CHAPTER 5

THE PSYCHONEUROIMMUNOLOGICAL INTERACTION IN TERMS OF THE CRH/HPA-AXIS.

The Central Role of CRH in the Psychoneuroimmunological Interaction of the Two Main Stress Axes

The previous two chapters demonstrated the psychoneuroimmunological interaction in terms of the first of the two major stress axes, i.e., the central noradrenergic/peripheral sympathoadrenomedullary system (CNA/SAM-axis). This chapter deals with psychoneuroimmunology in terms of the other major stress axis, i.e., the central corticotropin-releasing hormone/peripheral hypothalamo-pituitary-adrenocortical axis (CRH/HPA-axis). In the CNA/SAM-axis the neurotransmitter noradrenaline plays a pivotal role in both the central and peripheral effects, while cortisol is generally seen as the main effector hormone of the CRH/HPA-axis, both for immunological and behavioural functions. In depth scrutiny of the subject lead to the conclusion that the last assumption is a misconception. This chapter will show that a) CRH is the dominant neurohormonal factor of the CRH/HPA-axis and that, in this role, controls not only the neurological-behavioural functions, but also the immunological reactivity and status, and b) that it not only regulates CRH/HPA-axis activity, but is also in control of the CNA/SAM-axis. The aim of the first section of this chapter is to demonstrate the distribution of CRH neurons in the central nervous system, as well as the central role of CRH in the integration and regulation of autonomic nervous system activity, neuroendocrine function and in behaviour. The second section will deal with the central role of the CRH/HPA-axis in immunological homeostasis, i.e., the neuroimmunological role of the CRH/HPA-axis. The third section demonstrates the central role of CRH in psychoneuroimmunology in terms of both major stress axes.

Introduction

Chapter 2 provided evidence for an interaction between the psychological disposition and the immune system, i.e., for a psychoimmunological link. It focussed on providing prove that enough evidence exists for the interaction to be considered a normal phenomenon of all behavioural processes and psychological abnormalities, and that behaviour can in almost all circumstances become a biological response modifier and *vice versa*. The underlying mechanisms that link the psychological and immunological events were at that stage largely ignored. The next step was to show the main stress axes, i.e., the CNA/SAM-axis and the CRH/HPA-axis, as underlying psychoneuroimmunological mediators. The third and fourth chapters demonstrated that in terms of the CNA/SAM-axis, i.e., the third chapter dealt with the psychoneurological and the fourth chapter with the neuroimmunological interactions in terms of the CNA/SAM-axis. The current chapter concentrates on psychoneuroimmunology in terms of the CRH/HPA-axis. It demonstrates that corticotropin-releasing hormone (CRH), plays a central role in the integration of autonomic function, somatic motor function, neuroendocrine activity and behavioural functions, as well as in the neuroendocrine control of immunity.

The essence of psychoneuroimmunology in terms of the CRH/HPA-axis can be condensed into four large diagrams (Figures 5.1, 5.2, 5.3 and 5.4). These diagrams are presented right at the beginning of the chapter, followed by descriptive supporting evidence. A fifth key diagram (Figure 5.15) is found right at the end of the chapter and presents psychoneuroimmunology in terms of the two main stress axes. Other figures are included for explanatory purposes.

The contents of this chapter is thus summarized in Figures 5.1 to 5.4 and Figure 5.15. These figures are:

Figure 5.1: The psychoneurological interaction in terms of the CRH/ HPA-axis.
The central role of CRH in the control of the neurohormonal and behavioural stress response.

Figure 5.2: The neuroimmunological interaction in terms of the CRH/ HPA-axis. The central role of CRH in the neurohormonal control of immunity.

Figure 5.3: The effects of acute and chronic increases in glucocorticoids.

Figure 5.4: Outline of the central role of corticotropin-releasing hormone in psychoneuroimmunology in terms of the CRH/HPA-axis.

Figure 5.15: Psychoneuroimmunology in terms of the two main stress axes. The central role of corticotropin-releasing hormone.

In the paragraphs, following upon the figures, more detailed explanatory discussions will be provided. These explanatory discussions are subdivided into:

Section 5.1: The psychoneurological interaction in terms of the CRH/ HPA-axis. The central nervous system CRH system and the central role of CRH in the stress response.

In Section 5.1 the distribution of the CRH neurons throughout the CNS is discussed. It is demonstrated that the central, as well as the peripheral, stress response, including the CNA/SAM-axis, are under CRH control. The section explains and expands on Figure 5.1.

Section 5.2: The neuroimmunological interaction in terms of the CRH/ HPA-axis: The central role of CRH in the neurohormonal control of immunity

In this section it is shown that CRH is ultimately in control of the total immunological effects of the CRH/HPA-axis, as well as the immunological effects of other hormones of the stress response. The immunological effects of the hormones influenced by CRH will briefly be reviewed. This section explains and expands on Figure 5.2 and Figure 5.3.

Section 5.3: Psychoneuroimmunology in terms of the two main stress axes. The central role of corticotropin-releasing hormone.

This section combines work from the previous 2 sections, as well as from Chapter 3 and Chapter 4 in order to show CRH as the central element in psychoneuroimmunology in terms of the two main stress axes. It is summarized in Figure 5.15.

In the explanatory discussion of sections 1 and 2 some of the main figures are subdivided in order to facilitate the understanding of the chapter as a whole.

Figures 5.1 to 5.4, followed by their respective legends, are presented on the next eight pages.

