INSIGHTS TO NEUROIMMUNE BIOLOGY

Second Edition

Edited by

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FOREWORD

In this book, the neuroimmune regulation by neuropeptides is discussed. It was a pleasure to work on this book. It is clear that *Medicine* and animal medication will receive an actual face-lift from the new capabilities, which have been offered by these mediators. Now, there is a candidate peptide to treat almost any disease condition, such as inflammation, immunological problems, organ–tissue damage, infectious diseases, etc. You name it and there is a peptide to treat, and this is just the beginning. I am sure that more mediators will be discovered to resolve greater problems. We were present during the entire development of *Neuroimmune Biology* and we knew for long time that this book was coming. Finally it has come. Initially, the body has its own immunity against infections, hence the individuals are healthy. When things get astray, we might develop a disease. But now, salvation is on the way! Science will pay back all the due investment. Besides, we should also remember the results that have been obtained till date.

Istvan Berczi, Fabio Rotondo, Kalman Kovacs

PREFACE

The participation of the nervous system in inflammatory reactions was suggested over a century ago. Yet, as potentially important contributors to inflammatory mechanisms, nervous elements have been largely ignored for a long time. However, discovery of the highly specific pharmacological effects of capsaicin in the 1950s and the selective neurotoxic action of vanilloid compounds in the 1970s, on nociceptive sensory neurons, have revived interest in the study of neurogenic inflammatory processes. Early observations furnished firm evidence for the existence of an inflammatory response induced by a purely neurogenic route, resulting from the activation of nociceptive afferents. Morphological studies utilizing the neurotoxic/neurodegenerative actions of capsaicin demonstrated a widespread system of peptidergic and nonpeptidergic capsaicin-sensitive afferent nerves, which innervate the skin, mucous membranes, as well as most of the visceral organs and tissues. From studies conducted upon different organs, tissues, and cells, a complex system of primary sensory neurons has emerged, which parallels the autonomic nervous system not only in its extent, but also probably in its significance. Afferent nerves, once believed to serve merely as sensory receptors conveying impulses generated by noxious stimuli, have evolved into key players in a complicated local regulatory system that participates in the contractile, glandular, vascular, inflammatory, immune, protective, restorative, and trophic functions, of somatic and visceral tissues. Neuropeptides released from nociceptive afferents in response to tissue injury or to a wide variety of chemical stimuli, involving inflammatory mediators, tissue, and mast cell-derived agents, play a pivotal role in these processes and are potent modulators of inflammatory reactions. New facets of capsaicin-sensitive neuronal and cellular responses were revealed, following the cloning of the capsaicin/vanilloid receptor, now known as the *transient receptor potential vanilloid type 1 receptor* (*TRPV1*), which is primarily expressed in nociceptive primary sensory neurons, but also in some other neurons and cells. A number of contributions in this volume focus on the characterization and functional traits of nociceptor neurons and on the mechanisms, which activate them. Further chapters deal with the parts played by primary sensory neurons in inflammatory reactions and in the regulation/modulation of the functions of various organs and tissues under physiological and

pathological conditions. Certain chapters touch upon the therapeutic implications offered by the use of vanilloids, novel nonpeptide antagonists of peptide and vanilloid receptors. It is the editor's hope that this volume will contribute to and initiate new interest in the understanding of diverse roles fulfilled by primary afferent neurons, in the functioning of the body during health and disease.

G. Jancsó
Szeged, Hungary
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CHAPTER 1

Neuroimmune Regulation in Health and Disease

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1 INTRODUCTION

1.1 Health

The French scientist Claude Bernard was the first to recognize the fact that living organisms maintain their physiological and biochemical parameters within defined (normal) levels, which show only minor variations.[1] The scientific name of this condition is *homeostasis.* Every parameter in a healthy body that may be measured will stay within normal (physiological) levels. When we are healthy, we feel well with positive emotions and in general with a healthy mind, we are able to overcome and triumph over life's challenges. In *Medicine* there are books of physiology, internal medicine, pathology, pharmacology, and gynecology, which are the major subject areas that deal with *health and disease.* Information available on these subjects is incredibly large, and it definitely needs computer management to help with accessibility.

