# New Insights to Neuroimmune Biology

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# Foreword

Neuroimmune biology is a newly emerging multidisciplinary science that aims to collect, organize, and interpret the knowledge concerning the coordination and integration of bodily functions in higher animals and humans. After a long period of empiric observations, exact scientific methods were used for the first time in the mid-1950s, which initiated modest progress in the subject. With the advent of cellular and molecular biology, it became possible to take a second look at long-standing issues and problems in this field. This research started in the mid-1970s and this time it was possible to make major advances in this difficult and complex area of scientific inquiry. Today it is clear that, unlike originally believed, the immune system is not an autonomous, intelligent system capable of recognizing antigens and defending the host. Rather, the immune system has to coordinate with the homeostatic organization of the host. It receives regulatory signals from the neuroendocrine system via hormones, neurotransmitters, and neuropepties. In turn, the immune system provides feedback signals about the status of immune functions, which are delivered by cytokines. These discoveries both established and proved the existence of immune–neuroendocrine circuitry [1].

The field is now progressing rapidly, and it is becoming clear that the brain is itself capable of recognizing antigens and functioning as an immunocompetent organ. Moreover, cytokines are involved in the physiological regulation of many organs and tissues, including the nervous system. During acute illness, the entire organism is actively involved in host defense, through a complex network that constitutes the neuroimmune supersystem. In this book, various aspects of neuroimmune biology are presented by world-renowned authors.

Istvan Berczi

## Reference

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# Preface

The chapters of this book present and discuss various mechanisms that are relevant to neuroimmune biology. The investigators selected as contributors are in the forefront of research in their areas and are internationally recognized. The papers cover molecular regulation of cytokines in brain astrocytes, immunoregulation by the sympathetic nervous system, circadian regulation of immune reactions, antigen recognition by the central nervous system, modulation of the immune response in cases of head injury, neurogenic inflammation, the role of tachykinins in asthma and allergic disease, defense and defeat reactions, cytokines, behavior and affective disorders, and increased activity of type 1 helper T cell functions after reward stimulation.

This book has relevance and utility for the entire scientific community in the areas of biology, medicine, and veterinary medicine, as it discusses molecular, cellular, organic, and systemic aspects of neuroimmune interactions, as well as the physiological, pathophysiological, and behavioral mechanisms involved in this new and important discipline of general biology.

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# 1 The Brave New World of Neuroimmune Biology

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## 1.1 Introduction

### *1.1.1 How Did It Begin?*

Sporadic suggestions of neuroimmune interactions date back to the late nineteenth century. The students and followers of Pavlov in Russia thoroughly investigated the nature of immunoregulation by neuroimmune mechanisms and eventually concluded that the hypothalamus is a likely center of immunoregulation [1,2].

Using modern technology, Szentivanyi and colleagues observed that hypothalamic lesions inhibited the development of anaphylactic shock in immunized animals [3]. Tuber cinereum lesions (TBLs) in the hypothalamus inhibited anaphylaxis in preimmunized guinea pigs and (in later experiments) also in rabbits. Anaphylaxis was induced in immunized animals by intravenous (IV) injection of the immunizing antigen. TBLs also inhibited antibody production if the lesions were created prior to immunization. TBLs did not affect antigen–antibody reactions, nor did the release of tissue materials mediating anaphylaxis. Hypothalamic lesions temporarily increased histamine resistance and inhibited the anaphylactic reaction even when the animals were provided with passively transferred antibodies, which elicited lethal shock in control animals. The Schultz–Dale test, which was performed with small pieces of intestine *in vitro,* was also inhibited by TBLs. The Arthus reaction, turpentine-induced inflammation, and the Sanarelli–Shwartzman phenomenon were unaffected. Lesions of other areas of the hypothalamus or of the central nervous system (CNS) were ineffective in modulating immune phenomena. Further, electrical stimulation of the mammillary region of the hypothalamus had an inhibitory effect on the anaphylactic response and increased the resistance of animals to histamine [4–6]. In 1964, Korneva and Khai [7] confirmed that hypothalamic lesions in rabbits, guinea pigs, and rats inhibited the production of complement-fixing antibodies.

