Allergy 2001: 56: 470–477
Printed in UK. All rights reserved

Copyright © Munksgaard 2001
ALLERGY
ISSN 0105-4538

Review article

Immunity, hormones, and the brain

H. S. Haas, K. Schauenstein
Department of Pathophysiology, University of Graz, Graz, Austria

Professor Konrad Schauenstein, MD
Department of Pathophysiology
University of Graz
Heinrichstrasse 31A
A-8010 Graz
Austria

Accepted for publication 26 January 2001

Observations that the emotions affect somatic health and vice versa are as old as human medicine. Nevertheless, until recently, our Western, biologically oriented medicine largely denied ''psychosomatics'' as a significant pathogenic principle. Hence, the concept that the functions of the immune defense are regulated by signals of the neuroendocrine system and the central nervous system (CNS), as first suggested in the early 1970s by the experimental data of a handful of researchers, was met with great skepticism. At that time, immunologists were preoccupied by the vision of a self-regulating immune system with ''helper'' and ''suppressor'' T cells; furthermore, the respective data from studies in experimental animal models and/or cell cultures were often controversial and confusing, a phenomenon which will be referred to later on in this paper. The discipline of ''psychoneuroimmunology'', or ''neuroimmunomodulation'', owes its rise to modern molecular biologic techniques, by which it could be unequivocally proven that the communicative organs, i.e., the brain, endocrine system, and immune system, are speaking a common language by sharing common signal mediators and receptors. Thus, molecular analysis has led to a scientifically based reorientation of modern medicine toward holistic views, and it has shown that the slogan *mens sana in corpore sano* is valid also the other way round (*corpus sanum per mentem sanam*). In the present paper, we will review molecular mechanisms of the brain–immune system axis, comment on the emerging clinical relevance of these results, and propose future directions of research.

Molecular basis of the brain–immune system axis

One of the starting points of neuroendocrinoimmunology was the well-known immunoregulatory effect of glucocorticoids, which exert their effects via various mechanisms, such as the modification of cytokine synthesis (1, 2) and regulation of lymphocyte apoptosis (3), to name just two. The immunosuppressive effects of chronic stress were initially exclusively related to glucocorticoids as classical stress hormones. Later, however, lymphocytes were found to express functional receptors for virtually all of the endocrine components of the somatic stress reaction, such as catecholamines and the hormones of the anterior pituitary gland (4), with either stimulatory or suppressive effects on immune functions. Different stressors activate these components in different patterns, a fact which may explain how, depending on the quantity and/or quality of a stressor, stress can lead to either enhanced or suppressed immune functions (5).

Another milestone was the finding of Besedovsky et al. that the the activated immune system ''talks back'' via cytokine signals to the CNS, with measurable effects on the activity of the hypothalamo-pituitary-adrenal (HPA) axis, as evidenced by increased plasma glucocorticoids after an antigenic challenge (6–8). Later

it was realized that well-known phenomena associated with inflammatory reactions, such as fever and sickness behavior, are likewise the result of the central effects of cytokines released from activated leukocytes (9). Furthermore, it became obvious that the dialog with the immune system involves virtually the whole brain, including the cortex and, notably, structures of the ''limbic system'', i.e., the hippocampus and parts of the amygdala (10). In these areas, high densities of receptors for various cytokines have been detected, and it was shown that many of these mediators are locally produced by glial and/or neuronal cells, and have neurotransmitter-like functions. Taken together, these results suggest immediate mutual relationships between emotions and immune functions, relationships which may underlie the clinical observations that mood disorders are associated with increased susceptibility to infectious diseases or malignant tumors. In turn, diseases with massive activation of the immune system (trauma, sepsis, autoimmune disorders) can entail psychopathologic manifestations.

The last 15 years has brought an explosion of molecular data supporting brain–immune system interrelationships. Immune cells have been shown to express hormone-, neuropeptide-, and neurotransmitter-receptors at mRNA and protein levels (11, 12). Besides steroid receptors (13, 14), functional binding sites for substance P (15) and neuropeptide Y (16), corticotropin-releasing hormone (17), prolactin (18), products of the proopiomelanocortin (POMC) gene (19–21), catecholamines (22–24), acetylcholine (19–28), and serotonin (29–31) were detected. Some data also suggest binding sites for excitatory amino acids on immune cells (32–34). Furthermore, it turned out that lymphocytes and macrophages produce not only immune mediators, such as interleukins, but also neuropeptides and neurotransmitters, which may have paracrine, autocrine, and/or endocrine effects on both the immune and the nervous systems (27, 35–37).

On the other hand, neuronal and glial cells in different brain areas, depending on the state of activation, were found to express differentially a wide variety of cytokine receptors (38) and major histocompatibility complex (MHC) molecules (39–45). Steroid receptors are present within the CNS (46, 47), and brain cells themselves synthesize steroid hormones (neurosteroids), which regulate diverse brain functions (48–51). Furthermore, as mentioned above, microglia, astrocytes, and neurons are capable of secreting central cytokines (38, 52), which influence not only immune and neuroendocrine responses, but also CNS activities, such as synaptic transmission (53–56).

