Neural Responses to Antigenic Challenges and Immunomodulatory Factors

DAVID SAPHIER, Ph.D., HAIM OVADIA, Ph.D., AND ODED ABRAMSKY, M.D., Ph.D.

Department of Neurology, Hadassah University Hospital, Jerusalem, Israel

Received June 8, 1989

INTRODUCTION

Although the essential trends in scientific thinking have led to a high degree of compartmentalization of the living organism into discrete "systems," it has not been forgotten that there must be interactions between such systems in order to maintain normal functioning. We are now at a time when we are more informed about, and thus better able to appreciate, the inherent nature of the interactions between components of the different systems. Thus, the terms neuroimmunomodulation (NIM) and immunoneuroendocrinology have arisen to describe the bidirectional interactions thought to exist between the immune system and the central nervous system (CNS) [1,2].

The immune system is probably fully autonomous in its ability for "self versus non-self" discrimination. The identification of antigens and the propagation of immune effector mechanisms are mainly determined by the genome, since these processes can occur normally in clonal cell lines in vitro. CNS intervention in the activity of the immune system probably occurs primarily during the immunological processes that are

Abbreviations: ACTH: adrenocorticotropic hormone α-IFN: α-interferon CNS: central nervous system EEG: electroencephalogram HIS: histamine IL-1: interleukin 1 MUA: multi-unit activity NIM: neuroimmunomodulation NK: natural killer POA/AH: preoptic area/anterior hypothalamus PVN: paraventricular nucleus SRBC: sheep red blood cells THF: thymic humoral factor

Address reprint requests to: David Saphier, Ph.D., Dept. of Pharmacology and Therapeutics, Louisiana State University Medical Center, P.O. Box 33932, Shreveport, LA 71130-3932

Copyright © 1990 by The Yale Journal of Biology and Medicine, Inc. All rights of reproduction in any form reserved.
categorized as antigen-independent; such as those of ontogeny, cell turnover, cell migration, and signal sensitivity [2]. These processes are believed to be crucial for the determination of the intensity and duration of immune responses, thus enabling defense mechanisms of the host to be fully geared.

A great deal of evidence is now available indicating that the CNS is able to exert modulatory effects upon peripheral immune responses, so that psychological factors such as stress, e.g., following bereavement [3], personality type, or mental illness may lead to decreased immunocompetence and increased incidence of disease [1,4]. Effects of immune system activation upon the CNS may be less readily identified, however, despite the human condition of "malaise" when diseased, such feelings being generated within the CNS. How such information reaches the CNS is of primary importance to our understanding of the mechanisms underlying CNS-immune interactions. The immune system probably generates as yet unidentified signals which are capable of altering CNS activity, thereby modulating neuroendocrine responses and thus providing a feedback regulation upon its own activity. This communication, whereby the CNS provides a fine tuning of the immune system, is thought to be crucial to normal host defense responses [1,4].

Stress is a major biological phenomenon which is known to alter immune system function and thus enable the examination of the effects of the CNS upon immune function, since the physiological effects of stress are mediated via the CNS [5]. The best-accepted definition of stress is that of any stimulus capable of causing an activation of the hypothalamo-hypophyseal-adrenocortical neuroendocrine axis, resulting in an elevation of circulating plasma glucocorticoid hormone levels [5]. Acute exposure of experimental animals to stressors may result in a suppression of both humoral and cellular immune responses [6,7]. On the other hand, repeated exposure to the same stressor may result in adaptation and, in some cases, an enhanced immune response [7,8]; for example, the handling of animals may enhance immunocompetence [6]. Furthermore, it has been shown that the immune response may be modified following classical conditioning paradigms [9] and following the pairing of a neutral stimulus with an immunosuppressive drug, resulting in a Pavlovian-like conditioning of an immunosuppressive response [10]. Other studies have shown that CNS manipulations, such as electrolytic lesions or electrical stimulation of CNS structures, are able to cause changes in the activity of the immune system. Anterior hypothalamic lesions may cause a substantial decrease in the number of nucleated spleen cells and thymocytes, and in the blastogenic response to mitogens [11], as well as inhibiting some autoimmune diseases of the nervous system [12]. An effect of cerebral lateralization upon immune responses has also been demonstrated; lesions of the left cerebral neocortex in mice cause a selective depression of cell-mediated responses without affecting the B-cell response [13]. In another study, it was demonstrated that immune disorders, such as atopic diseases and autoimmune thyroiditis, are more frequent in left-handed members of the population, and their relatives, than in right-handed people [14].

