or infection) characterized by increased muscle protein breakdown (Figueras et al., 2004). In support of this hypothesis, IL-15 production is stimulated by several inflammatory mediators (Sugiura et al., 2002) such as IFN-γ, IL-1α IL-1β, TNF-α and LPS (for a more detailed review on IL-15 the reader is referred to Quinn, 2008).

IL-15 also has a direct action on adipocytes and lipid metabolism. In porcine adipocytes, interferon-γ upregulated IL-15 mRNA (Ajuwon et al., 2004) and IL-15 stimulated lipolysis in a dose-dependent manner and at a greater extent than either TNF-α, IL-6, or LPS (Ajuwon and Spurlock, 2004). These studies suggest that IL-15 may be produced in response to immune stress and likely has a role during the acute inflammatory response and infection in stabilizing muscle protein and oxidizing fat for energy partitioning.

Thus, current data indicate the existence of adipose- and muscle-derived molecular signals that integrate bidirectional communication between the endocrine and immune systems. This could be a promising field of research in domestic livestock with regard to energy production and muscle mass preservation in conditions such as stress or infection. However, it is clear that much more research is needed to confirm this hypothesis (Quinn, 2008). Furthermore, the specific contribution of adipocytes and myocytes to the increase of circulating cytokines during immune challenge and their negative effect on animal growth in field conditions remain unknown (Gabler and Spurlock, 2008).

To summarize, all available data suggests that further studies on the role of leptin and other adipokines during infection-induced anorexia and growth inhibition, and more consistent evidence concerning their property as immunomodulators, in farm animals are needed.

4. Conclusions

During infection, the immune response is modulated by an integrated neuroendocrine response which potentiates innate immunity, controls potential harmful effects and induces metabolic and nutritional modifications towards supporting immune function.

In the last decade a great deal of knowledge has been acquired on the molecular signals orchestrating this integrated adaptive response and has enabled research to focus on systemic mediators, which have a crucial role in driving and controlling an efficient protective response, and in signalling alterations and control pathway dysfunctions, which may be involved in the persistence and/or overexpression of inflammation and consequent tissue damage.

Increased understanding of the cooperation between immune activation mediators (cytokines) and hormonal changes could lead to further studies of the host's immune and metabolic response during infection and, consequently, to identify parameters for evaluating the efficiency of a normal return to the homeostatic state.

In turn, predictive markers for the severity of infection, increased end-organ damage and increased mortality could be also identified. High levels of IL-1, TNF-α, IL-6 and MIF may be predictive of tissue damage and uncontrolled inflammation, increasing susceptibility and mortality particularly if HPA axis and GC activity is altered. Future studies aimed at giving these findings clinical significance could provide data for early diagnosis and the development of therapeutic protocols for sepsis (Bornstein et al., 2008).

Evaluation of changes in IL-6 over time appears to be a sensible indicator of activation and control of the APR, whereas persistent levels could be a valuable tool for monitoring subclinical infections and chronicization of inflammation. The interactions of IL-6 with GH, Zn and thymic activity could also be of interest to study during infection in domestic animals for identifying potential markers of innate response efficiency.

Infections are considered to be a major contributing factor associated with reduced performance in food animals during growth. Particularly, persistent infections account for slow growth, suboptimal feeding efficiency and economic loss in the livestock industry. The study of the correlation between cytokines, hormones and metabolic alterations could provide details of key pathways causing retarded growth during infection and support experimental research to reduce the negative metabolic impact or to improve the animal's capacity to cope with an immune challenge. Comparative studies in multiple species could supply a full understanding of the biological roles of hormones and cytokines during stress adaptation and natural infection in field conditions; in this context, together with immune parameters, hormonal changes could be physiological parameters for a quantitative evaluation of animal welfare.

A new understanding on the changes of GH/IGF-1 axis during infection could provide new research opportunities and field approaches for controlling/preventing negative effects on growth and for increasing the efficiency of the immune response. For example, given the role of zinc in GH/IGF-1 immunomodulatory activity and thymic functions, specific studies could be aimed at elucidating how key nutritional elements could influence the response to infection.

Finally, more data on the involvement of adipose and muscle tissue as endocrine organs in inflammation and immunity could offer new ways to modulate the animal's response during immune challenge. This exciting field of study in adipose and muscle tissue biology could lead to the development of innovative strategies to support growth by improving body composition, energy balance and feed efficiency during fasting and wasting conditions such as stress and/or clinical/subclinical infections in domestic livestock (Quinn, 2008; Gabler and Spurlock, 2008).

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