It is the basic information in *Physiology* that doing your work requires energy and activity, so the basic values of heart rate, metabolism, and the function of our entire system will increase. But it should not go higher than the upper normal level. Age, sex, and other parameters influence normal levels. Physical work requires more effort than mental work.

Realistically the Yin-Yang hypothesis is valid in most cases. Many people live with minor, not life-threatening problems; they feel and act like a healthy person because they are only a "little bit sick." This means that little problems can be overlooked. However, the opposite condition is when someone is a "little bit healthy," but most of the time is miserable. A sick person is unable to function normally. The bodily parameters and functions are abnormal. This is a *disease*! Everybody has met people who used to be

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sick, acted like one, or looked like one. However, their disease could not be diagnosed. We come across such people less frequently with the advance of *Medicine*, but such patients still exist. Mental conditions more often cause problems with diagnosis of the patients.

Today, we know that higher animals and man have developed the neuroimmune super system (NISS),[2] whereby the central nervous system (CNS), endocrine system (ES), and immune system (IS) are joined together to create a central regulatory circuitry. NISS has to deal with everything happening in the body, right from conception to death. In healthy people NISS must function normally, and tissue and organs must be healthy. "Healthy body, healthy mind" expresses folk wisdom about the importance of mind–body interaction for being healthy.

2 DISEASE

2.1 A Brief History

In the ancient cultures of Persia, Greece, and in the Roman Empire, fever was believed to posses healing powers.[3] This sentiment was maintained until modern times, when Boivin[4] isolated the first pyrogen, lipopolysaccharide (LPS), or endotoxin, from Gram-negative bacteria. LPS is an outstanding pyrogen. Countless studies on LPS have indicated that it is capable of inducing a disease known as "endotoxin shock," which may have lethal consequences.[5] Later it was discovered that a subtoxic doses of endotoxin actually provided protection to animals against infectious diseases and other harmful infections. This condition was known as "endotoxin tolerance." LPS, especially in the detoxified form, could be used as an immunological adjuvant and was effective for the treatment of radiation diseases; drug-induced immunosuppression and bone marrow failure had a beneficial effect on a number of other pathological conditions.[6]

Now we have recognized that LPS is an evolutionally preserved cross-reacting antigen (e.g., all Gram-negative bacteria have LPS), which may be called homologous epitopes (or "*Homotopes*" for short).[7] LPS is an antigen for innate immunity (INIM). Throughout millennia, the INIM system evolved to recognize homotopes within infectious agents. Since these are cross-reacting antigens, recognition may be economized. For example, the INIM antigen receptor, toll-like receptor-4 (TLR4) is one receptor, which recognizes LPS, and with this single receptor the INIM system is able to control infections from all the species of Gram-negative bacteria. This is characteristic of the innate immune recognition.[7]

Table 1.1 Neuroendocrine responses to endotoxins

HPT and GLH	Responses	HPA axis	Responses	Sex hormones	Responses
TRH	↓	CRF	↑	LH	↑↓
TSH	0↓	AVP	↑	FSH	↓
T4	↓	ACTH	↑	E2	↑↓
T3	↓	GC	↑	TS	↑↓
PRL	↑↓	α-MSH	↑	DHEA	↓?
GH	↑↓	β-END	↑	PS	↑↓
IGF-I	↓	CAT	↑		
INS	↑				
GLU	↑				
LEP	↑				

HPT, hypothalamus; GLH, growth and lactogenic hormones; TRH, thyroxin-releasing hormone; T4, thyroxin; T3, tri-iodo-thyronin; PRL, prolactin; GH, growth hormone; IGF-I, insulin-like growth factor-1; GLU, glucagon; LEP, leptine; HPA axis, hypothalamus–pituitary–adrenal axis; CRF or rather CRH, corticotrophin; AVP, arginine–vasopressin; ACTH, adrenocorticotropic hormone; GC, glucocorticoids; α-MSH, alpha-melanocyte-stimulating hormone; β-END, beta-endorphine; CAT, catecholamine; sex hormones; LH, luteinizing hormone; FSH, follicle-stimulating hormone; E2, estradiol; TSH, thyroid-stimulating hormone; DHEA, dehydroepiandrosterone; PS, progesterone.