Increasingly it has been observed that the immune, nervous, and endocrine systems share common receptor sites for a variety of neurotransmitters, hormones, neuropeptides, and other neuroactive substances, and also the ability to synthesize and secrete such substances [15–19]. Thus, secretions from differing systems may be expected to influence components of the other systems under various conditions; data to this effect
are slowly becoming available from a number of laboratories, as referred to throughout this text.

Possible routes of direct communication between the CNS and the immune system have been indicated by morphological studies [20,21]. These studies have demonstrated extensive innervation of germinal centers in lymphoid tissues, thereby introducing the notion of direct neural interactions between the CNS and the immune system. A number of studies have now been able to demonstrate electrophysiological responses within the central nervous system following antigenic stimulation or the administration of various antigenic agents [22–26], and such changes have been shown to occur during the entire course of the immune response [25]. A role for adrenoglucocorticoid hormones in the suppression of immune responses is well documented and the immunosuppressive properties of such steroid hormones are frequently employed in the clinical context. It is probable that this neuroendocrine axis is of great importance in the feedback interactions between the immune and nervous systems [27]. For example, even the normal circadian rhythm of adrenal glucocorticoid hormone levels in plasma has been shown to be correlated with changes in immune cell traffic in man and animals [28,29], demonstrating the potent effects of such hormones upon the immune system, the secretions of which are known to be under neural control. Thus, in our studies, single and multi-unit neuronal responses were recorded in hypothalamic sites known to be of particular importance in the regulation of hypothalamo-hypophysial-adrenocortical activity [30] and which are known also to influence the course of immune responses and experimentally induced autoimmune diseases [11,12,31]. It is clear therefore that functional feedback circuits between the immune system and the CNS exist and that these are probably of considerable physiological significance in normal regulation of host-defense responses. In our studies, we have tried to describe further some of the components of the feedback circuits between the immune system and CNS, with a particular emphasis upon the regulation of the hypothalamo-hypophysial-adrenocortical axis and the role of immunomodulatory factors as mediators of the bidirectional information flow between the systems.

METHODS

All experiments were performed on adult male rats bearing chronically implanted recording electrode bundles, implanted under sodium pentobarbital anesthesia, and consisting of arrays of three 45 μm Teflon-coated wires which were twisted together and attached to the terminals of an appropriate plastic plug. For experiments involving intracerebroventricular administration of immunomodulatory factors, screws for recording cortical electroencephalograms (EEG) were implanted over the frontal and parietal cortices, and a guide cannula was implanted above the lateral ventricle; these devices were in addition to the recording electrode bundles. The entire assembly was fixed to the skull with dental cement and the rats allowed to recover for at least one week before use in any experimental procedures. Daily injections of sodium penicillin G were given intramuscularly for three days following the surgery in order to prevent infection [25,26].

Electrical activity was recorded, using differential recording between electrode pairs and amplification with standard electrophysiological equipment. Peak multi-unit activity (MUA) was discriminated using a voltage-window discriminator, with the baseline activity selected to be between 10 and 15 Hz [25,26]. The animals were sensitized with an intraperitoneal injection of a suspension of sheep red blood cells
(SRBC, 10 percent by volume) in physiological saline; this injection was administered on the second or third day after recording of the baseline POA/AH and PVN MUA levels, as observed between the preset voltage-window levels.

**EXPERIMENTAL FINDINGS**

*The First Immune Response*

In our first experiments, we have employed a conscious rat model bearing chronically implanted recording electrodes in the preoptic area/anterior hypothalamus (POA/AH) and hypothalamic paraventricular nucleus (PVN). The latter area is the primary site of cells that secrete corticotropin-releasing factor and of vasopressin-secreting neurones that regulate pituitary adrenocorticotropic hormone (ACTH) secretion. These two hypothalamic peptides are the principal ACTH regulatory secretagogues [32].