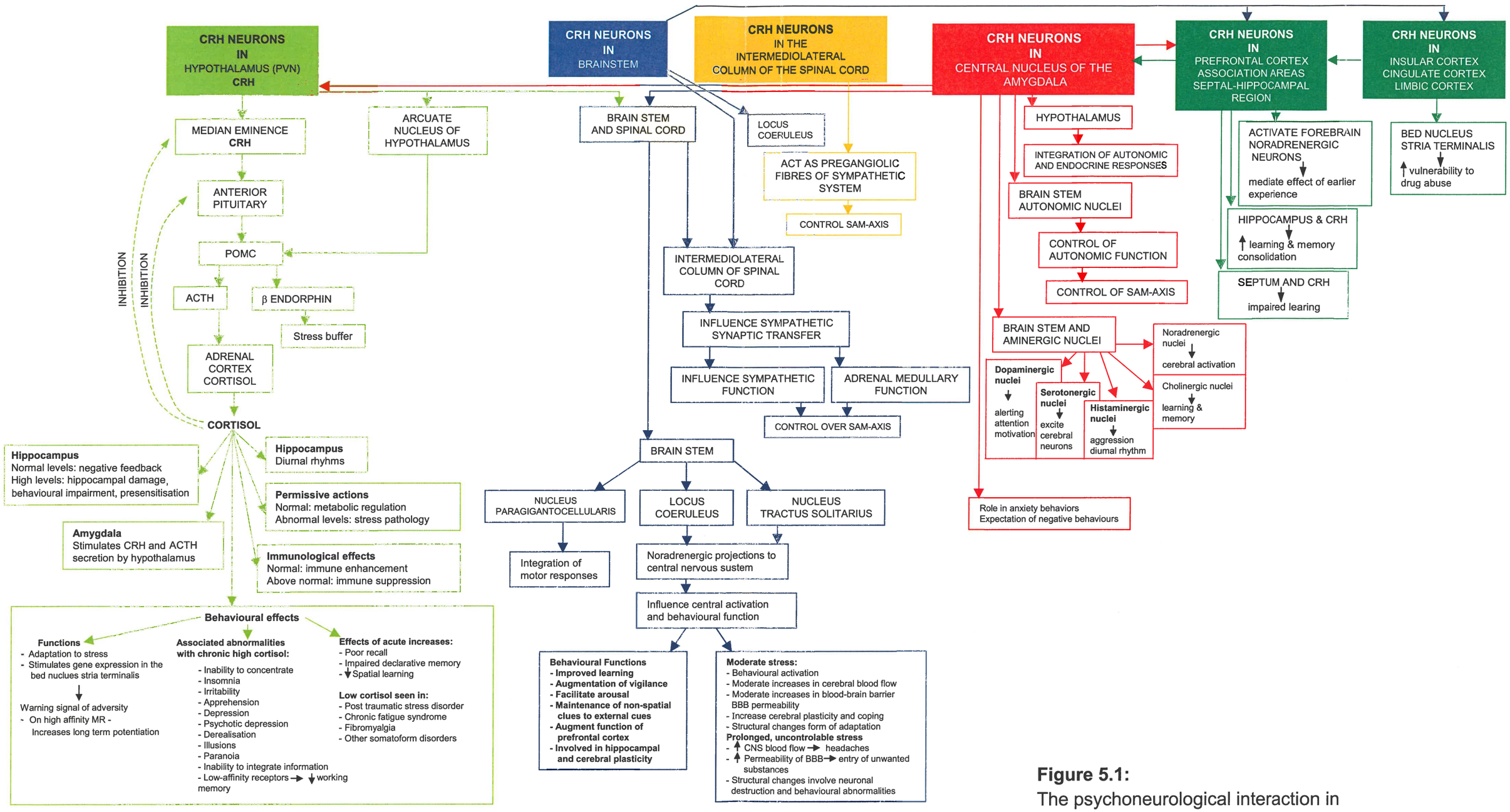
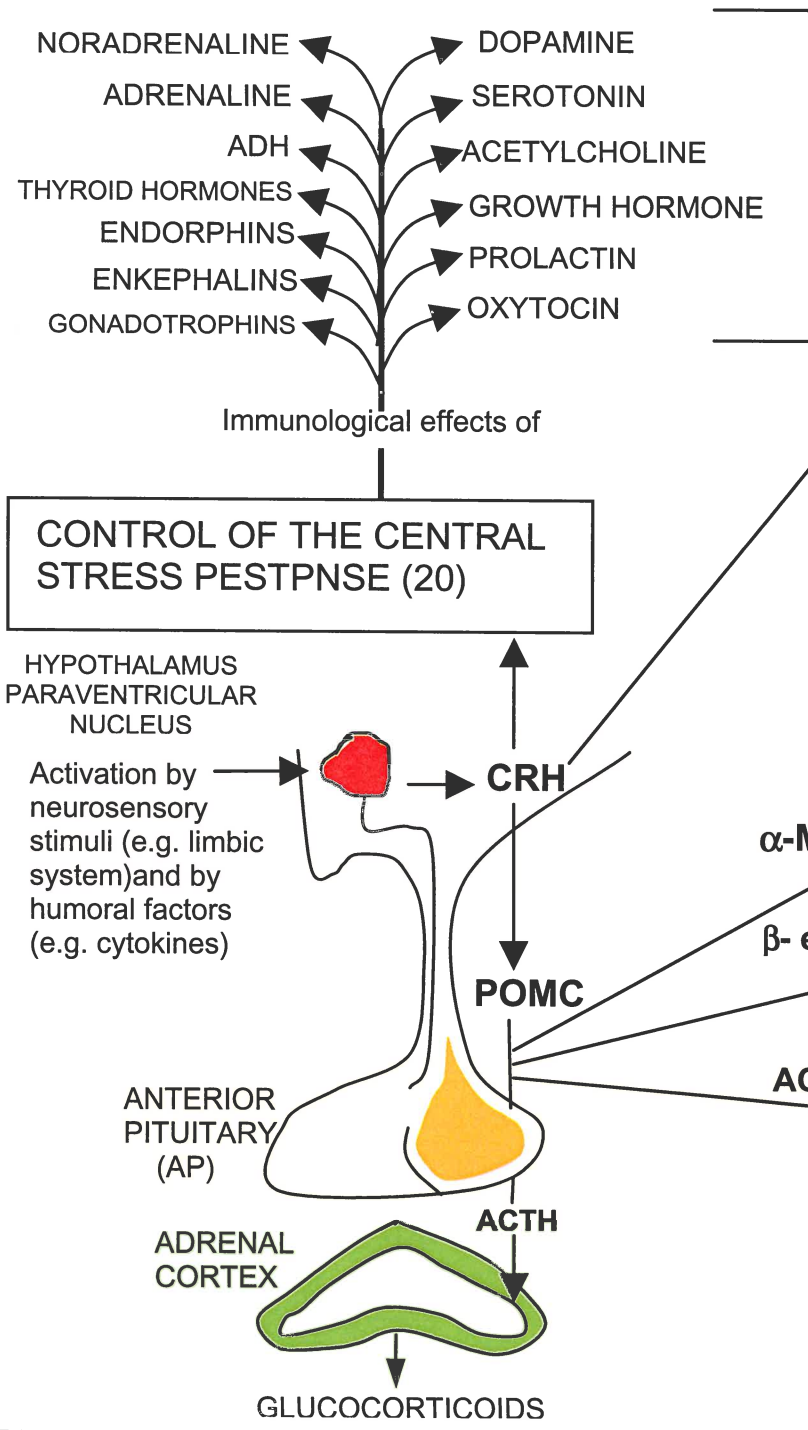


Figure 5.1:
The psychoneurological interaction in terms of the CRH/HPA-axis.
The central role of CRH in the control of the neurohormonal and behavioural stress response.

Legend to Figure 5.1

Figure 5.1: The psychoneurological interaction in terms of the CRH/ HPA-axis. The central role of CRH in the control of the neurohormonal and behavioural stress response.

