How stress influences the immune response

David A. Padgett[1] and Ronald Glaser[2]

[1]Ohio State University, Department of Oral Biology, 3180 Postle Hall, 305 W. 12th Avenue, Columbus, OH 43210, USA
[2]Ohio State University, Department of Molecular Virology, Immunology and Medical Genetics, 2175 Graves Hall, 333 W. 10th Avenue, Columbus, OH 43210, USA

In response to a stressor, physiological changes are set into motion to help an individual cope with the stressor. However, chronic activation of these stress responses, which include the hypothalamic–pituitary–adrenal axis and the sympathetic–adrenal–medullary axis, results in chronic production of glucocorticoid hormones and catecholamines. Glucocorticoid receptors expressed on a variety of immune cells bind cortisol and interfere with the function of NF-κB, which regulates the activity of cytokine-producing immune cells. Adrenergic receptors bind epinephrine and norepinephrine and activate the cAMP response element binding protein, inducing the transcription of genes encoding for a variety of cytokines. The changes in gene expression mediated by glucocorticoid hormones and catecholamines can dysregulate immune function. There is now good evidence (in animal and human studies) that the magnitude of stress-associated immune dysregulation is large enough to have health implications.

Studies on stress-associated immune dysregulation have interested scientists and clinicians in the field of psychoneuroimmunology (PNI). This field focuses on the interactions among the central nervous system (CNS), the endocrine system and the immune system, and the impact these interactions have on health. Modulation of the immune response by the CNS is mediated by a complex network of signals that function in bi-directional communication among the nervous, endocrine and immune systems. The hypothalamic–pituitary–adrenal (HPA) and the sympathetic–adrenal medullary (SAM) axes are the two major pathways through which immune function can be altered.

Lymphocytes, monocytes or macrophages and granulocytes, exhibit receptors for many neuroendocrine products of the HPA and SAM axes [1], such as cortisol and catecholamines, which can cause changes in cellular trafficking, proliferation, cytokine secretion, antibody production and cytolytic activity [2]. For example, treatment of peripheral blood leukocytes (PBLs) with catecholamines *in vitro* results in the suppression of interleukin-12 (IL-12) synthesis and an increase in IL-10 production [3]. This can cause a shift in the phenotype of $CD4^+$ T-helper (Th) cells, from a Th1 profile, which functions in cell-mediated immune activities, to a Th2 profile, which is involved in antibody production. A study using an academic stress paradigm by Marshall *et al.* [4] supports these *in vitro* studies. In medical students taking exams, psychological stress produced a shift in the cytokine balance toward a Th2 profile. The data showed decreased synthesis of Th1 cytokines, including interferon-γ (IFN-γ), and increased production of Th2 cytokines, including IL-10. Data from our laboratory are consistent with these results [5]. It is believed that this stress-induced decrease of Th1 cytokines results in dysregulation of cell-mediated immune responses.

Both major and minor stressful events can have direct adverse effects on a variety of immunological mechanisms; both animal and human studies have provided convincing evidence that these immune alterations are consequential for health. To help demonstrate causal relations between psychosocial stressors and the development of infectious illness, investigators have inoculated subjects with several different types of vaccines [6–11]. For example, among medical students taking exams, stress and the degree of social support affected the virus-specific antibody and T-cell responses to a hepatitis B vaccine [6,11]. In addition, the chronic stress associated with caregiving for a spouse with Alzheimer's Disease (AD) was associated with a poorer antibody response to an influenza virus vaccine compared to well matched control subjects [7]. Vaccine responses demonstrate clinically relevant alterations in an immunological response to challenge under well controlled conditions. Accordingly, they act as a proxy for responses to an infectious agent. Therefore, in individuals who produced delayed, weaker and shorter-lived immune responses to vaccines, it is reasonable to assume these same individuals would also be slower to develop immune responses to other pathogens. Consistent with this argument, adults who show poorer responses to vaccines also experience higher rates of clinical illness, as well as longer-lasting infectious episodes [12,13]. Therefore, from these vaccine studies, it is hypothesized that stress puts individuals at greater risk from more severe illness. In support of this idea, Cohen *et al.* showed that human volunteers who were inoculated with five different strains of respiratory viruses showed a dose-dependent relationship between stress and clinical symptoms observed after infection [14]. Taken together, these studies show that psychological stress can influence immune function, alter

Corresponding author: Ronald Glaser (glaser.1@osu.edu).

http://treimm.trends.com 1471-4906/03/$ - see front matter doi:10.1016/S1471-4906(03)00173-X

the pathophysiology of infection and have consequences for health.