POA/AH MUA increased from a basal level of 14.65 ± 2.07 Hz to a maximum of 33.06 ± 6.93 Hz (p < 0.005), five days following the SRBC injection; in some animals maximum POA/AH MUA was recorded on days 4 or 6. This increase was found to be
IMMUNE SYSTEM MODULATION OF CNS ACTIVITY

Correlated with the first appearance of SRBC serum antibodies. Decreases in MUA were recorded on days 3 and 8 following the sensitization, and basal POA/AH MUA levels were achieved again by the ninth day (Figs. 1 and 2). Significant increases in PVN MUA were also recorded after SRBC injection, but these increases were delayed when compared to those of the POA/AH; the maximum effect occurred on the sixth day (Fig. 1). Furthermore, in accordance with the works of others [22,33], we were able to demonstrate increases in plasma corticosterone levels on the eighth day following SRBC injection [unpublished observations]. We believe that the recorded changes in PVN MUA, and possibly also those in the POA/AH, may be related to the alterations in circulating corticosterone levels [25,30].

The Second Immune Response

In another group of rats also sensitized with 10 percent SRBC, three weeks before initiation of the same protocol described above, we recorded POA/AH MUA changes during induction of the secondary immune response to SRBC. The POA/AH MUA increased significantly between days 4 and 9 following the challenge, with the maximal increases recorded on day 6 (Fig. 3). The profile of this second response was different from that of the first because no decreases in MUA were recorded and the maximal increase appeared later. The increase was smaller in magnitude, and there were more days of significantly increased neural activity.

EFFECTS OF IMMUNOSUPPRESSIVE DRUG TREATMENT

Treatment of rats with the immunosuppressive drug cyclophosphamide (25 mg/kg daily intraperitoneal injection, following each recording period) was able to prevent both the production of anti-SRBC serum antibodies in response to the SRBC challenge and the increase of POA/AH MUA. This result was true for the majority of animals (five of six); however, a low titer of anti-SRBC antibodies was detected on the tenth day in one animal. This rat also exhibited an increase in POA/AH MUA on the fifth day following the SRBC challenge (Table 1). Although many immunosuppressive drugs, including cyclophosphamide, can increase plasma adrenocorticosteroid levels

FIG. 2. POA/AH MUA recorded before and after SRBC sensitization (arrow). Significance levels calculated with the t-test statistic: a, p < 0.05 compared with day 0; b, p < 0.005, compared with day 0; c, p < 0.05, compared with day 5. Reproduced by permission of the publisher, from [25].
[34,35], it is not the case that the immunosuppressive effects of these drugs are due solely to their effects upon adrenocortical secretion. It seems likely, therefore, that the neural responses recorded in the previous studies were a secondary effect of the immune system activation in response to the antigenic challenge.

EFFECTS OF IMMUNOMODULATORY FACTORS

Antibodies are limited in their ability to cross the blood-brain barrier; therefore, it is unlikely that these products of the immune system are responsible for the changes in neural activity following SRBC stimulation. The current consensus of opinion favors the idea that other soluble products elaborated during the course of immune responses are responsible for the above recorded changes in neural and neuroendocrine activity. Several laboratories have begun investigating the neural and neuroendocrine effects of various neuroimmunomodulatory factors. Effects of interleukin 1 (IL-1) and α-interferon (α-IFN) have been demonstrated in both the clinical and laboratory situations [36–39]. IL-1, a cytokine released especially by activated monocytes as well as other cell types including neural glial cells [40,41], is an endogenous pyrogen [42]; it is capable of activating the hypothalamo-hypophyseal-adrenocortical axis [43], induc-

| Experimental Group | % MUA Change (Days 5/6) | Anti-SRBC Titer (Day 10) |
|--------------------|-------------------------|--------------------------|
| SRBC – First response | +305                    | 1:128                    |
| SRBC – Second response | +220                  | ND                      |
| SRBC + CY (5 of 6 rats) | –1                      | ND                      |
| SRBC + CY (1 of 6 rats)* | +36                    | 1:32                    |

Rats were immunized with 10 percent SRBC and MUA was recorded every day. Values of the peak activity of each experimental group are illustrated for comparison. IgM antibodies against SRBC were detected by hemagglutination test in sera obtained at day 10 post-immunization. ND, not detected.