[The scheme illustrates the distribution of CRH neurons throughout the central nervous system. CRH neuronal cell bodies are found in the paraventricular nucleus (PVN) of the hypothalamus. These neurons are in control of the HPA-axis and its functions. By controlling the secretion of cortisol the PVN CRH neurons indirectly control and integrate the functions mediated by cortisol, including a) the permissive functions of cortisol on metabolic regulation, b) cortisol's behavioural effects, c) its immunological effects, d) its control of the stress response through negative feedback to the hippocampus, e) its stimulatory effect on the CRH neurons of the amygdala that in turn stimulate CRH and ADH neurons of the hypothalamus and, f) the effects of cortisol on diurnal rhythms. The CRH neurons of the PVN are mainly involved with the control of peripheral stress responses. However, PVN CRH neurons also project to other areas such as the arcuate nucleus, the brain stem and the spinal cord where they help to coordinate the stress response. CRH neurons are also found in the brain stem and intermediolateral column of the spinal cord where they influence and coordinate autonomic functions, somatic motor functions and behavioural functions and from where they control the CNA/SAM-axis. The most important group of CRH neurons, with regard to behavioural functions are found in the amygdala. They project to and stimulate the activity of the PVN CRH neurons of the hypothalamus where they integrate and control autonomic and endocrine functions, project to the autonomic nuclei of the brain stem to control SAM-axis activity, and project to the aminergic nuclei of the brain stem that, in turn, project back to the cortex to control the emotional and cognitive functions of the brain. These pervasive CRH projections from the amygdala greatly contribute to the integration of the neuroendocrine, autonomic nervous system and behavioural responses during psychologically–induced stress. Clusters of CRH neurons are further found in the cerebral association areas and limbic structures that help with the analysis of information and the formation of perceptions about potential stressors.]



All with their own immunomodulatory effects

Immunological effect of CRH from immune cells and nerve endings
Control the pain of inflammation by stimulation of the local release of opioid peptides (8)
Mast cell degranulation with vasodilation, increased vascular permeability, fluid extravasation and hypotension (19)
CRH receptors on immune cells and immune accessory cells, e.g. macrophages mast cells, leukocytes, as well as inflamed synovia (19)
CRH stimulates IL-1 secretion from monocyte (19)
CRH stimulates IL-2 secretion from lymphocytes (19)
CRH stimulates IL-6 secretion from mononuclear cells (19)
CRH stimulates IL-2 receptor expression (19)
CRH enhances chemotaxis (19)
Stimulates lymphocyte proliferation (19)
CRH stimulates the production of reactive oxygen radicals by macrophages (19)
Increased hypersecretion in human autoimmune inflammatory diseases and Hashimoto's thyroiditis (19)
Inhibition of certain immune and inflammatory responses points towards a bi-phasic action

Immunological effects of α-Melanocyte stimulating hormone
Antagonises pyrogenic and pro-inflammatory response
Effects production as well as secretion of cytokines (IL-1, IL-6, TNF, IFNγ) (11)
Reduces neurogenic aspects of inflammatory response (11)

Immunological effects of β- endorphin and other opioids
Inhibitory effect on most immune functions – independent of steroids (1)
Co-factors in determining Th1-Th2 response - favours Th2 response (1)
Decreases T-lymphocyte mitogenic response, IFN secretion, expression of HLA class 11 antigens, T-cell receptor CD3 complex IL-2 receptor,

Immunological effects of ACTH
Inhibits the immediate response to injury by suppression of vascular leakage (6).
Steroidogenic effect – stimulates secretion of immune active glucocorticoids
Exerts direct immunological effects as well as indirect through neuroendocrine modulation.
Influence phagocytosis processes (cellular migration,chemotaxis, endocytosis, etc) – usually
positively, in concert with cytokines and other immune modulators (15).
Dose-dependent effect on humoral immunity, but generally inhibitory (15).

Immunological effects of glucocorticoids (cortisol)
Primary lymphoid tissues:
Role in thymic cell development, T-cell selection, apoptosis of cells in thymus (2)
Secondary lymphoid tissue:
Role in splenic T-cell selection – peripheral T-cell selection - through clonal deletion and expansion (2).
Necessary for initial antigen-specific response (2) in secondary lymphoid tissues
Total *in vivo* immune response:
Generally anti-inflammatory at pharmacological levels – immune modulatory in physiological levels
Bi-phasic response – dose-dependent and exposure time-dependent
May be a prerequisite for the coordinated immune response (5)
Plays a role in maintaining the appropriate balance between the expression of inhibitors and effectors of apoptosis of cells (12)
Basal physiological and low acute stress levels of GC, in a time, dosage, and cytokine-dependent manner can enhance almost all aspects of immune function (normal regulation and acute adaptive stress response)
During infections: Excessive pro-inflammatory cytokines will stimulate HPA-axis to increase cortisol to immune-inhibitory levels (protection of body against systemic inflammatory response, self-damage and autoimmune processes)
Pharmacological dosages: generally immune suppressive – with a shift from proinflammatory to antiinflammatory cytokine response.
Allergic reactions to corticosteroids may develop (14)
Mechanisms:
Acute stress: ↑circulating neutrophils; ↓ circulating lymphocytes (Th, Tc, B-cells, NKC), monocytes. Represent redistribution of leukocytes rather than destruction (17).
Long acute to chronic: ↓ Total leukocyte numbers.
Modulation of the immunological effects (differentiation, cell proliferation, inflammatory and immune responses) of peptide hormones, metalloproteinases and of cytokines by interfering with the activity of other transcription factors such as CREB, AP-1 and NF-κB (3).
Inhibits antigen presentation by macrophages as well as their production of IL-1, IL-2, IL-6, IFNγ (18).
Arrests lymphocyte proliferation in stage G0 and G1 (18)
Suppresses the differentiation of monocytes to macrophages (18)
Important role in Th1/Th2 response: favours Th2 cytokine responses (autoimmunity linked to Th1-responses; allergy and asthma linked to Th2-responses) (2)
Upregulation of certain cytokine receptors – enhancement of cytokine action (2)
Induction of acute phase responses – including behaviour (2)