An important matter still awaiting definitive clarification is the route by which the peripheral immune and endocrine systems communicate with the brain, and vice versa. The most thoroughly examined afferent pathway with particular reference to the activation of hypothalamo-pituitary axes is the humoral route; i.e., circulating cytokines released from activated peripheral leukocytes bind to central cytokine receptors (57, 58). Several mechanisms for bypassing the blood–brain barrier (BBB) have been proposed in this context (59–61). However, besides this, neural pathways also play obviously important roles. This is shown in a number of studies implicating the vagus nerve in immune system–brain communications (62). As far as efferent (descending) routes are concerned, neuro-endocrine hormonal pathways are solidly established (63–65). In addition, it has been shown that the sympathetic nervous system, via catecholamines, conveys information from the CNS to the peripheral immune system (66–69), and several other neuro-transmitters, such as acetylcholine, serotonin, and excitatory/inhibitory amino acids and opioids, are involved in neuroimmune communications (70–77).

Our own studies aimed to elucidate the roles of the sympathetic and parasympathetic autonomic nervous systems within the brain–immune system axis. As for adrenergic effects on the immune system, most data suggest that adrenergic immunosuppression occurs via β-adrenergic stimulation. Our *in vivo* data in the rat model, however, suggest more complex mechanisms involving predominantly α-receptors (76). Mechanisms by which catecholamines control immune reactions appear to be modulation of cytokine expression, changes in leukocyte distribution, and the induction of apoptosis in lymphocytes (28). Several data strongly suggest that cholinergic signals also exert pronounced immunoregulatory effects. Immune cells express both muscarinic and nicotinergic receptors for acetylcholine (25–28), and an increased cholinergic tone was shown to lead to significant immunoenhancement (77). Furthermore, we found that *in vivo* treatment of rats with physostigmine leads to a disruption of the already mentioned immune-brain feedback, confirming that the cholinergic system is critically involved in the ''talking back'' of the immune system to the brain (77). The close relationships between the immune system and the adrenergic/cholinergic nervous system appear to be underlined by the findings that lymphocytes can synthesize and release catecholamines (36) and acetylcholine (27, 37), and there are initial indications that these nonneuronal transmitters may have paracrine and autocrine regulatory roles in the differentiation and functions of lymphocytes within the different compartments of the immune system (78).

All these data together demonstrate a complete feedback circuit between the brain and immune system that is secured by several mechanisms: the development and functions of the immune system are regulated by endocrine and neuroendocrine mediators, and cytokines released from activated immune cells in