*One rat treated with cyclophosphamide (CY) showed a significant change in POA/AH MUA and later developed serum antibodies to SRBC: see text.
ing fever probably via an action upon thermosensitive cells within the anterior hypothalamus [44], and causing release of acute-phase proteins [45]. IL-1 has also been shown to induce slow-wave sleep [37], although our data suggest that it may be able to cause a decrease in EEG synchronization, at least in the short term, following acute central administration [26]. α-IFN is synthesized by activated leukocytes and is known to exert a number of diverse biological effects in addition to its antiviral activity, including inhibition of DNA synthesis during the lymphoproliferative phase, suppression of antibody synthesis, and enhancement of natural killer (NK) cell activity [46]. Effects of α-IFN upon the CNS have been recognized in man, and these include modification of behavior [47] and other neurological or psychiatric effects [38]. Effects of α-IFN upon EEG and single units in the rat brain have been demonstrated [39], and there is evidence that such effects may be mediated by endogenous opioid receptor sites [48]. Effects of histamine (HIS) upon arousal [49] and adrenocortical activation [50] have been recognized for many years, and it is known that this biogenic amine, which is released by mast cells during allergic responses [51], is also found in neuronal systems of the CNS [49].

In our laboratory, we have investigated the effects of α-IFN, IL-1, HIS, and thymic humoral factor (THF, [52]) upon cortical EEG, POA/AH MUA, and circulating corticosterone levels following intracerebroventricular administration of these substances in conscious rats [26].

Saline did not alter POA/AH MUA, but the total time and duration of synchronized EEG periods was increased in the 45-minute period after injection. α-IFN and THF were found to reduce POA/AH activity significantly, increase EEG synchronization, and decrease plasma corticosterone levels (the latter particularly following daily administration for three days). HIS and IL-1 did not affect POA/AH MUA, but decreased the amount of EEG synchronization and increased plasma corticosterone levels. The results are summarized in Figs. 4, 5, and 6, and they demonstrate that

![Graph showing effects of immunomodulatory factors on POA/AH MUA](image-url)

**FIG. 4.** POA/AH MUA recorded before (Pre-Inj.), and 15 minutes and 45 minutes after intracerebroventricular injection of immunomodulatory factors as indicated. The number of test periods with each substance are shown at the base of each column. Significance levels were obtained by comparison with the pre-injection discharge rate. a, p < 0.05; d, p < 0.005.
several factors elaborated by the immune system are able to alter EEG activity, plasma levels of adrenocortical hormones, and multi-unit activity in an area of the brain that is known to be influenced by immune responses, and which modulates both immune and neuroendocrine secretory activity, vide supra.

DISCUSSION

The results of our studies confirm and extend the data of other authors and indicate that, during the course of normal immune responses, related changes in electrical activity in the brain occur, particularly in areas concerned with neuroendocrine regulatory mechanisms [22–26]. These changes appear to follow the course of the peripheral immune response, at least in terms of antibody production, and they may be altered by prior exposure to the antigen used. Some of these changes (in the PVN) appear to be related directly to the central neural regulation of the hypothalamo-hypophyseal-adrenocortical axis [30]. That immunosuppressive drug treatment is able...
to prevent the neurophysiological changes supports the concept that humoral signals, arising from the activated immune system, mediate these changes in neural activity. In this context, some identified immune system factors were found to have effects upon the EEG, POA/AH MUA, and plasma adrenocortical hormone levels, although the physiological significance of the data obtained remains to be clarified further.