From the table, it will be obvious that the HPA axis is activated in endotoxin shock, which is analogous to acute febrile illness or the APR. Every hormone is stimulated in the HPA axis. Interestingly insulin, glucagon, and leptin are also stimulated. These hormones must play an important role in the APR. The rest of the hormones are flatly inhibited or after temporary stimulation are inhibited (e.g., GH and PRL). Modified from Ref. [7].

When LPS is given to animals, it is capable of eliciting the syndrome of the infectious diseases caused by Gram-negative bacteria. There are neuroendocrine, metabolic, and immune alterations, just like in the disease (Table 1.1).[7]

If we carefully examine the data given in Table 1.1, we notice that during a disease, hormones of the hypothalamus–pituitary–adrenal (HPA) axis are all activated. This activation is very characteristic of the stress response, as described by Hans Selye[8] and today it is very clear that activation of the HPA axis follows infection, trauma, all sorts of injuries, and even mental illness. What does this mean? What does the HPA axis do? As stated, LPS can induce acute febrile illness, such as septicemia for instance. This is an emergency situation where bacteria are growing in the blood. This emergency situation cannot be handled by the *adaptive immune system* (ADIM) as here, lymphocytes have to grow and differentiate first and only after 5–7 days can respond in an immunological manner. On the other hand, LPS activates the INIM system, which produces interleukin (IL)-1-beta, IL-6, tumor necrosis (TNF)-alpha, and granulocyte–macrophage colony stimulating factor

(GMCSF). These cytokines activate the HPA axis, which are the major mediators of this system. The hypothalamus secretes corticotrophin (CRH) and vasopressin (VP); the adrenal secretes adrenocorticotropic hormone (ACTH), which rapidly releases glucocorticoids (GCs) and catecholamines (CAT). In turn GC and CAT stimulate INIM.[9] This system starts up immediately after the noxious stimulus and becomes fully active within 1 day, exerting maximum protection. So the IS is converted from a dual reactivity to the single INIM response. GC and CAT stimulate suppressor-regulatory T lymphocytes (Tsr), which play an important role in suppressing ADIM. The HPA axis is also suppressive. It can be noticed from Table 1.1 that after a transient initial stimulation, prolactin (PRL) and growth hormone (GH), will be suppressed during acute illness (*acute phase response* (APR)). These hormones maintain ADIM, and now they are not needed. But the INIM system is certainly up to the task of handling host defense. Most of us suffer numerous times febrile illness in a lifetime and normally we recover. This is how well INIM does the job![9]

Insulin, glucagon, and leptin are also activated during APR. These hormones play an important role in sick organisms. Thyroid hormones and sex steroid hormones are suppressed.[9]

The hypothalamic corticotrophin-stimulating hormone (CRH) controls APR, and VP supports CRH at this stage. However, when the acute phase subsides and the disease gets chronic, it is VP and not CRH that regulates the chronic inflammation. VP is capable of bringing about healing and recovery as it restores PRL and stimulates the HPA axis. So VP can create the homeostatic balance that is necessary for *healing*.[10]

The APR is an emergency host defense reaction. This is generally accepted today. APR is mediated by the central nervous system (CNS), ES, and IS, which form the NISS, which is the supreme regulator and protector of the host organism. NISS is with us for a lifetime.[11] Now we compare APR with the *stress reaction*. Stress was claimed to be host response to noxious (nocuous) agents, and brain, and the HPA axis, were involved. Selye himself recognized that stress causes a *"general adaptation syndrome,"*[8] which definitely indicates that the host handles difficulties of adapting to some noxious agents, infection, trauma, and toxins. The IS perfected adaptation an indeed INIM belongs to the stress system, as we know it today. So if stress and APR are identical and APR is a host defense reaction, this means that stress is also a host defense response. The HPA axis, whether mobilized by stress or by APR, is the first to respond and it is activated every time when there is disease or any other noxious agents are around. The host is

responding to control the situation.[11] Now we will examine the diseases where the HPA axis is activated.