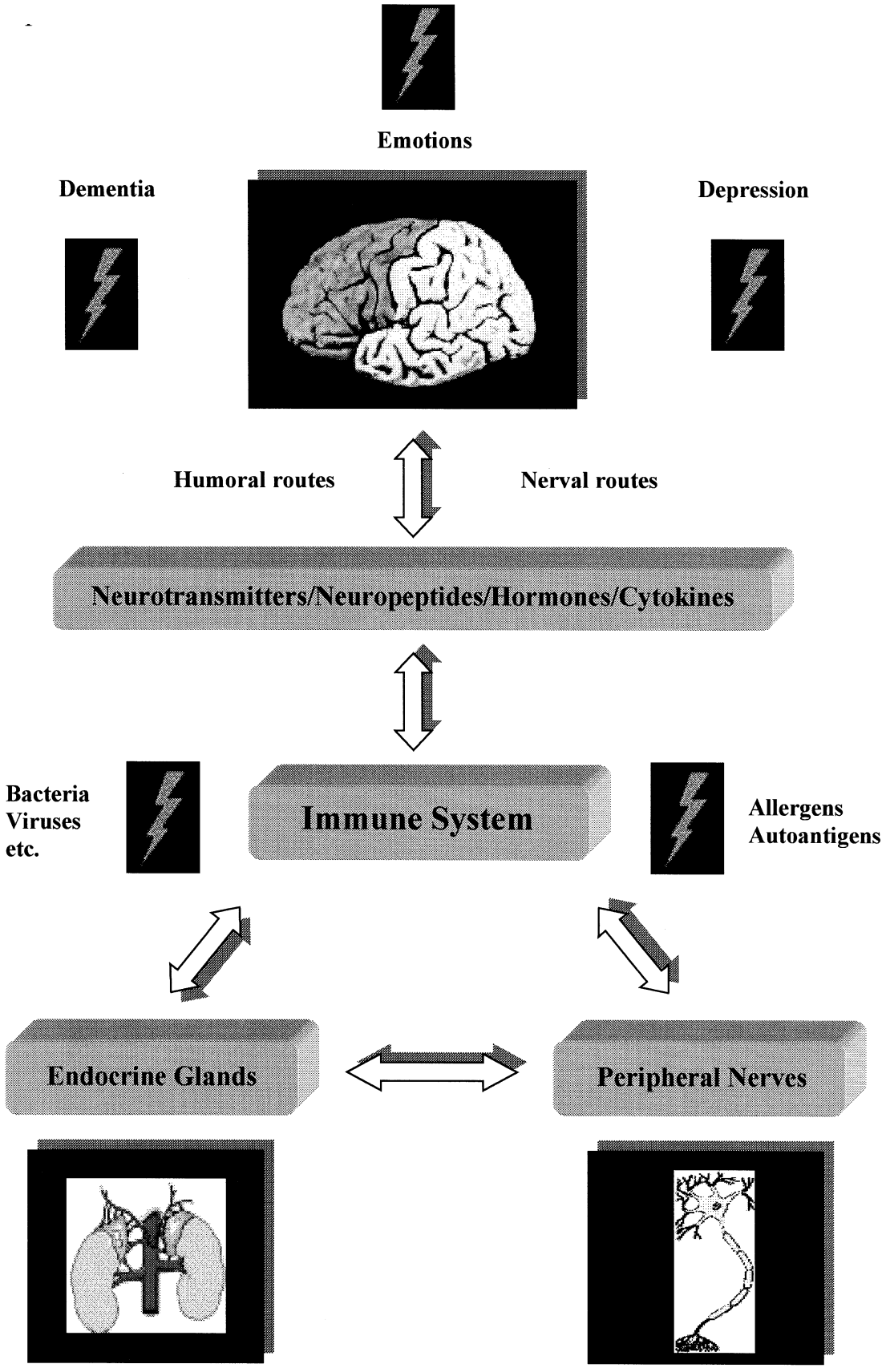

Figure 1. Psychoneuroimmunology – the network of bidirectional pathways between the immune, endocrine, and central/peripheral nervous systems.

turn modulate functions of the CNS. Defects at any point of this network are expected to affect all the systems involved (Fig. 1).

Clinical relevance

The results reviewed above strongly suggest that, besides glucocorticoids, a large array of hormones and transmitters exert pronounced immunoregulatory effects, and that the optimal functioning of the immune defense is critically dependent on the homeostasis of the neuroendocrine and/or central nervous systems. Loss of this homeostasis can lead to immune defects, as has been shown for chronic stress or depressive disorders, or it can significantly contribute to the occurrence of pathogenic immune reactions, such as allergy or autoimmune disease.

The pathogenesis of allergic diseases in general is known to have a strong psychosomatic component. Concerning type I hypersensitivity reactions within the respiratory tract, this is, on the one hand, due to the pronounced autonomic regulation of the small airways. On the other hand, there exist convincing data that the functions of mast cells and the T-cell-mediated regulation of the IgE response (79) are both under the control of neurohormones and -transmitters. β-Adrenergic agonists are among the established therapeutic tools to suppress mast-cell activation. More recently, it has been shown that the pleiotropic cytokine leukemia inhibitory factor (LIF), known as a modulator of HPA activity (80, 81), is synthesized and released by human eosinophils and has proinflammatory roles in allergic airway disorders (82). Classical neurotransmitters, including acetylcholine and serotonin, as well as neurotrophins such as nerve growth factor (NGF), have been revealed as important neuroimmune regulators in allergic inflammation and anaphylaxis (83–85). Receptors for the major central excitatory neurotransmitter glutamate have also been described in the periphery, e.g., the larynx and esophagus (86), and recent data suggest that activation of the *N*-methyl-D-aspartate (NMDA) subgroup of glutamate receptors is critically involved in the modulation of airway smooth-muscle responsiveness (87). These authors also discuss links between glutamate-mediated neurotransmission and the pathogenic mechanisms of bronchial asthma. Furthermore, the magnesium salt of *N*-acetyl-aspartyl-glutamate (Naaga), which is used in ophthalmic allergies, has been found to inhibit macrophage eicosanoid secretion (88). Finally, Espey & Basile (74) have reported that excitatory neural pathways are also involved in the regulation of Th1/Th2 shifts, as observed in the LP-BM5 model of retrovirus-induced immunodeficiency.

Type IV reactions, such as contact hypersensitivity, have also been shown to be under the control of neurohormones, such as the POMC-derived peptide alpha-melanocyte stimulating hormone (α-MSH) (89), which was shown to induce hapten-specific tolerance in mice (90). A mechanism contributing to these effects may be the inhibition of NF-κ B activation by α-MSH, as shown in experimental brain inflammation (91).

Autoimmune diseases originate from "forbidden" immune responses to autoantigens as a result of the loss of autotolerance of the patient's immune system. Autotolerance is supposedly secured by selection processes during lymphocyte maturation in the thymus, and is permanently maintained in the periphery by intrinsic and extrinsic mechanisms of immunoregulation. In this context, the feedback between brain and immune system via activation of the HPA axis appears to be of critical importance, as the elevation of peripheral glucocorticoids during an immune reaction may suppress the activation of low-affinity "forbidden" lymphocyte clones (7). This concept was supported by the results from several groups in animal models of spontaneous or experimentally induced autoimmune diseases, showing that a blunted glucocorticoid response after antigenic challenge is associated with an enhanced propensity to develop autoimmune disease (92–94). Our data in the rat model showing that an enhanced cholinergic tone in the periphery leads to a loss of the corticosterone peak in response to antigenic challenge (77) would suggest that the adrenergic/cholinergic homeostasis is relevant to the maintenance of autotolerance.