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Hans Selye described the stress syndrome in 1936 [8]. He established that the hypothalamus–pituitary–adrenal (HPA) axis was involved in mediating the stress response, which could be induced by various "nocuous" agents. The adrenal gland was stimulated by stress and the thymus and lymph nodes were involuted by glucocorticoids (GCs). He also observed gastrointestinal lesions [9]. Subsequently, Selye concluded that the stress response was a host defense reaction, which he called the "general adaptation syndrome" [10]. These observations clearly implied that the pituitary gland plays an important role in host defense. While I was in Selye's laboratory, I decided to learn more about the interaction of the pituitary gland and of the brain with immune host defense. We established that adaptive immune (ADIM) function is regulated by pituitary hormones: for example, prolactin (PRL) and growth hormone (GH) stimulated immune function, whereas the HPA axis was inhibitory and antagonized the stimulatory effect of PRL and GH. Human placental lactogen (HPL) was as efficient as PRL or GH in restoring ADIM function in this system. Initially we used young (100 g birth weight) hypophysectomized (Hypox) rats, and the antigen was always injected without adjuvant 7–10 days after operation. Treatment of intact animals with the dopamine-agonist drug bromocriptine was as effective as Hypox in suppressing ADIM function [11–13]. Others showed that immune-derived cytokines (CTKs) are capable of stimulating the HPA axis. This discovery revealed that ADIM function is regulated by the CNS and that the HPA axis, but also PRL and GH, receive feedback regulatory signals from immune-derived CTKs [14,15].

Ader and co-workers, and Gorczynski and Kennedy showed that immune function is subject to Pavlovian conditioning [16,17]. These observations imply that the host is able to activate immune defense when danger is anticipated. However, the mechanisms involved in immune conditioning are complex and poorly understood [18].

## 1.2 Recent Developments in Neuroimmune Biology

### *1.2.1 The Concept of Neuroimmune Biology*

During the past three decades, the field of neuroimmune interactions grew steadily, and has now evolved into a sophisticated and credible area of biology. A number of terms have been proposed to name this multidisciplinary science. Because this science deals with the physiology and pathophysiology of higher organisms, in 2000 we coined the term *neuroimmune biology* (NIB) [19], which has been accepted by the scientific community. It is clear that the CNS, the endocrine system (ES), and the immune system (IS) form a regulatory circuit, which integrates, coordinates, and regulates all functions in higher organisms from conception till death.

By now a lot of information has been accumulated about the recognition systems and signaling in this neuroimmune supersystem (NISS) [20]. The mediators for signaling are hormones, neurotransmitters, neuropeptides, CTKs, and chemokines, which are shared within the NISS. Indeed, sharing occurs throughout the entire organism, which makes it possible to signal efficiently within the animal or human being.

Additional communication is mediated by innervation and by recirculating leukocytes (Figure 1.1). Forward and feedback (or stimulatory and inhibitory) signaling is the rule. Under physiological conditions (homeostasis), all vital activities and values are maintained at "normal" or physiological levels.

Pathophysiological conditions (*allostasis*) occur in response to various insults by pathogenic microbes and agents. Pathological events may also be caused by endogenous abnormalities, defects, and malfunctions. Acute febrile illness leads to the acute phase response (APR), which is initiated by CTKs (e.g., interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), IL-6) released from the *innate immune* (INIM) *system*. Under these conditions, hypothalamic corticotropin-releasing hormone (CRH) and vasopressin (VP) stimulate the HPA axis and also induce sympathetic outflow. GCs and catecholamines (CATs) stimulate suppressor/regulatory T lymphocytes (Tsrs) and amplify INIM. Tsrs in turn suppress *ADIM function*. The synthesis of acute phase proteins is rapidly amplified in the liver, as is the synthesis of natural antibodies in specialized CD4+ B lymphocytes. The CNS, bone marrow, liver, and leukocytes are activated, whereas the function of other organs is reduced and catabolism prevails. *Fever* is a constant symptom of APR. APR is analogous to Selye's general adaptation syndrome. It is an emergency host defense reaction against diverse pathogenic agents, which leads to healing in the overwhelming majority of cases [21–28].