2.2 HPA Axis and Disease

2.2.1 New Observations Showing that Stress may be Beneficial

In contrast to the general view that stress is harmful, we were unable to find a harmful effect of chronic stress on the internal diseases (gastric ulceration and angina pectoris).[12] Increasing physical activity altered the measures of obesity in farm men and women but *did not affect mental health measures or cortisol secretion*.[13]

In experimental models of *neurodegenerative diseases*, chronic stress or GC treatment was found to exacerbate both clinical symptoms and neurodegenerative processes. However, recent evidence also shows that glucocorticoid receptor (GR) can *exert neuroprotective effects*. Thus, for any potential therapeutic strategy in these neurodegenerative diseases, we need to understand the precise modifications both in HPA axis and in GR activity, and find ways to harness their protective actions.[14]

Results support the notion of altered HPA axis regulation in chronically work-stressed teachers, with differential patterns of *hyper- and hyporeactivity* depending on individual stress conditions and the tested functional level of the HPA axis.[15]

Chronic psychosocial stressor exposure *impairs in vitro* ACTH responsiveness of both the left and right adrenal glands, *whereas in vivo adrenal responsiveness increases to an acute heterotypic stressor.* This suggests that an additional factor present during acute stressor exposure *in vivo* rescues left and right adrenal. ACTH sensitivity, or ACTH itself acts as a CORT secretagogue in chronically stressed chronic subordinate colony housing mice.[16]

2.2.2 Early Life Programming by GCs

The fetus is susceptible to internal and external stimuli that can lead to adverse long-term health consequences. *GCs* are important developmental *switches*, driving changes in gene regulation that are necessary for *normal growth and maturation*. The fetal-HPA axis is particularly susceptible to *long-term programming by GCs*; these effects can persist throughout the life of an organism. *Dysfunction of the HPA axis*, as a result of fetal programming, has been associated with impaired brain growth, altered behavior and increased susceptibility to chronic diseases (such as, metabolic and cardiovascular diseases). Moreover, the effects of GC-mediated programming are evident in subsequent generations, and transmission of these changes can occur through both maternal and paternal lineages.[17]

Low birth weight, a marker of an *adverse in utero environment*, is associated with cardiometabolic disease and brain disorders in adulthood. The adaptive changes made by the fetus in response to the intrauterine environment result in permanent changes in physiology, structure, and metabolism, a phenomenon termed *early life programming*. We have carried out detailed studies in men and women showing that high levels of endogenous GCs, or treatment with exogenous GCs, is associated with an adverse metabolic profile, increased cardiovascular disease, altered mood, and cognitive decline. Studies in humans have now demonstrated that *high maternal cortisol* in pregnancy and/or *inhibition of HSD2* are associated with programmed outcomes in childhood including higher blood pressure, behavioral disorders as well as altered brain structure. Alterations in DNA methylation of genes, important in regulating cortisol levels, tissue GC action, blood pressure, and fetal growth, are present in adulthood in association with both early life parameters and cardiometabolic risk factors.[18]

This is the first evidence for long-lasting effects of *antenatal synthetic GC exposure* on HPA-axis reactivity in term-born children. These findings may bear important implications regarding the vulnerability for stress-related physical and psychiatric disorders, for which *dysregulation of the HPA axis* has been discussed as a potential causal factor.[19]