Although >150 clinical studies have shown that stress can alter immune function and contribute to poor health, human studies have a limited ability to show a direct connection owing to practical and ethical limitations. However, experiments using animal models support the findings in the studies with human subjects and have advanced the knowledge base on mechanisms. These animal studies have enabled investigation of the effect of various stressors on the pathophysiology of infectious agents administered at a variety of anatomical sites. Such studies are not possible in humans. Therefore, animal models are able to provide the tools to conduct a comprehensive analysis of neuroendocrine–immune interactions under a variety of experimental conditions.

Confirming results from studies with human subjects, data from studies using animal models have shown that stress diminishes vaccine responses, exacerbates viral and bacterial pathogenesis, slows wound healing and alters autoimmune diseases [15–18]. These studies have demonstrated that stress hormones inhibit the trafficking of neutrophils, macrophages, antigen-presenting cells, natural killer (NK) cells and T and B lymphocytes, suppress the production of proinflammatory cytokines and chemokines, downregulate the production of cytokines necessary for the generation of adaptive immune responses and impair effector functions of macrophages, NK cells and lymphocytes.

Data from both human and animal studies show that the connections between the neuroendocrine system and immune system provide a finely tuned regulatory system required for health. Disturbances at any level of the stress response can lead to an imbalance of physiology of the body and can lead to enhanced-susceptibility to infection and inflammatory or autoimmune disease. Endocrine tissues have an integral part in the human response to stress. As mentioned earlier, the two main pathways by which the immune system is modulated by psychological stress include the HPA and SAM axes.

HPA axis and glucocorticoid hormones

The hypothalamus receives and monitors information about the environment and coordinates responses through nerves and hormones. Visual information, smell, hearing, temperature sensation and pain alert the hypothalamus to emergencies or environmental hazards. The emotional portions of the brain also relay information to the hypothalamus. From this integrative center, the brain controls hormone secretion from the pituitary gland and other tissues, such as the adrenal glands. For example, corticotrophin-releasing hormone is secreted from the paraventricular nucleus of the hypothalamus into the hypophyseal portal blood supply and subsequently stimulates the expression of adrenocorticotrophic hormone (ACTH) in the anterior pituitary gland. ACTH then circulates in the bloodstream to the adrenal glands where it induces the expression and release of glucocorticoid (GC) hormones. These hormones affect cardiovascular and renal function and metabolism and act together with the nervous system to adjust our responses to the environment. As one of the 'core stress responses' originally described by Selye in 1936 [19,20], the acute production of GC hormones from the adrenal cortex stimulates the metabolism of glucose to provide for energy to flee or combat an immediate threat. However, when chronically activated, the HPA axis can cause deterioration in general health and worsen existing diseases.

Since the 1940s and 1950s, GC hormones have been prescribed clinically because of their inherent and powerful anti-inflammatory properties. The 1950 Nobel Prize in Medicine was bestowed on Edward Kendall, Tadeus Reichstein and Philip Hench for their studies on hormones of the adrenal cortex. Building on their early observations, it has become increasingly clear that GC hormones can regulate a wide variety of immune-cell functions. They modulate cytokine expression, chemoattractant expression, adhesion-molecule expression and immune-cell trafficking, proliferation, differentiation and effector function (reviewed in Refs [21–23]). How do GC hormones mediate their wide spectrum of immunological influence? Although the definitive answer to that question remains to be determined, over the past decade or so, substantial new information has been obtained that helps in understanding their mode of action.