Stimulatory effect on early B-cell responses (Th2-response) (2)
The type 1 GC receptor-cortisoi compiex acts as functional antagonist of the type 2 rece
which means that cortisol can induce opposing effects (20).
The affinity of GC receptors are determined by genetic polymorphisms, associations wit
immunophilins, and by various cytokines (20)
In inflammation:
Inhibits the immediate inflammatory response to injury by suppression of vascular leakage (6).
Many of the anti-inflammatory effects mediated through a combination of the up-regulation of anti-inflammatory mediators and the down-regulation of pro-inflammatory mediators
Binds to GRE on glucocorticoid-responsive genes and increases the transcription of genes coding for anti-inflammatory proteins (lipocortin-1, IL-10, IL-1 receptor antagonist,, neutral endopeptidases) (7)
Inhibits the expression of multiple inflammatory genes (pro-inflammatory cytokines, enzymes, receptors, adhesion molecules) through direct inhibitory interaction between activated GC receptors and activated transcription factors (7).
Can suppress gene expression of immune-related substances by changing chromatin structure (7).
Stimulates lipocortin-1 production that in turn inhibits phospholipase A_2 activity with a resultant decrease in the production of inflammatory mediators such as prostaglandins and leukotrienes (18)
Stimulates the secretion of neutrophil-derived lipocortin-1, which inhibits neutrophil extravasation in response to chemotaxic stimuli (9)
Decreases the expression of the gene that codes for cyclooxygenase-2 – thus further suppresses the production of inflammatory prostaglandins (18)
Control local inflammation through lipocortin-induced detachment of neutrophils from postcapillary venules (4).
Inhibits the gene that encodes for nitric oxide synthase (18)
Stabilises lysosomal membranes - thus reduces local release of proteolytic enzymes and hyaluronidase (18)
Inhibits the differentiation and proliferation of mast cells (18)
Suppresses the proliferation of fibroblasts, as well as their synthesis and deposition of fibrils (18)
Not only does GC regulate cytokine secretion, but cytokines modulate the function and expression of GC receptors (13)
Mediates the production of thymosin β sulfoxide by monocytes which inhibits neutrophil chemotaxis, lowers neutrophil adhesion to endothelial cells and causes neutrophil dispersion (10)
Mediates expression of adhesion molecules (glucocorticoid-induced adhesion match) through stimulation of the production of cytokines and lipocortins which control adhesion molecule expression (18)

Figure 5.2 The neuroimmunological interaction in terms of the CRH/HPA-axis. Central role of CRH in the neurohormonal control of immunity.

Legend to Figure 5.2

Figure 5.2: The neuroimmunological interaction in terms of the CRH/ HPA-axis. The central role of CRH in the neurohormonal control of immunity.

[CRH controls the secretion of pro-opiomelanocortin (POMC) that contains within its structure β-endorphin, α-MSH and ACTH. Each of these hormones has their own immunological effects. ACTH also regulates the release of cortisol – a steroid hormone with both immuno-enhancing and immunosuppressive effects. CRH is, in addition in control of the activity of the neurohormonal factors of the central stress response. Each of these substances has either immuno-enhancing or immunosuppressive effects or both. CRH thus controls the immune system directly through its own effects on the immunological processes and indirectly a) through its control of the POMC-derived substances and the ACTH-controlled release of cortisol, as well as b) its control over the neurohormonal substances of the central stress response.]

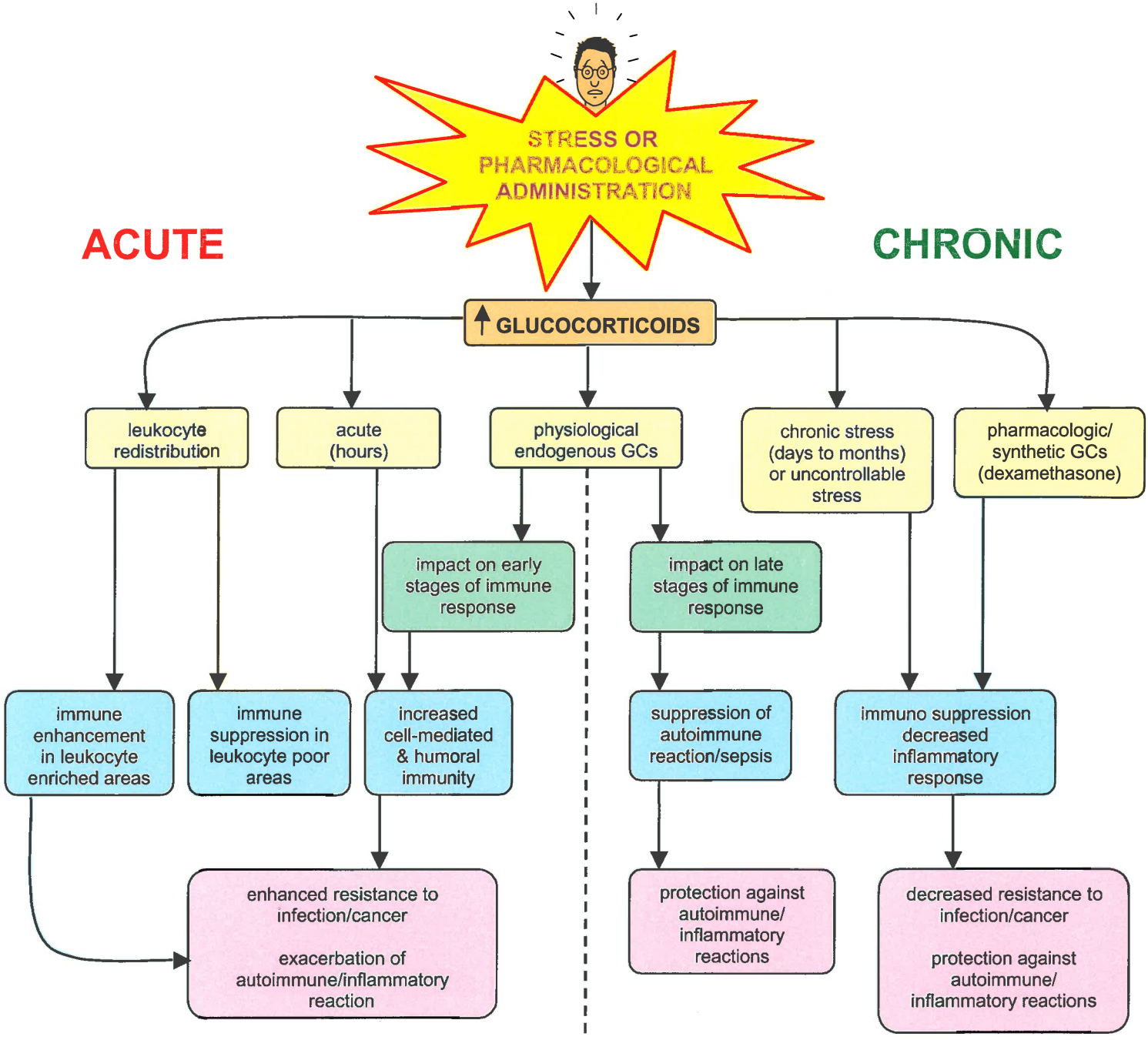


Figure 5.3 : The effects of acute and chronic increases in glucocorticoids. On the left is shown acute -induced immune enhancement, i.e., redistribution of areas where needed and a totalse in innate, humoral and cellular immunity. This seen as an adaptational response to protect the body against infections, but autoimmune and inflammatory responses.On the right is shown immune prolonged ds of stress or at pharmacological levels. This can predispose to development of cancer but offer some protection against autoimmune and

Legend to Figure 5.3

Figure 5.3: The difference between chronic and acute stress-induced stimulation of the HPA-axis.