Early-life stress can impact health in later stages but less is known about how early-life stress impairs HPA axis activity, contributing to *maladaptation* of the stress–response system. Early-life *stress exposure* (either prenatal or in the early postnatal period) can impact developmental pathways resulting in lasting structural and regulatory changes that *predispose to adulthood disease*. Epidemiological, clinical, and experimental studies have demonstrated that early-life stress produces *long-term hyperresponsiveness to stress* with exaggerated circulating *GCs,* and enhanced *anxiety and depression-like behaviors*. Recently, evidence has emerged on early-life stress-induced *metabolic derangements*, for example, *hyperinsulinemia* and altered *insulin sensitivity* on exposure to a high-energy diet later in life.[20]

Pregnancy and *long-term adverse "programming" effects* on the offspring. The consequences of social stress exposure depends on whether during pregnancy the stress occurs, and many of the effects on the offspring are sex specific. Stress during early pregnancy tends to result in pregnancy loss. Stress exposure later in pregnancy results in programmed offspring of low birth weight: a risk factor for various adulthood diseases. Neuroendocrine and behavioral responses to stress in the offspring are particularly sensitive to *fetal programming by prenatal stress,* indicated by enhanced *HPA axis responses*

and increased anxiety behavior, which results from permanent changes in the offspring's brain. The hypothalamic–pituitary–gonadal axis may also be affected. Prenatal social stress also *programs future maternal behavior.*[21]

Male stress exposure occurs either throughout puberty or in adulthood. Remarkably, offspring of sires from both paternal stress groups displayed significantly *reduced HPA stress axis responsiveness.* Gene set enrichment analysis in offspring stress-regulating brain regions, the *paraventricular nucleus (PVN) and bed nucleus of the stria terminalis* revealed global pattern changes in transcription suggestive of *epigenetic reprogramming* and consistent of altered offspring stress response, including *increased expression of GC-responsive genes in the PVN.* By examining potential epigenetic mechanisms of germ cell transmission, we found robust changes in *sperm microRNA* (miR) content.[22]

Infants exposed to *chorioamnionitis with funisitis* had a significantly different patterns of cortisol across the samples compared with infants with *chorioamnionitis alone* or no prenatal inflammation ($F(4,139) = 7.3996$, $P < 0.0001$). Postnatal infections, necrotizing enterocolitis, and chronic lung disease were not significantly associated with the cortisol pattern at 18 months CA.[23]

2.2.3 Schizophrenia

Selective abnormalities of GC receptor mRNA (GR mRNA) expression in the *lateral orbitofrontal cortex (OFC) in psychiatric illness*, which are more specific and may be less influenced by NR3C1 genotype than those of the dorsolateral prefrontal cortex reported previously. Our results suggest that the *GRα-D1 protein isoform may be upregulated widely across the frontal cortex in psychiatric illness*.[24]

Abnormal HPA axis function, as indexed by elevated diurnal cortisol levels and/or a blunted *cortisol awakening response (CAR)*, has been observed among patients with first episode psychosis and associated with neurocognitive deficits in this population. *Family history of illness* (FHx) in children, but not *multiple antecedents of schizophrenia* (ASz) children, was characterized by a blunted CAR relative to *typically developing* (TD) *peers* (effect size = −0.73, $P = 0.01$) that was not explained by psychosocial stress exposure or by distress relating to these experiences. Neither FHx nor ASz children were characterized by elevated diurnal cortisol. *Between FHx and ASz children, more pronounced HPA axis function abnormalities (i.e., higher diurnal cortisol levels and greater blunting of the CAR) were associated with poor performance on test of verbal memory and executive function. Hormonal abnormality precedes a disease!*[25]

HPA activity may be chronically elevated; in melancholic depression, panic disorder, obsessive–compulsive disorder, and schizophrenia. The HPA axis may be more reactive to stress in social anxiety disorder and autism spectrum disorders. In contrast, HPA activity is more likely to be low in PTSD and atypical depression. Antidepressants are widely considered to inhibit HPA activity, although inhibition is not unanimously reported in the literature. There is evidence, also uneven, that the mood stabilizers, *lithium*, and *carbamazepine* have the potential to augment HPA measures, while *benzodiazepines,* atypical antipsychotics, and to some extent, typical antipsychotics have the potential to inhibit HPA activity.[26]

2.2.4 Alzheimer's Disease (AD)

Given the capacity of GCs and corticotropin-releasing hormone to induce AD-associated pathologies, a role has been suggested for circadian cortisol hypersecretion in the initiation of sporadic AD; and a temporal mechanism for AD development featuring neuroinflammation-mediated suppression of central GR signaling, has been proposed. The latter may represent a critical phase in AD development, where the density of functional GR is proposed to underlie the "cognitive reserve."