Mechanisms of action for GC hormones

Being lipophilic molecules, GC hormones readily pass through the plasma membrane of all cells in the body. If a cell possesses a GC receptor (GR), that cell can be a target for action. There are two receptors for GC hormones, the GR and the mineralocorticoid receptor (MR). Because corticosterone has a higher affinity for MR than for GR [24], at low circulating levels glucocorticoid hormones bind preferentially to MR. Only at high circulating or tissue levels (i.e. during stress) is the GR occupied [25]. In immune cells, such as macrophages and T lymphocytes, the primary receptor for glucocorticoid hormones is GR; more specifically, the influence of glucocorticoid hormones on immune function is mediated by the GR [26].

The GR is a member of the steroid hormone-receptor superfamily. Structurally, it can be divided into three distinct regions. It possesses an N-terminal domain that is involved in transactivation [27]; its middle section is termed the DNA-binding domain and as the name suggests, is involved in DNA binding mediated by two zinc fingers [28]. The C-terminal domain or ligand-binding domain of the GR is responsible for ligand binding and is also involved in transactivation, dimerization and heat shock protein 90 (HSP90) binding [29,30]. In its unactivated state, the GR is located in the cytoplasm where it is part of an oligomeric complex containing HSP90, which is thought to hold the GR in a conformation that is available to incoming cortisol or corticosterone. On ligand binding, GRs dissociate from this complex and translocate to the nucleus where they bind as a homodimer to target elements or glucocorticoid response elements (GREs) through zinc fingers of the DNA-binding domain [28]. The bound GR–ligand complexes can then influence gene expression by modulating transcription through several proposed mechanisms. As homodimers, GC receptors recognize the putative hormone response element,

GAACAnnnTGTTC (where nnn represents any three bases) [31]. Armed with this knowledge, it was believed that GC hormones function as direct 'enhancers' or 'repressors' of transcription. Interestingly, many of the proteins (cytokines) that are regulated by GCs do not possess this putative hormone response element. Thus, this simple model for transactivation does not provide the complete answer for GC regulation of cytokine gene expression.

In 1995, two publications presented data that GC hormones could interfere with NF-κB activity [32,33]. Specifically, these two studies showed that GC hormones could transactivate an inhibitor of NF-κB activity. The hypothesis is that the GC induces the transcription of IκBα, which then sequesters NF-κB in the cytoplasm and prevents it from translocating to the nucleus and inducing gene activation. This is a logical explanation for the broad spectrum of cytokine suppression mediated by GCs. Many of the cytokines produced by macrophages and by Th cells are under the control of NF-κB [34], therefore, if GCs could repress activation, then individual cytokines would not need to possess the putative hormone response elements for GCs. Instead, by inhibiting NF-κB transcriptional activity, multiple cytokine genes could be turned off simultaneously. Unfortunately, the story is not this clear. Several subsequent publications showed that, in some cell types, IκBα synthesis was not necessary for NF-κB inhibition by GCs [35,36]. Additionally, the anti-GC drug RU486 was also capable of inhibiting NF-κB to some extent [37]. Together, these observations suggest that *de novo* gene transcription induced by GCs is not required for NF-κB inhibition.

Another model proposes that there is substantial cross-talk between NF-κB and the GR that might prevent gene expression. The activated GC receptor has the capability of binding directly to NF-κB and preventing its transmigration to the nucleus [38–40]. Also, the activated GC receptor has the capability of binding directly to NF-κB as it is attached to its putative κB DNA binding locus [41]. In this configuration, the GC receptor prevents the productive assembly of the polymerase complex for gene transcription. The region of the GR required for physical repression of NF-κB has been located to the zinc finger region of the DNA-binding region of the GR.

A third model has also been suggested in which glucocorticoid repression of NF-κB activity could be caused by competition between the GR and NF-κB for limited cofactors, such as CBP (cAMP response element binding protein) and SRC-1 (steroid receptor coactivator-1) [42]. In some cell types GR repression of NF-κB can be alleviated by excess cofactor [43]. However, McKay and Cidlowski showed that CBP did not mediate GR repression of NF-κB using a competitive model but rather that CBP functioned as an integrator to enhance the physical interaction between the GR and NF-κB [40,44].