Besides immunopathologic conditions, neuroimmunoendocrine interactions have been found to play important roles in pain states, such as hyperalgesia and allodynia (95); in neurologic and psychiatric diseases, such as Alzheimer's disease, multiple sclerosis, depression, and schizophrenia (96–98); in bowel disorders, such as irritable bowel syndrome und ulcer disease (96–104); in skin diseases (105–107); and in cancer (108, 109).

Conclusions

The broad clinical application of psychoneuroimmunology and its discoveries is still in the initial stage and requires intensive basic research. One obvious problem lies in the high complexity of the organ systems involved, such as the brain, the endocrine system, and the immune system, a problem which may account for the fact that the results of the mutual interactions show high individual variabilities and are not always predictable for a given patient. A good example is the sensitivity of the immune system to stress, which, according to the nature of the respective stressor as well as the individual stress-specific experience, can lead to either immunoenhancement or -suppression. Besides, it is evident that the immunoregulating effects of

hormones and transmitters are critically dependent on the activation state of lymphocytes, as was shown long ago for glucucorticoids, where the initial phase of an immune response is much more sensitive to the suppressive effects than the established immune reaction (1). The inverse seems to be true for immunoregulation by catecholamines, as lymphocytes from patients with rheumatoid arthritis showed a significantly increased sensitivity to β_2-adrenergic activation (110). Only when we better understand the complex relationships between signal generation, signal effects, and activation states within the communicative systems will we be able to make use of the potent immunoregulatory properties of neurohormones and -transmitters in clinical therapy. One means to tackle this problem will be increasingly to complement conventional experimental strategies of single-point observations by modern multiparameter analysis techniques, in order to recognize changes in expression patterns of multiple components within the immune system or the CNS.

The results so far of psychoneuroimmunology provide convincing and scientifically sound arguments for the consideration and integration of psychologic aspects in the therapy of somatic diseases – they are an important first step toward an increased understanding of health, disease, and a "mindful" medicine.

Acknowledgments

This study was supported by the Austrian Science Foundation (projects 9925, 11130, 10422, 11921, 12579, and 12679) and the Jubiläumsfonds der Österreichischen Nationalbank (projects 5692 and 6730).

References

1. Gillis S, Crabtree GR, Smith KA. Glucocorticoid-induced inhibition of T cell growth factor production. II. The effect on the *in vitro* generation of cytolytic T cells. J Immunol 1979;**123**:1632–1638.
2. Richards DF, Fernandez M, Caulfield J, Hawrylowicz CM. Glucocorticoids drive human CD8(+) T cell differentiation towards a phenotype with high IL-10 and reduced IL-4, IL-5 and IL-13 production. Eur J Immunol 2000;**30**:2344–2354.
3. Riccardi C, Zollo O, Nocentini G, et al. Glucocorticoid hormones in the regulation of cell death. Therapie 2000;**55**:165–169.
4. Schedlowski M, Benshop RJ. Neuroendocrine system and immune functions. In: Schedlowski M, Trewes U, editors. Psychoneuroimmunology – an interdisciplinary introduction. New York: Kluwer Academic/Plenum, 1999:185–207.
5. Rinner I, Schauenstein K, Mangge H, Porta S, Kvetnansky R. Opposite effects of mild and severe stress on *in vitro* activation of rat peripheral blood lymphocytes. Brain Behav Immun 1992;**6**:130–140.
6. Besedovsky HO, Sorkin E, Keller M, Müller J. Changes in blood hormone levels during the immune response. Proc Soc Exp Biol Med 1975;**150**:466–470.
7. Besedovsky HO, Del Rey A, Sorkin E. Antigenic competition between horse and sheep red blood cells is a hormone-dependent phenomenon. Clin Exp Immunol 1979;**37**:106–113.
8. Besedovsky HO, Del Rey A, Sorkin E, Dinarello CA. Immuno-regulatory feedback between interleukin-1 and glucocorticoid hormones. Science 1986;**233**:652–654.
9. Dantzer R. Sickness behaviour. A neuroimmune-based response to infectious disease. In: Schedlowski M, Trewes U, editors. Psychoneuroimmunology – an interdisciplinary introduction. New York: Kluwer Academic/Plenum, 1999:235–257.
10. Haas HS, Schauenstein K. Neuroimmunomodulation via limbic structures – the neuroanatomy of psychoimmunology. Prog Neurobiol 1997;**51**:195–222.
11. Carr DJ, Blalock JE. From the neuroendocrinology of lymphocytes toward a molecular basis of the network theory. Horm Res 1989;**31**:76–80.
12. Heijnen CJ, Kavelaars A. The importance of being receptive. J Neuroimmunol 1999;**100**:197–202.
13. Lowy MT. Quantification of type I and II adrenal steroid receptors in neuronal, lymphoid and pituitary tissues. Brain Res 1989;**503**:191–197.
14. Miller AH, Spencer RL, Pearce BD, et al. Glucocorticoid receptors are differentially expressed in the cells and tissues of the immune system. Cell Immunol 1998;**186**:45–54.
15. Lai JP, Douglas SD, Ho WZ. Human lymphocytes express substance P and its receptor. J Neuroimmunol 1998;**86**:80–86.
16. Petitto JM, Huang Z, McCarthy DB. Molecular cloning of NPY-Y1 receptor cDNA from rat splenic lymphocytes: evidence of low levels of mRNA expression and [^{125}I]NPY binding sites. J Neuroimmunol 1994;**55**:81–86.
17. Radulovic M, Dautzenberg FM, Sydow S, Radulovic J, Spiess J. Corticotropin-releasing factor receptor 1 in mouse spleen: expression after immune stimulation and identification of receptor-bearing cells. J Immunol 1999;**162**:3013–3021.
18. Leite De Morales MC, Touraine P, Gagnerault MC, Savino W, Kelly PA, Dardenne M. Prolactin receptors and the immune system. Ann Endocrinol (Paris) 1995;**56**:567–570.
19. Borboni P, Di Cola G, Sesti G, et al. Beta-endorphin receptors on cultured and freshly isolated lymphocytes from normal subjects. Biochem Biophys Res Commun 1989;**163**:642–648.
20. Buggy JJ. Binding of alpha-melanocyte-stimulating hormone to its G-protein-coupled receptor on B-lymphocytes activates the Jak/STAT pathway. Biochem J 1998;**331(Pt 1)**: 211–216.
21. Clarke BL. Binding and processing of (125)I-ACTH by isolated rat splenic lymphocytes. Biochem Biophys Res Commun 1999;**266**:542–546.
22. Sanders VM. The role of adrenoceptor-mediated signals in the modulation of lymphocyte function. Adv Neuroimmunol 1995;**5**:283–298.
23. Caronti B, Calderaro C, Passarelli F, Palladini G, Pontieri FE. Dopamine receptor mRNAs in the rat lymphocytes. Life Sci 1998;**62**:1919–1925.