In the absence of the HPA axis, there is excessive CTK response after immune activation/inflammation, which may have lethal consequences for the host. Even immunization with complete Freund's adjuvant, which contains mycobacterial antigens (acts on toll-like receptor-4 (TLR-4)), would kill Hypox animals (unpublished results). Further, the sensitivity to bacterial lipopolysaccharide (LPS, also acts on TLR-4) of adrenalectomized (ADRX) mice is elevated by 500–1,000 times when compared to normal animals. TNF levels, induced by the same dose of LPS, were 60 times higher in ADRX mice than in intact controls. Dexamethasone restored the resistance of ADRX mice to LPS [29]. These experiments indicate that stimulation of the INIM system in the absence of the HPA axis results in excessive CTK production, which could kill the host. Further, Korneva and Novikova showed that after immunization, the C-fos gene is expressed in the hypothalamus. C-fos expression indicated that the cells were activated in the hypothalamus after immunization, which was true for several different types of antigens [30]. These experiments demonstrate that there is mutual and continuous regulatory interaction between the hypothalamus and the IS during immunization.

VP is the dominant hypothalamic regulatory hormone during chronic inflammatory conditions. VP stimulates both PRL and the HPA axis, and thus it is capable of maintaining both the ADIM and INIM systems in homeostasis and harmony. Indeed, our experiments revealed that VP maintains adaptive immunocompetence. On this basis it has been suggested that recovery from disease is regulated by VP [28].

### 1.2.2 INIM–ADIM Interactions

It is very well established that monocytes and macrophages, which are related cells, play a fundamental regulatory role in the INIM system and also present antigen to