These three models provide insight into potential mechanisms by which GC hormones can regulate the expression of the wide range of immunologically related genes. Although quite different, it is plausible that these three models are not mutually exclusive. However, they could be dependent on cell type. For example, the mechanism of repression of NF-κB, in which the GC induces IκB synthesis might be limited to certain cell types, such as monocytes and lymphocytes.

Sympathetic nervous system, adrenal medulla and catecholamines

In addition to regulation of immune function by glucocorticoid hormones associated with distress, it is known that catecholamines also modulate a range of immune functions, including cell proliferation, cytokine and antibody production, cytolytic activity and cell trafficking (reviewed in Refs [1,45,46]). Catecholamines often act in concert with activation of the HPA axis. For example, paralleling the increase of GC-hormone production from the adrenal cortex, activation of the HPA axis also results in catecholamine production from the adrenal medulla [47]. Cells in the adrenal medulla synthesize and secrete norepinephrine and epinephrine. In humans, ~80% of the catecholamine output of the medulla is epinephrine [48]. Norepinephrine is released from sympathetic nerve fibers in direct approximation with target tissues. If acutely activated, these catecholaminergic systems can provide the body with a needed 'boost' to deal with an immediate threat; the typical and most obvious effect of stress-induced epinephrine and norepinephrine is the establishment of the primitive mammalian fight or flight reaction, in which there is increased heart rate and increased blood flow to skeletal muscles.

If the SAM is chronically activated, these molecules can dysregulate immune function. A link from the sympathetic nervous system to the immune system is supported by the observations that noradrenergic sympathetic nerve fibers run from the CNS to both primary and secondary lymphoid organs [49]. Evidence suggests that sympathetic nerve terminals synapse with neighboring immune cells; in this synapse the sympathetic nerves release noradrenalin [45]. In addition, once released from the adrenal medulla, epinephrine courses through the circulation and binds to specific adrenergic receptors on immune cells, where they induce essentially the same effects as direct sympathetic nervous stimulation.

Mechanism of action for catecholamines

Catecholamines mediate their effect on target tissues through adrenergic receptors and numerous cells of the immune system, including lymphocytes and macrophages, express adrenoreceptors. These are G-protein coupled receptors that can be divided into two subgroups, the α- and β-adrenergic receptors. It appears that the most important receptor for the immune system is the β2-adrenergic receptor [46]. β-adrenergic receptors function as intermediaries in transmembrane signaling pathways that involve receptors, G-proteins and effectors [50].

The β2-adrenergic receptor is a seven membrane-spanning, serpentine receptor embedded in the plasma membranes of many cell types, including macrophages and T lymphocytes. Once bound to ligand, the β2-adrenergic receptor communicates with the cytoplasm by stimulating the activation of a G-protein complex. This G protein is formed from three distinct protein subunits, α, β and γ. When in its inactive form, the three G-protein subunits are bound together in a heterotrimeric complex. In its inactive

state, the G-α subunit is bound to guanosine diphosphate (GDP); when active, it binds the triphosphate form (GTP). When the β-adrenergic receptor activates the G protein as a result of binding of a catecholamine, the α subunit releases GDP and binds GTP. Once this happens, the GTP-bound α subunit loses affinity for the receptor and for the β and γ subunits, dissociates from them, and subsequently activates adenylate cyclase. In turn, adenylate cyclase catalyzes the synthesis of cAMP from ATP; this reaction involves the release of the β and γ phosphates from ATP and the linking of the surviving α phosphate (still attached to the 5′ hydroxyl of ribose) to the 3′ hydroxyl as well, forming cAMP (reviewed in Refs [51,52]).