24. Ricci A, Bronzetti E, Mignini F, Tayebati SK, Zaccheo S, Amenta F. Dopamine D1-like receptor subtypes in human peripheral blood lymphocytes. J Neuroimmunol 1999;**96**:234–240.
25. Maslinski W. Cholinergic receptors on lymphocytes. Brain Behav Immun 1989;**3**:1–14.
26. Sato KZ, Fujii T, Watanabe Y, et al. Diversity of mRNA expression for muscarinic acetylcholine receptor subtypes and neuronal nicotinic acetylcholine receptor subunits in human mononuclear leukocytes and leukemic cell lines. Neurosci Lett 1999;**266**:17–20.
27. Kawashima K, Fujii T. Extraneuronal cholinergic system in lymphocytes. Pharmacol Ther 2000;**86**:29–48.
28. Schauenstein K, Felsner P, Rinner I, et al. *In vivo* immunomodulation by peripheral adrenergic and cholinergic agonists/antagonists in rat and mouse models. Ann N Y Acad Sci 2000;**917**:618–627.
29. Iken K, Cheng S, Fargin A, Goulet AC, Kouassi E. Serotonin upregulates mitogen-stimulated B lymphocyte proliferation through 5-HT1A receptors. Cell Immunol 1995;**163**:1–9.
30. Khan NA, Poisson JP. 5-HT3 receptor-channels coupled with Na^+ influx in human T cells: role in T cell activation. J Neuroimmunol 1999;**99**:53–60.
31. Stefulj J, Jernej B, Cicin-Sain L, Rinner I, Schauenstein K. mRNA expression of serotonin receptors in cells of the immune tissues of the rat. Brain Behav Immun 2000;**14**:219–224.
32. Malone JD, Richards M, Kahn AJ. Human peripheral monocytes express putative receptors for neuroexcitatory amino acids. Proc Natl Acad Sci U S A 1986;**83**:307–310.
33. Sung V, Venkateshan CN, Williamson L, et al. Immuno-electron microscopy reveals that the excitotoxin quinolinate is associated with the plasma membrane in human peripheral blood monocytes/macrophages. Cell Tissue Res 1997;**290**:633–639.
34. Kostanyan IA, Merkulova MI, Navolotskaya EV, Nurieva RI. Study of interaction between L-glutamate and human blood lymphocytes. Immunol Lett 1997;**58**:177–180.
35. Weigent DA, Blalock JE. Production of peptide hormones and neurotransmitters by the immune system. Chem Immunol 1997;**69**:1–30.
36. Bergquist J, Tarkowski A, Ewing A, Ekman R. Catecholaminergic suppression of immunocompetent cells. Immunol Today 1998;**19**:562–567.
37. Rinner I, Kawashima K, Schauenstein K. Rat lymphocytes produce and secrete acetylcholine in dependence of differentiation and activation. J Neuroimmunol 1998;**81**:31–37.
38. Rothwell NJ, Luheshi G, Toulmond S. Cytokines and their receptors in the central nervous system: physiology, pharmacology, and pathology. Pharmacol Ther 1996;**69**:85–95.
39. Phillips LM, Simon PJ, Lampson LA. Site-specific immune regulation in the brain: differential modulation of major histocompatibility complex (MHC) proteins in brainstem vs. hippocampus. J Comp Neurol 1999;**405**:322–333.
40. Lidman O, Olsson T, Pichl F. Expression of nonclassical MHC class I (RT1-U) in certain neuronal populations of the central nervous system. Eur J Neurosci 1999;**11**:4468–4472.
41. Kiss JZ, Wang C, Olive S, et al. Activity-dependent mobilization of the adhesion molecule polysialic NCAM to the cell surface of neurons and endocrine cells. EMBO J 1994;**13**:5284–5292.
42. Neumann H, Cavalié A, Jenne DE, Wekerle H. Induction of MHC class I genes in neurons. Science 1995;**269**:549–552.
43. Neumann H, Schmidt H, Cavalié A, Wekerle H. Major histocompatibility complex (MHC) class I gene expression in single neurons of the central nervous system: differential regulation by interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha. J Exp Med 1997;**185**:305–316.
44. Itoh K, Stevens B, Schachner M, Fields RD. Regulated expression of the neural cell adhesion molecule L1 by specific patterns of neural impulses. Science 1995;**270**:369–1372.
45. Itoh K, Ozaki M, Stevens B, Fields RD. Activity-dependent regulation of N-cadherin in DRG neurons: differential regulation of N-cadherin, NCAM, and L1 by distinct patterns of action potentials. J Neurobiol 1997;**33**:735–748.
46. Lowy MT. Quantification of type I and II adrenal steroid receptors in neuronal, lymphoid and pituitary tissues. Brain Res 1989;**503**:191–197.
47. Joels M, Vreugdenhil E. Corticosteroids in the brain. Cellular and molecular actions. Mol Neurobiol 1998;**17**:87–108.
48. Baulieu EE. Neurosteroids: a novel function of the brain. Psychoneuroendocrinology 1998;**23**:963–987.
49. Jung-Testas I, Do Thi A, Koenig H, et al. Progesterone as a neurosteroid: synthesis and actions in rat glial cells. J Steroid Biochem Mol Biol 1999;**69**:97–107.
50. Tsutsui K, Ukena K, Usui M, Sakamoto H, Takase M. Novel brain function: biosynthesis and actions of neurosteroids in neurons. J Neurosci Res 2000;**36**:261–273.
51. Compagnone NA, Mellon SH. Neurosteroids: biosynthesis and function of these novel neuromodulators. Front Neuroendocrinol 2000;**21**:1–56.
52. Raber J, Sorg O, Horn TFW, et al. Inflammatory cytokines: putative regulators of neuronal and neuro-endocrine function. Brain Res Rev 1998;**26**:320–326.
53. Pauli S, Linthorst AC, Reul JM. Tumour necrosis factor-alpha and interleukin-2 differentially affect hippocampal serotonergic neurotransmission, behavioural activity, body temperature and hypothalamic-pituitary-adrenocortical axis activity in the rat. Eur J Neurosci 1998;**10**:868–878.
54. O'Connor JJ, Coogan AN. Actions of the pro-inflammatory cytokine IL-1 beta on central synaptic transmission. Exp Physiol 1999;**84**:601–614.
55. Schneider H, Pitossi F, Balschun D, Wagner A, Del Rey A, Besedovsky HO. A neuromodulatory role of interleukin-1 beta in the hippocampus. Proc Natl Acad Sci U S A 1998; **95**:7778–7783.
56. D'Arcangelo G, Tancredi V, Onofri F, D'Antuono M, Giovedi S, Benfenati F. Interleukin-6 inhibits neurotransmitter release and the spread of excitation in the rat cerebral cortex. Eur J Neurosci 2000;**12**: 1241–1252.
57. Turnbull AV, Lee S, Rivier C. Mechanisms of hypothalamic-pituitary-adrenal axis stimulation by immune signals in the adult rat. Ann N Y Acad Sci 1998;**840**:434–443.
58. Da Silva JA. Sex hormones and glucocorticoids: interactions with the immune system. Ann N Y Acad Sci 1999;**876**:102–117.
59. Gutierrez EG, Banks WA, Kastin AJ. Murine tumor necrosis factor alpha is transported from blood to brain in the mouse. J Neuroimmunol 1993;**47**:169–176.
60. Blatteis CM. The afferent signalling of fever. J Physiol 2000;**526(Pt 3)**:470.