Speculation concerning the physiological significance of some of the effects demonstrated may be made. For example, both α-IFN and THF, which have immunostimulatory properties [46,52], were found to decrease plasma corticosterone levels, increases in which are usually able to cause immunosuppression [27–29, 53–56]. This finding suggests that these factors exert a positive feedback effect upon their own actions. Thus THF, secreted by the thymus gland, inhibits basal corticosteroid secretion, permitting an up-regulation of thymic activity, which is usually suppressed by glucocorticoid hormones [55,56], and potentiating its other actions upon the immune system [52]. On the other hand, activation of the hypothalamo-hypophyseal-adrenocortical axis by histamine, released during allergic responses [50,51], may be able to cause confinement of the response to the site of insult, thus preventing the development of a generalized anaphylactic reaction, by virtue of the anti-inflammatory effects of glucocorticoid hormones.

Although the studies have demonstrated extensive influences of immune activity upon the central nervous system, the sites of action and the mechanisms of induction and action, as well as the physiological significance of the recorded effects, require further study. In particular, the elucidation of the factors involved in the neurophysiological responses await identification, as do the responsive neural elements and their efferent targets.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the invaluable contributions made to these studies by Dr. J. Weidenfeld, Dr. D. Kidron, Mr. G. Mor, and Ms. A. Maimon. Our thanks also to Professors N. Trainin, M. Pecht, and Y. Burstein, of the Weizmann Institute of Science, Rehovot, Israel, for the supply of THF.

This work was supported by grants from the Israeli National Council for Research and Development and the European Economic Community and from the Joint Research Fund of the Hebrew University-Hadassah Medical School. Further funding was also provided by the Lena P. Harvey Endowment Fund for Neurological Research and the Jacob and Hilda Blaustein Foundation.

REFERENCES

1. Ader R (ed): Psychoneuroimmunology. New York, Academic Press, 1981, 661 pp
2. Cohn M: What are the must elements of immune responsiveness? In Neural Modulation of Immunity. Edited by R Guillemot, M Cohn, T Melnechuk. New York, Raven Press, 1985, pp 3–25
3. Bartrop RW, Lazarus L, Luckherst E: Depressed lymphocyte function after bereavement. Lancet i:834–836, 1977
4. Solomon GF: Psychoneuroimmunology: Interactions between central nervous system and immune system. J Neurosci Res 18:1–9, 1987
5. Szentagothai J, Flerko B, Mess B, Halasz B: The role of the hypothalamus in the control of adrenocorticotropic function of the anterior pituitary gland. In Hypothalamic Control of the Anterior Pituitary. Budapest, Akademiai Kiado, 1968, pp 220–248
6. Solomon GF: Stress and antibody response in rats. Int Arch Allergy 35:97–104, 1969
7. Monjan AA, Collector MI: Stress-induced modulation of the immune response. Science 196:307–308, 1977
8. Gisler RH: Stress and the hormonal regulation of the immune response in mice. Psychother Psychosom Med 23:192–208, 1974
9. Metal'nikov S, Chorine V: The role of conditioned reflexes in immunity. Ann Pasteur Inst 40:893–900, 1926
35. Corticosterone levels. Immunomodulatory drugs and immunologic changes. J. Immunol. 135:858-861, 1985

10. Ader R, Cohen N: Behaviorally conditioned immunosuppression. Psychosom Med 37:333-340, 1975

11. Rosjman TL, Cross RJ, Brooks WH, Marksbery WR: Neuroimmunomodulation. Effects of neural lesions on cellular immunity. In Neural Modulation of Immunity. Edited by R. Guillemin, M. Cohn, T. Melnechuk. New York, Raven Press, 1985, pp 95-109

12. Wertman E, Ovadia H, Feldman S, Abramsky O: Prevention of EAE by anterior hypothalamic lesions in rats. Neurology 35:1468-1470, 1985

13. Biziere K, Guillaumin JM, Degenne D, Bardos P, Renoux M, Renoux G: Lateralized neocortical modulation of the T cell lineage. In Neural Modulation of Immunity. Edited by R. Guillemin, M. Cohn, T. Melnechuk. New York, Raven Press, 1985, pp 81-94