[On the left is shown acute stress-induced immunoenhancement, i.e., redistribution of leukocytes to areas where needed and a total increase in innate, humoral and cellular immunity. This should be seen as an adaptational response to protect the body against infectious stressors, but can predispose to autoimmune and inflammatory complications. On the right is shown immunosuppression that occurs during prolonged periods of uncontrollable stress or at pharmacological levels of glucocorticoids. This can predispose to infections, allergies and cancer development, but offer some protection against autoimmune and chronic inflammatory conditions.]

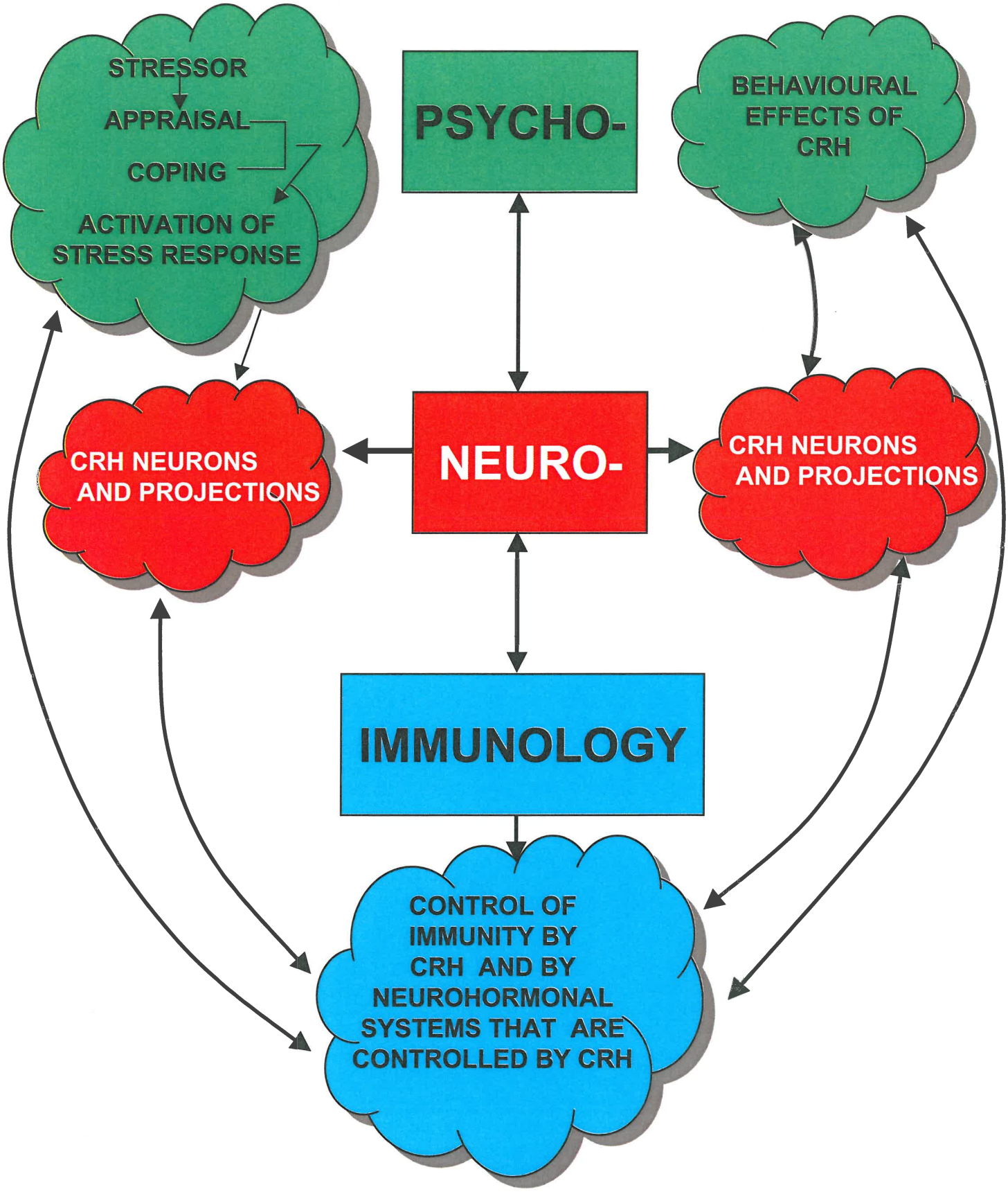


Figure 5.4 Outline of the central role of CRH in psychoneuroimmunology in terms of the CRH/HPA-axis

Legend to Figure 5.4

Figure 5.4: Outline of the central role of CRH in psychoneuroimmunology in terms of the CRH/HPA-axis

[The psychoneuroimmunological integration is shown in four layers with the top horisontal layer representing the *psycho-*, the middle layer the *neuro-* and the bottom layer the *immunological aspects*. A more detailed presentation of the psychoneuroimmunological interaction is incorporated into Figure 5.15]

5.1 The central nervous system CRH system and the central role of CRH in the neurohormonal and behavioural stress response.

The aim of this section is to show, firstly, the distribution of CRH neurons throughout the nervous system and secondly the central nervous system CRH neuronal system as integrator between the various psychological and physiological functions of the stress response. This section describes the information shown in Figure 5.1.

Around 1956 Hans Selye described the role of the hypothalamo-pituitary-adrenocortical (HPA) axis in the stress response (22). He also described the stress reaction that follows upon psychological stressors as the non-specific stress response. Although we know today that large variations in the pattern of the non-specific stress may occur, the term non-specific stress response, as coined by Selye, is still used to distinguish it from the homeostatic disturbances caused by specific stimuli where homeostasis can be returned to normal by feedback mechanisms specific for the disturbance. Perhaps it is at this stage necessary to mention that the non-specific stress response is, in contrast to the specific stress response, not a correction of the disturbed homeostasis, but rather, a new homeostasis aimed at helping to cope with the stressor. Today it has, in certain circles, become customary to refer to allostasis rather than to the non-specific stress response. Allostasis is seen as the regulation of the internal milieu through neurohormonal changes – in other words to keep internal stability through adaptational changes in the neurohormonal homeostasis (23,24). The term allostatic load can be seen as the equivalent for the description "the effects of chronic stress", i.e., it is the price the body and mind pay for containing the effects of arousing stimuli and for the anticipations of negative events (25).

Formal recognition of the relativity of the non-specificity in the so-called non-specific stress response started around 1968 with the writings of Mason (26). Mason's big problem with the theory of Selye was that only the efferent leg of the stress response was taken into consideration and that very little was said about the nature, strength and chronicity of the stimulus input (26).