61. Rivest S, Lacroix S, Vallieres L, Nadeau S, Zhang J, Laflamme N. How the blood talks to the brain parenchyma and the paraventricular nucleus of the hypothalamus during systemic inflammatory and infectious stimuli. Proc Soc Exp Biol Med 2000;**223**:22–38.
62. Maier SF, Goehler LE, Fleshner M, Watkins LR. The role of the vagus nerve in cytokine-to-brain communication. Ann N Y Acad Sci 1998;**840**:289–300.
63. Sternberg EM. Neuroendocrine factors in susceptibility to inflammatory disease: focus on the hypothalamic-pituitary-adrenal axis. Horm Res 1995;**43**:159–161.
64. Torpy DJ, Chrousos GP. The three-way interactions between the hypothalamic-pituitary-adrenal and gonadal axes and the immune system. Baillieres Clin Rheumatol 1996;**10**:181–198.
65. Savino W, Arzt E, Dardenne M. Immunoneuroendocrine connectivity: the paradigm of the thymus-hypothalamus/pituitary axis. Neuroimmunomodulation 1999;**6**:126–136.
66. Friedman EM, Irwin MR. Modulation of immune cell function by the autonomic nervous system. Pharmacol Ther 1997;**74**:27–38.
67. Rinner I, Felsner P, Liebmann P, et al. Adrenergic/cholinergic immunomodulation in the rat model – *in vivo veritas*? Dev Immunol 1998;**6**:245–252.
68. Schorr EC, Arnason BG. Interactions between the sympathetic nervous system and the immune system. Brain Behav Immun 1999;**13**:271–278.
69. Basu S, Dasgupta PS. Dopamine, a neurotransmitter, influences the immune system. J Neuroimmunol 2000;**102**:113–124.
70. Song DK, Suh HW, Jung JS, Wie MB, Song JH, Kim YH. Involvement of NMDA receptor in the regulation of plasma interleukin-6 levels in mice. Eur J Pharmacol 1996;**316**:165–169.
71. Bergeret M, Khrestchatisky M, Tremblay E, Bernard A, Gregoire A, Chany C. GABA modulates cytotoxicity of immunocompetent cells expressing GABA A receptor subunits. Biomed Pharmacother 1998;**52**:214–219.
72. Mossner R, Lesch KP. Role of serotonin in the immune system and in neuroimmune interactions. Brain Behav Immun 1998;**12**:249–271.
73. Hegg CC, Thayer SA. Monocytic cells secrete factors that evoke excitatory synaptic activity in rat hippocampal cultures. Eur J Pharmacol 1999;**385**:231–237.
74. Espey MG, Basile AS. Glutamate augments retrovirus-induced immunodeficiency through chronic stimulation of the hypothalamic-pituitary-adrenal axis. J Immunol 1999;**162**:4998–5002.
75. Roy S, Loh HH. Effects of opioids on the immune system. Neurochem Res 1996;**21**:1375–1386.
76. Felsner P, Hofer D, Rinner I, Porta S, Korsatko W, Schauenstein K. Adrenergic suppression of peripheral blood T cell reactivity in the rat is due to activation of peripheral α_2-receptors. J Neuroimmunol 1995;**57**:27–34.
77. Rinner I, Schauenstein K. The parasympathetic nervous system takes part in the immuno-neuroendocrine dialogue. J Neuroimmunol 1991;**34**:165–172.
78. Rinner I, Globerson A, Kawashima K, Korsatko W, Schauenstein K. A possible role for acetylcholine in the dialogue between thymocytes and thymic stroma. Neuroimmunomodulation 1999;**6**:51–55.
79. Aebischer I, Stampfli MR, Zurcher A, et al. Neuropeptides are potent modulators of human *in vitro* immunoglobulin E synthesis. Eur J Immunol 1994;**24**:1908–1913.