14. Geschwind N, Behan P: Left-handedness: Association with immune disease, migraine and developmental learning disorder. Proc Natl Acad Sci USA 79:5097-5100, 1982

15. Blalock JE, Harbour-McMenamin D, Smith EM: Peptide hormones shared by the neuroendocrine and immunologic systems. J. Immunol. 135:858-861, 1985

16. Hall NR, Goldstein AL: Neurotransmitters and the immune system. In Psychoneuroimmunology. Edited by R. Ader. New York, Academic Press, 1981, pp 521-544

17. McCann N, Ono O, Khorram S, Kentrovi S, Aguila C: The role of brain peptides in neuroimmunomodulation. Ann NY Acad Sci 496:173-181, 1987

18. Plotnikoff NP, Muro AJ, Miller GC, Corder CN, Faith RE: Enkephalins: Immunomodulators. Fed Proc 44:118-122, 1985

19. Smith EM, Blalock JE: Human lymphocyte production of corticotropin and endorphin-like substances: Association with leukocyte interferon. Proc Natl Acad Sci USA 78:7530-7534, 1981

20. Bulloch K: Neuroanatomy of lymphoid tissue: A review. In Neural Modulation of Immunity. Edited by R. Guillemin, M. Cohn, T. Melnechuk. New York, Raven Press, 1985, pp 111-141

21. Felten DL, Felten SY, Carlson SL, Olschowka JA, Livnat S: Noradrenergic and peptidergic innervation of lymphoid tissue. J. Immunol 135:755a-765a, 1985

22. Besedovsky H, Sorkin E, Felix D, Haas H: Hypothalamic changes during the immune response. Eur J Immunol 7:325-328, 1977

23. Grigoriev VA: Dynamics of DC potential of hypothalamic structures in early terms of immune reaction development. Physiol J USSR 5:463-467, 1981

24. Korneva EA: Electrophysiologocal analysis of brain reactions to antigen. Ann NY Acad Sci 496:318-337, 1987

25. Saphier D, Abramsky O, Mor G, Ovadia H: Multiunit electrical activity in conscious rats during an immune response. Brain Behav Immun 1:40-51, 1987

26. Saphier D, Kidron D, Abramsky O, Trainin N, Pecht M, Burststein Y, Ovadia H: Neurophysiological changes in the brain following central administration of immunomodulatory factors. Isr J Med Sci 24:261-263, 1988

27. MacLean D, Rechlin S: Neuroendocrinology and the immune system. In Psychoneuroimmunology. Edited by R. Ader. New York, Academic Press, 1981, pp 475-520

28. Abo T, Kawate T, Itoh K, Kuwagi K: Studies on the bioperiodicity of the immune response: Circadian variations of human T, B, and K traffic in the peripheral blood. J Immunol 120:1360-1363, 1981

29. Kawate T, Abo T, Hinuma S, Kamgai K: Studies on the bioperiodicity of the immune response, covariations of murine T and B cells and a role of corticosteroid. J Immunol 126:1364-1367, 1981

30. Saphier D, Feldman S: Effects of stimulation of the preoptic area on paraventricular nucleus unit activity and corticosterone secretion in freely moving rats. Neuroendocrinology 42:167-173, 1986

31. Jankovic BD, Isakovic K: Neuro-endocrine correlates of immune response. I. Effects of brain lesions on antibody production, Arthus reactivity and delayed hypersensitivity in the rat. Int Arch Allergy Appl Immunol 45:360-372, 1973

32. Swanson LW, Sawchenko PE, Rivier J, Vale W: Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: An immunohistochemical study. Neuroendocrinology 36:165-186, 1983

33. Shek PV, Sabiston BH: Neuro-endocrine regulation of immune processes—change in circulating corticosterone levels induced by the primary antibody response in mice. Int J Immunopharmacol 5:23-33, 1983

34. Di Renzo GF, Schettini G, Preziosi P: Effects of some antineoplastic agents on plasma levels of corticosterone, prolactin and thyroid stimulating hormone. Arch Int Pharmacodyn 230:324-329, 1977