Since the work of Mason many contributors have shown that the nature of the so-called non-specific stress response is determined by factors such as the context in which it occurs, the psychosocial environment, and the perception of the individual about the stressor, which, in turn, is determined by earlier cognitive and emotional experiences and genetics. In short, the major determinants would appear to be the extent to which the individual sees the situation as potentially controllable – a phenomenon largely dependent on coping skills and the need for the individual to be in control. Of the two major stress axes, activation of the HPA-axis is the least likely to have a set pattern of activation and is most probably to the largest extent influenced by the psychological factors just mentioned in the previous sentence. This would be born out by subsequent writings.

The aim of this section is to demonstrate the ubiquitous distribution of CRH neurons throughout the central nervous system, and to demonstrate the central role of CRH, the first hormone of the HPA-axis, in the stress response and in the integration of the behavioural, neuroendocrine, autonomic nervous system, somatic motor and immune responses to stress. This was summarised in Figure 5.1. The following paragraphs will provide a brief description, with the necessary references, of the information presented in Figure 5.1.

Figure 5.1 illustrates the distribution of CRH neurons throughout the central nervous system, as well as the pervasiveness of their projections – through which the CRH system coordinates and integrates the various modalities of the stress response. It has in fact been hypothesized that the major function of CRH is to regulate and coordinate the body's autonomic, endocrine, metabolic, behavioural and emotional responses to stressors (27).

Through its influence on, and control of the HPA-axis and the CNA/SAM-axis, as well as the co-operative control of the two axes on other neurohormonal systems, the CRH system occupies a central role in the stress response. The claim of the hypothesis that CRH controls the functions of the CNA/SAM-axis is supported by the results of pharmacological administration of CRH. Pharmacological administration of CRH leads to the typical "fight-or-flight" circulatory pattern (28), increased firing of the sympathetic

nerves, increased blood levels of adrenaline and noradrenaline, an increase in blood sugar (29), decreased parasympathetic activity, increased motor activity, decreased sexual drive, appetite, and water intake (27) and an increase in the firing rate of the nucleus coeruleus (30).

The distribution of CRH neurons, their projections and coordinating functions are shown in Figure 5.1. The largest collection of CRH neurons is found in the paraventricular nucleus (PVN) of the hypothalamus (20,31). These are the neurons known to initiate and regulate HPA-axis activity and which are ultimately the primary stimulators of cortisol secretion. This was shown on the left side of Figure 5.1 and the relevant section of it is reproduced at this point as Figure 5.5 - in an attempt to facilitate the reading of this section.

Figure 5.5 schematically shows that the CRH neurons of the paraventricular nucleus project to the median eminence from where the secreted CRH travels via a portal system to the anterior pituitary. In the anterior pituitary CRH stimulates the release of pro-opiomelanocortin (POMC). From the POMC molecule are derived several hormones, amongst others the adrenocorticotropic hormone (ACTH) and β-endorphin. β-Endorphin is a major stress buffer and counteracts many of the stress response reactions of the other stress hormones. ACTH travels via the circulation to the adrenal cortex where it stimulates the production and release of cortisol. The secretory activities of CRH, as well as the role of cortisol in the stress response – especially its behavioural effects - will be discussed on the next couple of pages.

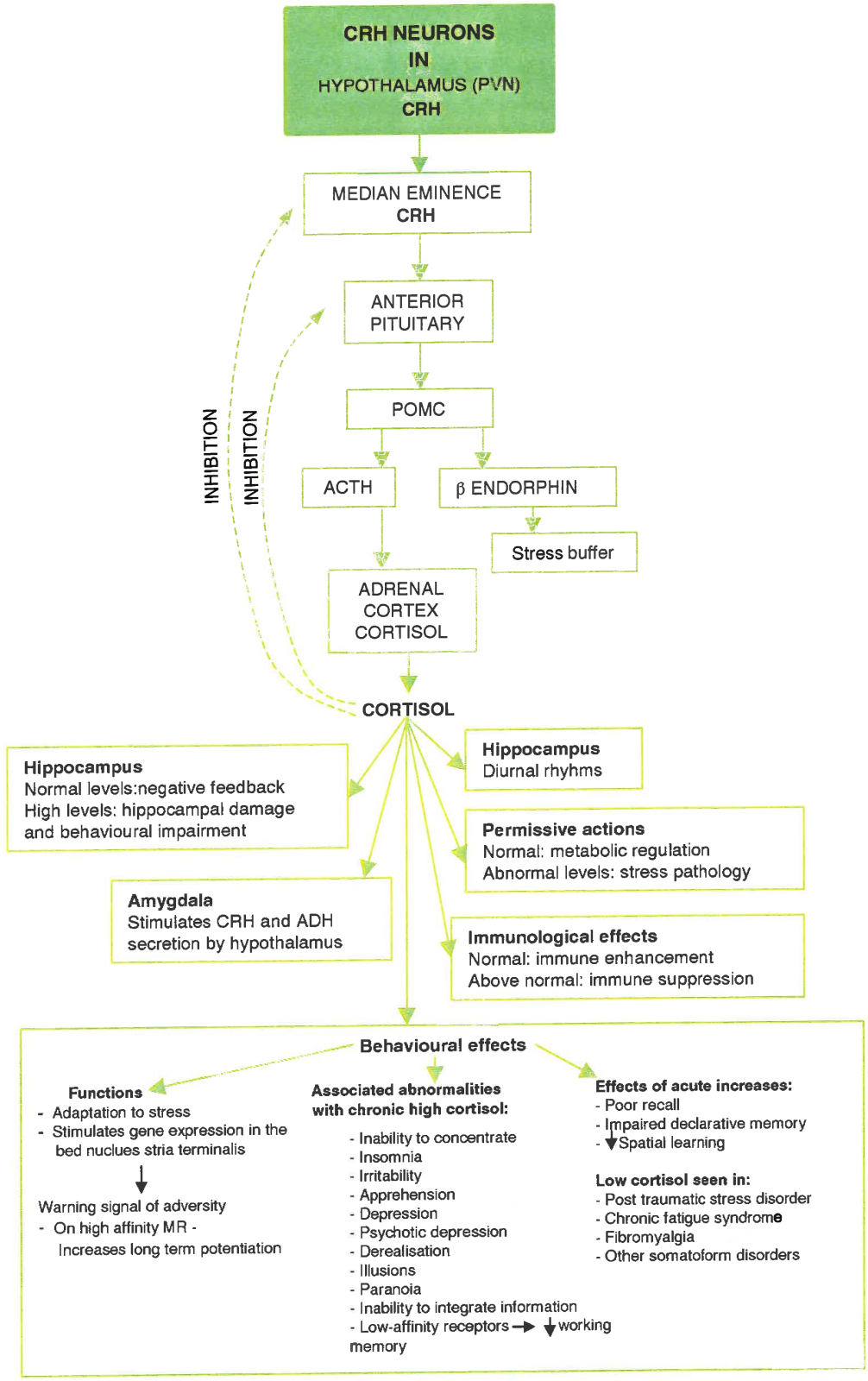


Figure 5.5: The integrative role of the paraventricular nucleus CRH neurons in the central stress response.