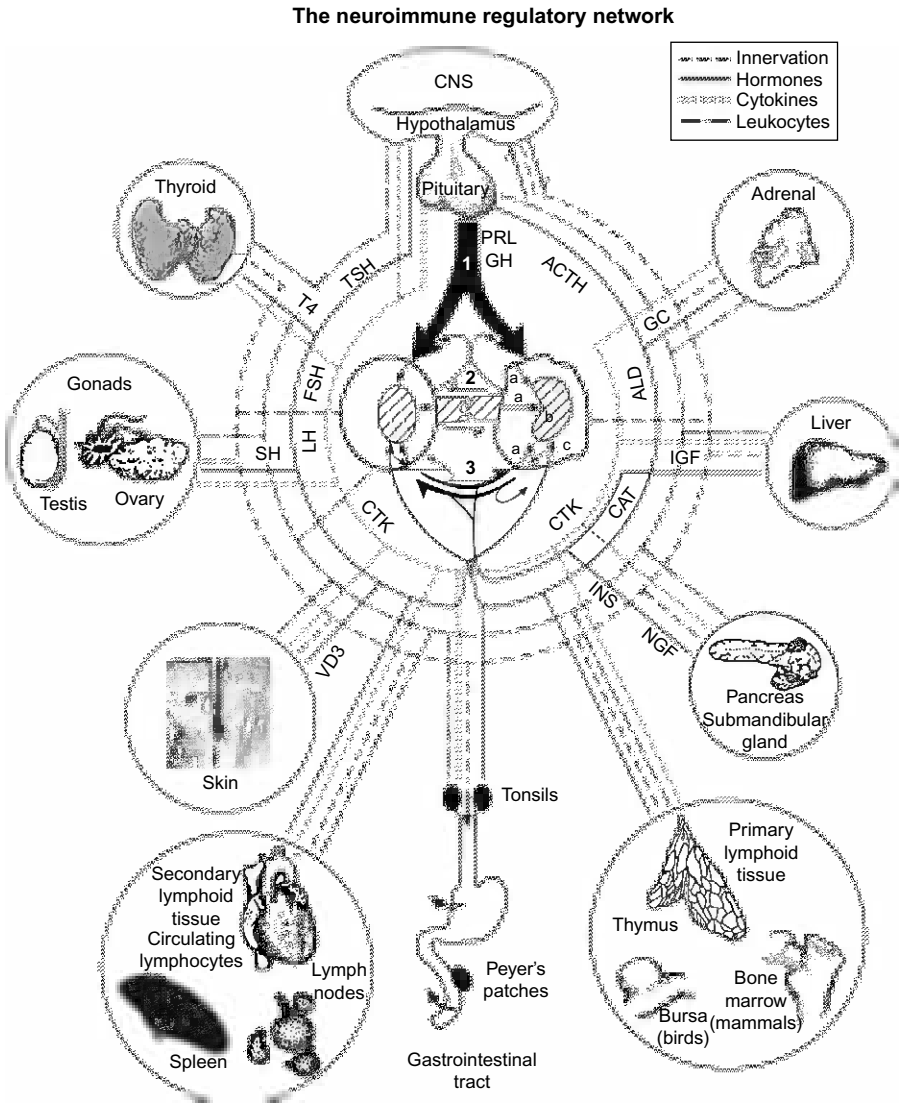


**Figure 1.1 The NISS.**

This figure shows the major systemic neuroimmune regulatory pathways during homeostasis. In the center, two cells are interacting, which is the rule for all tissues and organs, where stromal and parenchymal cells interact. As an example, we use here the phenomenon of antigen presentation to a naïve T lymphocyte, which is an ADIM cell, by a macrophage, a cell of the INIM system. Macrophages are phagocytic: they recognize infectious agents and foreign materials via innate immune receptors (INIRs), engulf the microbe/foreign material, digest it, and present peptides (epitopes) of the antigen on their MHC-II surface molecules to T cells. T lymphocytes proliferate upon exposure to the antigen (phagocytic pathway). Monocytes, dendritic cells, and B lymphocytes are also antigen-presenting cells. Further, all nucleated cells can present cytosolic antigens to T lymphocytes (cytosolic pathway).

T lymphocytes within the ADIM system. The related dendritic cells are regarded as "professional" antigen-presenting cells of the ADIM system. Monocytes recirculate in the blood and macrophages are distributed in tissues throughout the entire host organism. These phagocytic cells recognize infections and other noxious agents through their INIRs, engulf the microbe/foreign material, digest (process) it, and present peptides via their major histocompatibility-II (MHC-II) surface antigens to T lymphocytes of the ADIM system. This is the *phagocytic pathway* of antigen presentation. Therefore, monocyte–macrophage activation within the INIM system almost inevitably activates T cells of the ADIM system, so that the entire NISS is mobilized to fight the intruding pathogen/noxious agent. This conclusion is further supported by the fact that *all nucleated cells* are capable of presenting cytosolic antigen via their surface MHC-I to T cells [20–22].

Once the ADIM system is activated, cytotoxic and helper effector T cells are produced. As a rule, antibody formation also follows after B lymphocytes present antigen to helper T cells and such T cells stimulate B lymphocytes to form antibodies. Immunoglobulins D (IgD) and M (IgM) are formed as surface immunoglobulins by B cells. After an immune response, IgM is secreted first, and later the same B cell may switch to making IgG, IgA, or IgE, depending on the regulatory environment of the cell. All the different classes of antibodies made by one B cell are specific for a single epitope of the antigen to which the cell was responding [21,22].

IgM, IgG, and IgA are able to fix complement after combining with the antigen. *Complement* is an enzyme system belonging to the INIM system. Moreover, all leukocytes express receptors for fraction C (Fc) the binding of antibodies to their surface, and use such antibodies for better identification of pathogens/noxious agents. Here INIM cells use ADIM antibodies. The complement system has three pathways for activation: by

**Figure 1.1 (cont.)**

The primary immune response is dependent on pituitary PRL and GH. These pituitary hormones regulate cell growth throughout the entire organism according to this principle. IGF-1 acts like a second messenger in most situations. The HPA axis inhibits ADIM and stimulates NATIM. CATs support the immunoregulating activity of the HPA axis.

Type I CTKs produced within the IS will gradually take over the role of PRL/GH, and the secondary response gradually becomes independent of pituitary hormones. Memory T cells, B lymphocytes, and NK cells survive severe illnesses by HP and regenerate immune function during healing. The hypothalamic hormone VP stimulates PRL and the HPA axis and thereby regulates the process of healing, and maintains ADIM and NATIM in homeostatic harmony.

This figure illustrates that the entire host organism communicates and cooperates with the central regulatory network. Innervation, hormones, CTKs, chemokines, and recirculating leukocytes serve as communication pathways. These pathways of communication are open at all times. No immune response, inflammation, or infection can occur in any tissue/organ in the body without signaling the hypothalamus, PVN about such events. Therefore, infection, inflammation, and immune reactions are under continuous surveillance within the NISS. During homeostasis, this system protects us very efficiently, without disturbing any physiological functions in the body.

*Source:* Adapted from Ref. [124].

antigen–antibody complexes (ADIM, classical pathway); by microbes (INIM, alternative pathway); and by lectins (INIM) [21,22].