35. Fast PE, Hatfield CA, Franz CL, Adams EG, Licht NJ, Merritt MV: Effects of treatment with immunomodulatory drugs on thymus and spleen lymphocyte subpopulations and serum corticosterone levels. Immunopharmacol 5:135-155, 1982
36. Besedovsky HO, del Rey A, Sorkin E, Dinarello CA: Immunoregulatory feedback between interleukin 1 and glucocorticoid hormones. Science 233:652–654, 1986

37. Blatteis CM: Central nervous system effects of interleukin 1. In The Physiologic, Metabolic, and Immunologic Actions of IL-1. Edited by MJ Kluger, JJ Oppenheim, MC Powanda. New York, Alan Liss, 1985, pp 107–120

38. Smedley H, Katrak M, Sikora K, Wheeler T: Neurological effects of recombinant human interferon. Brit Med J 286:262–264, 1983

39. Dafny N, Prieto-Gomez B, Reyes-Vazquez C: Does the immune system communicate with the central nervous system? Interferon modifies central nervous activity. J Neuroimmunol 9:1–12, 1985

40. Gery I, Waksman BH: Potentiation of the T-lymphocyte response to mitogens. J Exp Med 136:143–155, 1972

41. Fontana A, Kristensen F, Dubs R, Gemsa D, Weber E: Production of prostaglandin E and an interleukin-1 like factor by cultured astrocytes and C6 glioma cells. J Immunol 129:2413–2419, 1982

42. Murphy PA, Simon PLR, Willoughby WF: Endogenous pyrogens made by rabbit peritoneal exudate cells are identical with lymphocyte activating factors made by rabbit alveolar macrophages. J Immunol 124:2498–2501, 1980

43. Besedovsky HO, Sorkin E: Hormonal control of immune processes. Endocrinology 2:504–513, 1977

44. Eisenman JS: Electrophysiology of the anterior hypothalamus: Thermoregulation and fever. In Pyretics and Antipyretics. Edited by AS Milton. Berlin, Springer, 1982, pp 187–217

45. Sztein MD, Vogel SN, Sipe JD, Murphy PA, Mizel SB, Oppenheim JJ, Rosenstreich DL: The role of macrophages in the acute phase response: SAA induced is closely related to lymphocyte activating factor and endogenous pyrogen. Cell Immunol 63:164–176, 1981

46. Friedman RM, Vogel SN: Interferon with special emphasis on the immune system. Adv Immunol 34:97–138, 1983

47. Adams F, Quesada JR, Gutterman JV: Neuropsychiatric manifestations of human leukocyte interferon therapy in patients with cancer. JAMA 252:938–941, 1984

48. Nakashima T, Hori T, Kuriyama K, Kiyohara T: Naloxone blocks the interferon-α induced changes in hypothalamic neuronal activity. Neurosci Lett 82:332–336, 1987

49. Pollard H, Schwartz J-C: Histamine neuronal pathways and their functions. Trends Neurosci 10:86–89, 1977

50. Roberts F, Calcutt CR: Commentary: Histamine and the hypothalamus. Neuroscience 9:721–739, 1983

51. Kazimierczak W, Diamant B: Mechanisms of histamine release in anaphylactic and anaphylactoid reactions. Prog Allergy 24:295–365, 1978

52. Trainin N, Handzel ZT, Pecht M: Biological and clinical properties of THF. Thymus 7:137–150, 1985

53. Gillis S, Crabtree GR, Smith KA: Glucocorticoid-induced inhibition of T cell growth factor production: II. The effect of the in vitro generation of cytolytic T cells. J Immunol 123:1632–1638, 1979

54. Ahlqvist J: Endocrine influences on lymphatic organs, immune responses, inflammation and autoimmunity. Acta Endocrinol (Copenhagen) Supplement 206 and Almqvist & Wiksell Intl, Stockholm, 1976

55. Westphal U: Steroid-Protein Interactions. Berlin, New York, Springer, 1971

56. Dougherty TF: Effect of hormones on lymphatic tissue. Physiol Rev 32:379–401, 1952