A number of facts should be considered when viewing these CRH neurons in terms of the stress response:

- The paraventricular nucleus (PVN) CRH neuronal activity is stimulated, to a large extent, primarily by neurosecretory stimuli from brain centra involved in higher brain functions and by humoral factors such as immune cell-derived cytokines. Peripheral sensory information reaches the PVN either via the reticular formation or via the hypothalamus to the cerebral cortex, to the limbic system – the latter of major importance with regard to CRH secretion in response to stress (32).
- The HPA-axis, which is mainly stimulated by PVN CRH activity, is under negative feedback control due to the effect of cortisol on a) the hypothalamus, where cortisol inhibits gene expression, b) the anterior pituitary, where the rate of POMC synthesis is inhibited at nuclear level and, c) at the hippocampus – where stimulation of the hippocampal cortisol receptors lead to inhibition of CRH production and CRH release from the hypothalamus (33,34,35). The effect of cortisol on the hippocampus is of great importance for the behavioural functions, as the hippocampus plays a role in long-term declarative memories, as well as in the integration of emotional and cognitive processes (36).
- The paraventricular nucleus contains neurons that secrete mainly CRH and neurons that secrete CRH, as well as ADH (20,31).
- A synergistic cooperation exists between CRH and ADH with regard to the stimulation of ACTH from the anterior pituitary and arcuate nucleus. ADH increases the effectivity of CRH by a factor four (20,31).
- The same synergism between CRH and ADH is seen with regard to the effects of CRH effects on behavioural functions (20,31).
- During prolonged stress, impulses from the amygdala cause an increase in the ratio between paraventricular nucleus neurons that secrete both ADH and CRH and neurons that secrete only CRH (20,31).
- Cortisol has a ten times stronger negative feedback on the neurons that secrete only CRH than on neurons that secrete both CRH and ADH – in fact, the negative feedback to the latter is rather weak (20,31).

- The activity of CRH during periods of prolonged stress is thus effectively several times higher during chronic stress as a result of a) the synergism between ADH and CRH, b) the stress-induced effect of the amygdala on the CRH:CRH/ADH neuronal ratio and c) the difference in the negative feedback on the two types of CRH producing neurons (20,31).
- During prolonged periods of distress the negative feedback of the high cortisol levels on the HPA-axis, via the hippocampus, is further reduced due to cortisol-induced damage to the hippocampus. The hippocampal control of the HPA-axis is the most important of the various negative feedbacks on the HPA-axis and cortisol–induced damage to the hippocampus and inhibition of hippocampal function may lead to further increases in cortisol production, adrenocortical hypertrophy and eventually damage to both the adrenal cortex and the hippocampus. The cortisol-induced hippocampal damage is accompanied by behavioural alterations such as poor explicit memory. The total picture of stress-induced hypercortisolaemia, with the accompanied hippocampal damage and memory impairment, is known as the glucocorticoid cascade hypothesis (37).

The indirect psychological, as well as physiological effects of CRH, i.e., those exerted via the HPA-axis, are extremely pervasive. Cortisol alone has several types of functions, all contributing to the integration of the stress response:

- The permissive functions of cortisol, probably the best known of its functions, are those where cortisol plays a major endocrine regulatory role in the control of metabolic processes. These effects and their contribution to psychopathological and pathophysiological processes are well known (38).
- Cortisol also plays a very important role in the control of many potentially harmful stress-related responses, in fact, cortisol is a very important factor in the adaptation to stress (31).
- It has a major impact on the diurnal rhythmicity, with alterations in its own diurnal secretory pattern seen during periods of chronic stress (31).

- It is further know that cortisol, in addition to its role as negative feedback mechanism of its own secretion via the hippocampus and hypothalamus, may also feedback to the amygdala and amygdalar outflow and to the hippocampus, i.e., to structures involved with the formation of emotions and memory (39).
- Cortisol influences behaviour in a variety of ways. Direct effects of cortisol on behaviour were published even before the 60's (32), as can be seen from reports of
  - The inability to concentrate, drowsiness, restlessness, insomnia, irritability, and apprehension reported in some patients with adrenal insufficiency
  - Reports of depression and sometimes psychosis in some patients with Addisons disease
  - Various psychological disturbances reported in a number of patients with Cushing's syndrome or with ultra-long term therapeutic administration of high dosages of cortisol, including confusion, anxiety, insomnia, delusions, hallucinations, derealisation or psychotic depression, but sometimes also the opposite such as euphoria, elation and an increase in social activity
  - Alterations in mental state upon cessation of long term steroid treatment, including illusions, paranoia, derealization and bizarre behaviour
  - Associations seen between certain mental disturbances and abnormalities of cortisol metabolism. In general it would appear that cortisol may be a factor in the exacerbation of psychological disturbances during new, aversive situations, with failure of ego defense mechanisms, ego disintegration, and loss of control. Hypocortisolaemia has been implicated as a contributing factor in the inability to selectively concentrate attention and the inability to correctly receive and integrate information – both processes of major importance in the development of appropriate perception
- More recent work further confirms a clear connection between cortisol and the behavioural functions
  - Cortisol, at chronic stress-induced levels, is now generally accepted to give rise to loss of hippocampal neurons with a loss of some of the hippocampal-associated behavioural functions (40) and memory impairment

- Occupancy of low-affinity hippocampal receptors at stress levels of glucocorticoids can lead to (41)
    a. transient reduction in long-term potentiation – perhaps giving rise to stress-induced and diurnal variations in working memory
    b. suppression of hippocampal neurogenesis
    c. atrophy of apical dendrites
- Occupancy of high-affinity mineralocorticoid receptors (MR) by low levels of glucocorticoids prolongs long term potentiation (42)
- Stimulation of the bed nucleus stria terminalis by cortisol increases CRH gene expression which signals adversity – a sort of early warning system of potential danger (43)
- Clinical correlations between high cortisol levels and cognitive impairment are seen in
    a. Cushing's disease, Alzheimer's disease, aging and depression where links were shown between cortisol-related cognitive deficits and loss of hippocampal volume (44,45,46,47,48)
    b. Childhood physical and sexual abuse, loss of hippocampal volume and cognitive deficits such as memory impairment (49)
- Acute stress-induced cortisol secretion has, in addition to the effect of long term exposure to glucocorticoids with the accompanying hippocampal damage, also been shown to impair cognitive function. The connection was seen in mental arithmic tests by an inverse correlation between cortisol response and mental performance (50), poor retention of word lists during stress-induced high cortisol secretion (51) and in impaired declarative memory and spatial learning upon cortisol administration (51). This acute effect of cortisol is in direct contrast to the cognitive enhancement of acute stress-induced catecholamine secretion, discussed in a previous chapter.