One major cellular effect of the activation of the cAMP cascade is the stimulation of transcription after phosphorylation of transcription factors by cAMP-dependent protein kinase A (PKA) [53]. One such transcription factor, called CREB (cAMP response element binding protein) binds to the conserved consensus cAMP response element, TGACGTCA, present in the promoter regions of responsive genes [54]. CREB stimulates basal transcription of cAMP response element-containing genes and mediates induction of transcription on phosphorylation. For example, a conserved palindromic cAMP response element has been identified in the promoter of various genes regulated by cAMP (i.e. IL-6). After phosphorylation on Ser133 by PKA, CREB binds as a homodimer to this palindromic element and stimulates elevated transcription [55]. As such, the expression of numerous immune response genes can be modified by elevated catecholamine production during times of stress.

Conclusions

This Review has focused on GC hormones and catecholamines as the two major mediators of the stress effects on immune responses. However, other physiologic pathways are undoubtedly involved in the interplay. For example, endogenous opioids have recently been shown to diminish NK-cell cytotoxicity. In addition, a neuropeptide, substance P, is able to reduce inflammatory responses by suppressing IL-16 production by eosinophils. Whereas the focus of the anti-inflammatory effects of GC center on NF-κB inhibition, the GR undoubtedly interferes with the function of other transcriptional regulators. It is thought that protein–protein interactions similar to those described for GR–NF-κB are involved with GC inhibition of activator protein-1 (AP-1) and nuclear factor of activated T lymphocytes (NF-AT). The interesting point about each of these limitations is that each of them shows a strong connection among the immune, nervous and endocrine systems.

Data continue to be generated and are providing more insight on the mechanisms to help understand the interplay among these three body systems. It is now widely accepted that stressful life events can impact the health of an individual, including immunological health. Although there are many specific details yet to be delineated, it is becoming increasingly clear that products of the endocrine system, such as GC hormones, and products of the nervous system, such as catecholamines, can alter the function of macrophages and lymphocytes as well as other cells of the immune system.

Acknowledgements

This research was supported in part by NIH grants P50 DE13749 and PO1 AG16321, MH42096 MERIT AWARD, NIH General Clinical Research Center Grant MO1-RR-0034, and Ohio State University Comprehensive Cancer Center Core Grant CA16058.

References

1 Rabin, B.S. (1999) *Stress, Immune Function, and Health: The Connection*, Wiley-Liss & Sons
2 Madden, K.S. and Livnat, S. (1991) Catecholamine action and immunologic reactivity. In *Psychoneuroimmunology*, 2nd edn, (Ader, R. *et al.*, eds), Academic Press
3 Elenkov, I. *et al.* (1996) Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications. *Proc. Assoc. Am. Physicians* 108, 374–381
4 Marshall, G.D. Jr *et al.* (1998) Cytokine dysregulation associated with exam stress in healthy medical students. *Brain Behav. Immun.* 12, 297–307
5 Glaser, R. *et al.* (2001) Evidence for a shift in the Th-1 to Th-2 cytokine response associated with chronic stress and aging. *J. Gerontol. A Biol. Sci. Med. Sci.* 56, M477–M482
6 Glaser, R. *et al.* (1992) Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. *Psychosom. Med.* 54, 22–29
7 Kiecolt-Glaser, J.K. *et al.* (1996) Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc. Natl. Acad. Sci. U. S. A.* 93, 3043–3047
8 Glaser, R. *et al.* (2000) Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. *Psychosom. Med.* 62, 804–807
9 Morag, M. *et al.* (1999) Psychological variables as predictors of rubella antibody titers and fatigue-A prospective, double blind study. *J. Psychiatr. Res.* 33, 389–395
10 Vedhara, K. *et al.* (1999) Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. *Lancet* 353, 627–631
11 Jabaaij, L. *et al.* (1996) Modulation of immune response to rDNA Hepatitis B vaccination by psychological stress. *J. Psychosom. Res.* 41, 129–137
12 Burns, E.A. and Goodwin, J.S. (1990) Immunology and infectious disease. In *Geriatric Medicine* (Cassel, C.K. *et al.*, eds), pp. 312–329, Springer-Verlag
13 Patriarca, P.A. (1994) A randomized controlled trial of influenza vaccine in the elderly. *JAMA* 272, 1700–1701
14 Cohen, S. *et al.* (1991) Psychological stress and susceptibility to the common cold. *N. Engl. J. Med.* 325, 606–612
15 McCabe, P.M. *et al.* (2000) Animal models of disease. *Physiol. Behav.* 68, 501–507
16 Padgett, D.A. *et al.* (1998) Restraint stress slows cutaneous wound healing in mice. *Brain Behav. Immun.* 12, 64–73
17 Teunis, M.A. *et al.* (2002) Maternal deprivation of rat pups increases clinical symptoms of experimental autoimmune encephalomyelitis at adult age. *J. Neuroimmunol.* 133, 30–38
18 Dowdell, K.C. *et al.* (1999) Neuroendocrine modulation of chronic relapsing experimental autoimmune encephalomyelitis: a critical role for the hypothalamic-pituitary-adrenal axis. *J. Neuroimmunol.* 100, 243–251
19 Selye, H. (1936) A syndrome produced by diverse nocuous agents. (Lond). *Nature* 138, 32
20 Selye, H. (1936) Thymus and adrenals in the response of the organism to injuries and intoxication. *Br. J. Exp. Pathol.* 17, 234
21 Elenkov, I.J. and Chrousos, G.P. (2002) Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Ann. N. Y. Acad. Sci.* 966, 290–303
22 Ashwell, J.D. *et al.* (1992) Glucocorticoids in T cell development and function. *Annu. Rev. Immunol.* 18, 309–345
23 Russo-Marie, F. (1992) Macrophages and the glucocorticoids. *J. Neuroimmunol.* 40, 281–286
24 Muller, M. *et al.* (2002) Genetic modification of corticosteroid receptor