We proposed that the Tsrs is a member of the innate INIM. The evidence comes from the activation of Tsrs by CATs and GCs. These hormones activate INIM cells and suppress ADIM cells [31]. During severe trauma or infectious disease, APR develops whereby ADIM is suppressed and the INIM system takes over command for the highly coordinated and very intensive immunological battle to save the host organism [26–28]. The INIM system, which is with us at birth, initiates most of the immune responses against microbes and other noxious agents; it regulates adaptive immunity by antigen presentation and by Tsr cells that suppress ADIM. Therefore, the INIM system is the first to protect the host, and it continues to protect the host till the last moment of survival [27].

### 1.2.3 The Role of Innervation, Neurotransmitters, and Neuropeptides

Lymphoid organs, such as the spleen, thymus, and bone marrow, are innervated [32]. This fact indicates that the CNS is in permanent contact with the IS. In addition, neurotransmitters and neuropeptides regulate inflammation and immunity [33]. The mediators involved may stimulate or inhibit immune and inflammatory processes. Substance P, neurokinin A and B (collectively known as *tachykinins*), calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP) are pro-inflammatory mediators capable of eliciting an inflammatory response. These mediators also enhance various immune responses. In contrast, somatostatin and galanin are anti-inflammatory and immunosuppressive mediators [31,33,34].

Alpha-adrenergic mechanisms stimulate immunity and inflammation, whereas beta-adrenergic mechanisms inhibit inflammation, allergy, and asthma and exert an immunosuppressive effect. Cholinergic mechanisms are both anti-inflammatory and immunosuppressive [35–37].

### 1.2.4 Hormonal Immunoregulation

Adaptive immunity is under pituitary control. Growth and lactogenic hormones (GLH) stimulate adaptive immunocompetence, and the HPA axis is inhibitory. The secondary antibody response is partially independent of the pituitary. This observation suggests that memory cells are able to operate independent of pituitary hormones [38]. GCs and CATs promote natural immunity (NATIM) and inhibit the ADIM system by the stimulation of suppressor/regulatory T cells. Numerous other hormones, CTKs, neurotransmitters, and peptides also modulate immune function [28].

Innate immunity functions in the absence of the pituitary gland. From our experiments, it appears that VP stimulates the INIM system, but this result remains to be confirmed. The HPA axis exerts an important moderating effect on CTK production. Excessive CTK production can occur after INIM stimulation if the HPA axis is not functional (see Section 1.2.1).

### 1.2.5 Immune–Hypothalamic Feedback Signals

Healthy people and animals show only trace amounts of CTKs in their serum, which is not sufficient to deliver immune-derived signals to the hypothalamus. Sensory nerves fulfill this function, as they are stimulated locally by CTKs released in immune organs and at other sites where immune/inflammatory reactions occur. Sensory nerves transmit information about inflammation and immune reactions to the hypothalamic *paraventricular nucleus* (PVN), which is the center regulating ADIM. The vagus was also shown to have similar capabilities. However, recent results indicate that the vagus contains sensory nerve fibers, which serve as immuno-sensors and transmit information toward the hypothalamus [33,39,125].

#### 1.2.5.1 Feedback by CTKs

CTKs act on the brain; on nerve terminals; on the pituitary, adrenals, gonads, thyroid, epithelium, endothelium, leukocytes, and fibroblasts; and more. In fact, the entire organism uses CTKs to communicate (Figure 1.1). On this basis it is possible to suggest that CTKs are able to activate/suppress the major regulatory circuits in the body, at any level, in case of acute febrile illness.

The stress hormones PRL and GH are elevated soon after LPS injection and during the initial phase of stress [13]. Subsequently, it was discovered that during acute stress, both adaptive and INIM functions are significantly boosted within peripheral tissues, which leads to long-lasting immunity. This was termed the *physiological stress response* [40]. The enhancement of adaptive immunity is fully justified in this case, as both GH and PRL levels are increased; so is the HPA axis, which explains the augmentation of NATIM.

During acute febrile illness, the concentrations of IL-1β, TNFα, and IL-6 are elevated in the serum, which initiates APR. Later, during the course of the disease, numerous other CTKs will contribute. Additional CTKs that were found to activate the HPA axis are IL-2, -11, -12, and interferon (IFN) [13]. Gp 130 CTKs, such as ciliary neurotropic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin, IL-11, and cardiolipin, potentiated the activation of the HPA axis by IL-1 [39,41]. Leptin plays a role in regulation of the gonadotropic axis [42].