Supporting evidence for this mechanism is drawn from the brain regional locations of *AD neuropathologies*, and from risk factors for AD development (aging, ApoE-4 genotype, and hypertension). Thus, it is argued that *basal hypercortisolemia* merits further scrutiny regarding AD causation and development.[27]

Intracerebroventricular (i.c.v.) injection of amyloid-β(25–35) peptide (Aβ(25–35)) in rat, is a validated acute model of AD. Aβ(25–35) induces memory impairment, alteration of anxiety responses, HPA axis hyperactivity, GR, and mineralocorticoid receptor (MR) increases in brain regions related to HPA axis functions. GRs are progressively translocated into neurons' nucleus, while membrane version of MR is evidenced in all structures considered. The MR/GR ratio was modified in all structures considered.[28]

2.2.5 Huntington's Disease (HD)

The early *Huntington's disease (HD)* group had significantly lower morning cortisol levels relative to pre-HD and controls. In contrast, the early-HD group with at least mild or greater levels of depression symptoms had a comparable cortisol concentration to pre-HD and controls.[29]

Of these two classification approaches, HD motor sign severity was more strongly associated with *high evening cortisol* levels and both reduced

information encoding and memory retrieval. Separately, there was also a trend of *higher cortisol levels in pre-HD*. The findings suggest hypercortisolism and the underlying pathological changes may begin many years before a clinical diagnosis is made! But the memory decline associated with HPA axis disturbance may only become detectable once motor signs become pronounced.[30]

We have examined HPA axis response of R6/1 mice following *acute stress* and have found evidence of a *female-specific dysregulation of the HPA axis in R6/1 mice*, which we further isolated to a *hyperresponse of adrenal cortical cells to stimulation* by adrenocorticotrophin hormone. Interestingly, the adrenal pathophysiology was not detected in mice that had been housed *in environmentally enriching conditions*, an effect of enrichment that was also reproduced *in vitro*. This constitutes the first evidence that environmental enrichment can in fact exert a lasting influence on peripheral organ function. *Cognitive stimulation* may therefore not only have benefits for mental function, but also for overall physiological wellbeing.[31]

We found that *CORT consumption did not alter rotarod performance of R6/1 HD or wild-type (WT) littermates. However, the onset of hippocampal-dependent Y-maze deficits was accelerated in male R6/1 mice by 5 days of CORT treatment,* whereas short-term memory of WT and female R6/1 mice was unaffected. We then further investigated the male HD susceptibility to CORT by measuring TrkB activation, BDNF and GR expression, as well as the level of cell proliferation in the hippocampus. *CORT treatment increased the levels of phosphorylated TrkB in male R6/1 mice only*.[32]

2.2.6 Multiple Sclerosis (MS)

Cortisol release as well as *glucocorticoid sensitivity* (GCS) were strongly correlated with time since diagnosis but not with neurological disability. Patients with shorter disease duration (2–12 months) expressed a significantly higher cortisol stress response while MS patients with longer disease duration (14–36 months) showed a significantly diminished HPA response as well as lower poststress GCS.[33]

HPA axis activation in untreated MS drifts from hypothalamo–pituitary to more adrenal activation, consistent with adrenal sensitization or hypertrophy due to chronic HPA axis activation. HPA system regulation remains more stable in MS patients on DMT.[34] High cortisol levels were associated with slower disease progression, especially in females with secondary progressive MS. Interestingly, normal-appearing white matter (NAWM) of patients with high cortisol levels displayed elevated expression of *GC-responsive*