signalling: novel insights into pathophysiology and treatment strategies of human affective disorders. *Neuropeptides* 36, 117–131
25 DeRijk, R.H. *et al.* (2002) Glucocorticoid receptor variants: clinical implications. *J. Steroid Biochem. Mol. Biol.* 81, 103–122
26 Marchetti, B. *et al.* (2001) Stress, the immune system and vulnerability to degenerative disorders of the central nervous system in transgenic mice expressing glucocorticoid receptor antisense RNA. *Brain Res. Brain Res. Rev.* 37, 259–272
27 Hoeck, W. and Groner, B. (1990) Hormone-dependent phosphorylation of the glucocorticoid receptor occurs mainly in the amino-terminal transactivation domain. *J. Biol. Chem.* 265, 5403–5408
28 La Baer, J. and Yamamoto, K.R. (1994) Analysis of the DNA-binding affinity, sequence specificity and context dependence of the glucocorticoid receptor zinc finger region. *J. Mol. Biol.* 239, 664–688
29 Kanelakis, K.C. *et al.* (2002) Nucleotide binding states of hsp70 and hsp90 during sequential steps in the process of glucocorticoid receptor hsp90 heterocomplex assembly. *J. Biol. Chem.* 277, 33698–33703
30 Howard, K.J. *et al.* (1990) Mapping the HSP90 binding region of the glucocorticoid receptor. *J. Biol. Chem.* 265, 11928–11935
31 Berg, J.M. (1989) DNA binding specificity of steroid receptors. *Cell* 57, 1065–1068
32 Scheinman, R.I. *et al.* (1995) Role of transcriptional activation of IκBα in mediation of immunosuppression by glucocorticoids. *Science* 270, 283–286
33 Auphan, N. *et al.* (1995) Immunosuppression by glucocorticoids: Inhibition of NF-κB activity through induction of IκB synthesis. *Science* 270, 286–289
34 Li, Q. and Verma, I.M. (2002) NF-κB regulation in the immune system. *Nat. Rev. Immunol.* 2, 725–734
35 Adcock, I.M. *et al.* (1999) Ligand-induced differentiation of glucocorticoid receptor (GR) trans-repression and transactivation: preferential targetting of NF-κB and lack of I-κB involvement. *Br. J. Pharmacol.* 127, 1003–1011
36 Wissink, S. *et al.* (1998) A dual mechanism mediates repression of NF-κB activity by glucocorticoids. *Mol. Endocrinol.* 12, 355–363
37 Hofmann, T.G. *et al.* (1998) Various glucocorticoids differ in their ability to induce gene expression, apoptosis and to repress NF-κB-dependent transcription. *FEBS Lett.* 441, 441–446
38 Reichardt, H.M. *et al.* (2001) Repression of inflammatory responses in the absence of DNA binding by the glucocorticoid receptor. *EMBO J.* 20, 7168–7173
39 Adcock, I.M. and Caramori, G. (2001) Cross-talk between pro-inflammatory transcription factors and glucocorticoids. *Immunol. Cell Biol.* 79, 376–384