The CTKs IL-1, IL-2, and IL-6 stimulate the pituitary release of PRL, whereas IFN-γ and endothelin-3 are inhibitory [43]. In rats, administration of exogenous IL-1β stimulated the expression of IL-1β mRNA in the hypothalamus by 99%, but not that of IL-6. IL-1 also significantly elevated the plasma levels of adrenocorticotropic hormone (ACTH), PRL, corticotropin, and cortisol production in the adrenal glands [44]. Rats treated with IFN-γ for 5 days (10 IU/kg body weight) showed a 43% increase in circulating PRL [45]. Two of the most potent cytokines regulating anterior pituitary cell function are LIF and IL-6, which belong to the CTK family that uses the common gp130 signal transducer. IL-11 and CNTF exerted a similar stimulatory effect on GH mRNA expression in somatotropic monolayer cell cultures from acromegalic tumors, but these CTKs had no significant influence on GH secretion. CNTF stimulates PRL secretion in lactotropic monolayer cell cultures from patients with prolactinoma. In monolayer cell cultures from normal rat anterior

pituitary, IL-11 and CNTF had no significant effect on the release of either GH or PRL, or on GH mRNA. However, when the cells were cultured in aggregates, in which the three-dimensional structure of the cells is reconstituted, both CTKs, in doses at which they had no effect on monolayer cultures, significantly stimulated both PRL and GH secretion [46].

The presence of L-NAME (1 mM), an inhibitor of NO synthase (NOS), in the incubation medium significantly blunted the inhibition of PRL release produced by TNF-α (50 ng/ml) in female rats. TNF-α increased nitrite release to the incubation medium. The activity of NOS was significantly enhanced when anterior pituitary cells were incubated with TNF-α for 8 hours or more. Also, TNF-α induced iNOS gene expression in anterior pituitary cells [47].

Stromal cell-derived factor-1 (SDF1), via its receptor CXCR4, stimulated the proliferation of the pituitary adenoma cell line GH4C1, and released both PRL and GH through a complex network of intracellular signals [48].

C3a receptors are expressed in pituitary hormone-secreting and nonhormone-secreting (folliculostellate) cells. Both C3a and C3adesArg (a noninflammatory metabolite) stimulate pituitary cell cultures to release PRL, GH, and adrenocorticotropin. Serum levels of these hormones, together with adrenal corticosterone, increase dose dependently with recombinant C3a and C3adesArg administration *in vivo* [49].

Erythropoetin administration to patients with amyotrophic lateral sclerosis caused a significant reduction of serum PRL levels, maximal 60 minutes after administration [50].

GCs and CATs stimulate IL-4, IL-10, and transforming growth factor (TGFβ), which exert negative feedback on excess CTK production during APR [51]. These CTKs are produced by Tsrs [28].

Several mechanisms have been proposed for conveying the CTK signal across the blood–brain barrier (BBB). Once the signal is transmitted across the BBB, the signal travels through neural pathways as follows: area postrema→nucleus tractus solitarius→ventrolateral medulla→paraventricular nucleus, which initiates HPA axis responses. Descending pathway: PVN→brainstem cell groups→thoracic spinal cord preganglionic neurons→via sympathetic projections to the end organs such as the thymus and spleen [52].

Several of the effects of pro-inflammatory CTKs exerted in a “healthy” brain are amplified in the CNS by the following mechanisms: (a) peripheral CTKs, such as IL-1, have the capacity to elicit their own synthesis in the brain; and (b) a sustained increase in neuronal activity also induces production of physiologically significant amounts of these mediators. The brain-borne IL-1 and IL-6 fulfill physiological roles when their production is not the result of pathological events in the CNS. These CTKs stimulate the HPA axis, and they are involved in physiologic brain mechanisms such as synaptic plasticity, memory formation, and the control of glucose homeostasis [53]. CTKs are now being investigated also for their synaptic and inflammatory action in the CNS. These proteins and their receptors can be synthesized in the brain by glial and neuronal cells and contribute to two main types of action: modulation of neuronal excitability and local inflammatory responses [54].