80. Auernhammer CJ, Chesnokova V, Melmed S. Leukemia inhibitory factor modulates interleukin 1β-induced activation of the hypothalamo-pituitary-adrenal axis. Endocrinology 1998;**139**:2201–2208.
81. Chesnokova V, Auernhammer CJ, Melmed S. Murine leukemia inhibitory factor gene disruption attenuates the hypothalamo-pituitary-adrenal axis stress response. Endocrinology 1998;**139**:2209–2216.
82. Zheng X, Knight DA, Zhou D, et al. Leukemia inhibitory factor is synthesized and released by human eosinophils and modulates activation state and chemotaxis. J Allergy Clin Immunol 1999;**104**:136–144.
83. Javed NH, Wang YZ, Cooke HJ. Neuroimmune interactions: role for cholinergic neurons in intestinal anaphylaxis. Am J Physiol 1992;**263**:G847–G852.
84. Bonini S, Lambiase A, Bonini S, Levi-Schaffer F, Aloe L. Nerve growth factor: an important molecule in allergic inflammation and tissue remodelling. Int Arch Allergy Immunol 1999;**118**:159–162.
85. Eum SY, Norel X, Lefort J, Labat C, Vargaftig BB, Brink C. Anaphylactic bronchoconstriction in BP2 mice: interactions between serotonin and acetylcholine. Br J Pharmacol 1999;**126**:312–316.
86. Robertson BS, Satterfield BE, Said SI, Dey RD. *N*-methyl-D-aspartate receptors are expressed by intrinsic neurons of rat larynx and esophagus. Neurosci Lett 1998;**244**:77–80.
87. Said SI. Glutamate receptors and asthmatic airway disease. Trends Pharmacol Sci 1999;**20**:132–134.
88. Jambou D, Lapalus P. Effect of *N*-acetyl-aspartyl-glutamate (Naaga) on *in vitro* leukotriene synthesis by macrophage cell line P388D1. Int J Tissue React 1990;**12**:273–280.
89. Luger TA, Kalden D, Scholzen TE, Brzoska T. Alpha-melanocyte-stimulating hormone as a mediator of tolerance induction. Pathobiology 1999;**67**:318–221.
90. Grabbe S, Bhardwaj RS, Mahnke K, Simon MM, Schwarz T, Luger TA. Alpha-melanocyte-stimulating hormone induces hapten-specific tolerance in mice. J Immunol 1996;**156**:473–478.
91. Ichiyama T, Sakai T, Catania A, Barsh GS, Furukawa S, Lipton JM. Systemically administered alpha-melanocyte-stimulating peptides inhibit NF-kappaB activation in experimental brain inflammation. Brain Res 1999;**836**:31–37.
92. Schauenstein K, Faessler R, Dietrich H, Schwarz S, Kroemer G, Wick G. Disturbed immune-endocrine communication in autoimmune diseases. Lack of corticosterone response to immune signals in Obese Strain chickens with spontaneous autoimmune thyroiditis. J Immunol 1987;**139**:1830–1833.
93. Sternberg EM, Hill JM, Chrousos GP, et al. Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats. Proc Natl Acad Sci U S A 1989;**86**:2374–2378.
94. Mason D, Macphee I, Antoni F. The role of the neuroendocrine system in determining genetic susceptibility to experimental allergic encephalomyelitis in the rat. Immunology 1990;**70**:1–5.
95. Watkins LR, Maier SF. Implications of immune-to-brain communication for sickness and pain. Proc Natl Acad Sci U S A 1999;**96**:7710–7713.
96. Köller H, Siebler M, Hartung H-P. Immunologically induced electrophysiological dysfunction: implications for inflammatory diseases of the CNS and PNS. Prog Neurobiol 1997;**52**:1–26.
97. Dietrich DE, Schedlowski M, Bode L, Ludwig H, Emrich HM. A viro-psycho-immunological disease-model of a subtype affective disorder. Pharmacopsychiatry 1998;**31**:77–82.

98. Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. Am J Psychiatry 2000;**157**:683–694.
99. Muller MJ, Hunt RH. Inflammation, acid and ulcers. Yale J Biol Med 1994;**67**:135–144.
100. Kanemasa K, Okamura H, Kodama T, Kashima K, Ibata Y. Time course of the induction of VGF mRNA in the dorsal vagal complex in rats with cysteamine-induced peptic ulcers. Mol Brain Res 1995;**34**:309–314.
101. Walker MM, Crabtree JE. *Helicobacter pylori* infection and the pathogenesis of duodenal ulceration. Ann N Y Acad Sci 1998;**859**:96–111.
102. Bueno L, Fioramonti J. Effects of inflammatory mediators on gut sensitivity. Can J Gastroenterol 1999;**13 Suppl A**:42A–46A.
103. Furness JB, Kunze WA, Clerc N. Nutrient tasting and signaling mechanisms in the gut. II. The intestine as a sensory organ: neural, endocrine, and immune responses. Am J Physiol 1999;**277**:G922–G928.
104. Shanahan F. Brain-gut axis and mucosal immunity: a perspective on mucosal psychoneuroimmunology. Semin Gastrointest Dis 1999;**10**:8–13.
105. Bilkis MR, Mark KA. Mind-body medicine. Practical applications in dermatology. Arch Dermatol 1998;**134**:1437–1441.
106. Buske-Kischbaum A, Jobst S, Hellhammer DH. Altered reactivity of the hypothalamo-pituitary-adrenal axis in patients with atopic dermatitis: pathologic factor or symptom? Ann N Y Acad Sci 1998;**840**:747–754.
107. Hautmann G, Campanile G, Bianchi B, Lotti T. Alcohol intake, cytokines, neuropeptides, and the skin. Clin Dermatol 1999;**17**:391–394.
108. Besedovsky HO, Herberman RB, Temoshok LR, Sendo F. Psychoneuroimmunology and cancer: Fifteenth Sapporo Cancer Seminar. Cancer Res 1996;**56**:4278–4281.
109. Kiecolt-Glaser JK, Glaser R. Psychoneuroimmunology and cancer: fact or fiction? Eur J Cancer 1999;**35**:1603–1607.
110. Lombardi MS, Kavelaars A, Schedlowski M, et al. Decreased expression and activity of G-protein-coupled receptor kinases in peripheral blood mononuclear cells of patients with rheumatoid arthritis. FASEB J 1999;**13**:715–725.