40 Schaaf, M.J. and Cidlowski, J.A. (2002) Molecular mechanisms of glucocorticoid action and resistance. *J. Steroid Biochem. Mol. Biol.* 83, 37–48
41 Hofmann, T.G. and Schmitz, L.M. (2002) The promoter context determines mutual repression or synergism between NF-kappaB and the glucocorticoid receptor. *Biol. Chem.* 383, 1947–1951
42 De Bosscher, K. *et al.* (2000) Glucocorticoids repress NF-κB-driven genes by disturbing the interaction of p65 with the basal transcription machinery, irrespective of coactivator levels in the cell. *Proc. Natl. Acad. Sci. U. S. A.* 97, 3919–3924
43 Sheppard, K.A. *et al.* (1998) Nuclear integration of glucocorticoid receptor and nuclear factor-κB signaling by CREB-binding protein and steroid receptor coactivator-1. *J. Biol. Chem.* 273, 29291–29294
44 McKay, L.I. and Cidlowski, J.A. (2000) CBP (CREB binding protein) integrates NF-κB (nuclear factor-κB) and glucocorticoid receptor physical interactions and antagonism. *Mol. Endocrinol.* 14, 1222–1234
45 Sanders, V.M. and Kohm, A.P. (2002) Sympathetic nervous system interaction with the immune system. *Int. Rev. Neurobiol.* 52, 17–41
46 Madden, K.S. (2003) Catecholamines, sympathetic innervation, and immunity. *Brain Behav. Immun.* 17 (Suppl 1), 5–10
47 Carrasco, G.A. and Van de Kar, L.D. (2003) Neuroendocrine pharmacology of stress. *Eur. J. Pharmacol.* 463, 235–272
48 Goldfien, A. (2001) Adrenal medulla. In *Basic and Clinical Endocrinology* (Greenspan, F.S. and Gardner, D.G., eds) pp. 399–421, Lange Medical Books, McGraw-Hill
49 Felten, S.Y. *et al.* (1992) Noradrenergic and peptidergic innervation of lymphoid organs. *Chem. Immunol.* 52, 25–48
50 Gilman, A.G. (1987) G proteins: transducers of receptor-generated signals. *Annu. Rev. Biochem.* 56, 615–649
51 Gardner, D.G. (2001) Mechanisms of hormone action. In *Basic and Clinical Endocrinology* (Greenspan, F.S. and Gardner, D.G., eds) pp. 59–79, Lange Medical Books, McGraw-Hill
52 Simonds, W.F. (1999) G protein regulation of adenylate cyclase. *Trends Pharmacol. Sci.* 20, 66–73
53 Barradeau, S. *et al.* (2002) Intracellular targeting of the type-I α regulatory subunit of cAMP-dependent protein kinase. *Trends Cardiovasc. Med.* 12, 235–241
54 Vallejo, M. (1994) Transcriptional control of gene expression by cAMP-response element binding proteins. *J. Neuroendocrinol.* 6, 587–596
55 Shaywitz, A.J. and Greenberg, M.E. (1999) CREB: a stimulus-induced transcription factor activated by a diverse array of extracellular signals. *Annu. Rev. Biochem.* 68, 821–861