In just looking at the effects of cortisol we can already, as shown in the previous pages, see how CRH, via its cortisol-stimulating effect, can integrate endocrine, metabolic, diurnal, stress regulatory and behavioural functions. The influence of the paraventricular

nucleus CRH neurons is, however, much more pervasive than that mediated through its control of the HPA-axis functions and cortisol secretion. Additional effects, as will be seen in the following paragraphs, are mediated via projections from the paraventricular nucleus CRH neurons to the arcuate nucleus, the brain stem and the intermediolateral column of the spinal cord. The section of Figure 5.1 that deals with these projections is reproduced below as Figure 5.6.

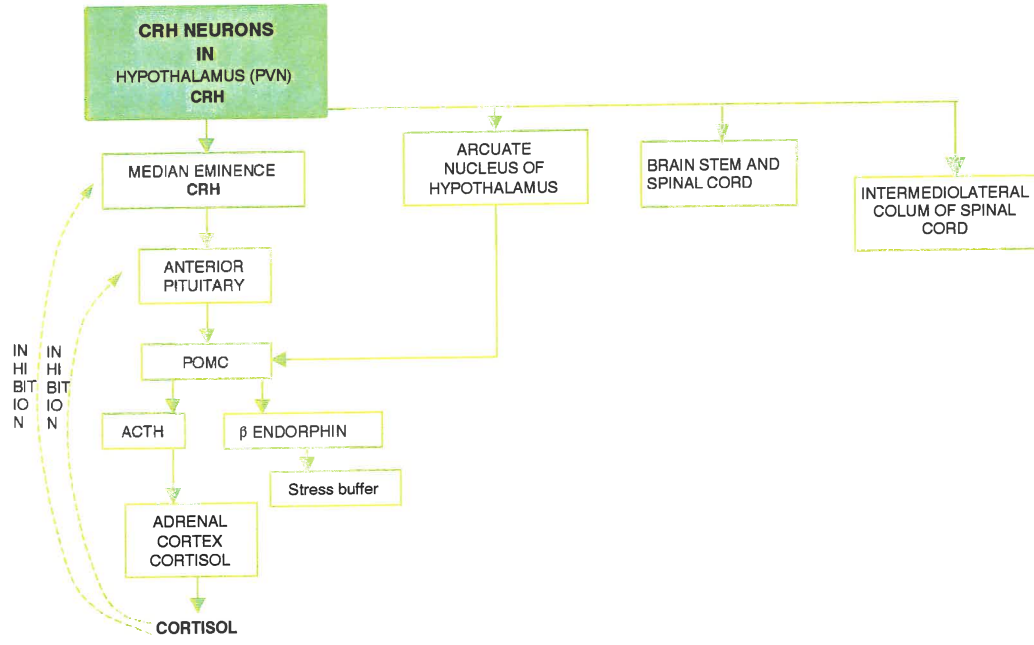


Figure 5.6: CRH projections from the paraventricular nucleus (PVN) CRH neurons of the hypothalamus to the arcuate nucleus, brain stem and intermediolateral column of the spinal cord

CRH projections from the paraventricular nucleus to the brain stem synapse with a) the nucleus paragigantocellularis, through which they influence functions such as the integration of motor responses associated with the nucleus paragigantocellularis, b) the nucleus tractus solitarius, which is involved with sympathetic regulation of cardiovascular responses and c) the locus coeruleus, i.e., the major brain stem noradrenergic nucleus from where fibres project to, and activate virtually all areas of the central nervous system. The noradrenergic fibres from the locus coeruleus is a major source of cerebral activation, as well as an important factor in mood determination (32,52). These projections thus represent indirect CRH effects on CNS activation. These detailed interactions of CRH neurons with brain stem nuclei are shown in Figure 5.1 and Figure 5.7.

CRH projections from the paraventricular nucleus, also reach the intermediolateral column of the spinal cord where the cell bodies of the preganglionic sympathetic neuronal fibres are located. By influencing the transfer of information in the intermediolateral column, CRH can virtually affect sympathetic functions throughout the body – including the secretory activity of the adrenal medulla. The sympathetic nervous system can further be influenced by CRH due to the fact that some of the preganglionic neurons are in fact CRH neurons. These are just two of the possible ways in which the HPA-axis can regulate functions of the SAM-axis. Another example, previously mentioned, is through projections to the brain stem autonomic nuclei. It is in fact now known that CRH can produce all the physiological characteristics of the "fight-or flight" response, i.e., the typical SAM-axis stress response (20,31,53).

In addition to the CRH projections to the brain stem, clusters of CRH neuronal cell bodies can also be found in the brain stem (Figure 5.1 and Figure 5.7 on the next page). These neurons project to the intermediolateral column of the spinal cord grey matter where they, as mentioned before, influence the peripheral SAM-axis functions. This is accomplished by influencing the transfer of information to the preganglionic sympathetic fibres situated in the intermediolateral column of the spinal cord. Projections from the brain stem CRH neurons also go to the prefrontal cortex, i.e., the supramodal association

areas involved in higher cognitive functions such prolonged thought processes, the elaboration of thought, working memory and other higher cognitive functions, as well as to other cerebral association areas where CRH influences the processing of information and the perceptions. A third important area which receives projections from, and is influenced by CRH projections from the brain stem is the limbic system, especially areas such as the insular cortex - an area necessary for unimodal association involving somesthetic information, the cingulate cortex – an area also involved in unimodal associations, and the hippocampus – an area of great importance for long-term declarative memory (20,32).

The brain stem CRH influence on the behavioural functions are further extended by the stimulatory effect of CRH on the brain stem locus coeruleus neurons– the major group of central nervous system noradrenergic (CNA) neurons (see Chapter 3 for references). These neurons, as well as their functions and interactions with other neuronal systems of the brain were discussed in great detail in chapter 3. Some of the behavioural functions of the central noradrenergic system are summarised in Figure 5.7. It is shown that moderate controllable stress leads to adaptational changes in the brain, as well as to increases in adaptational plasticity of the noradrenergic system. Uncontrollable stress, in contrast will generally lead to negative effects on the brain and noradrenergic system.

In looking at the appropriate section of Figure 5.1, as reproduced on the next page as Figure 5.7, it should be clear that the brain stem CRH neurons and its projections can help to integrate and coordinate the behavioural functions, CNA/SAM-activity, and motor functions of the stress response.

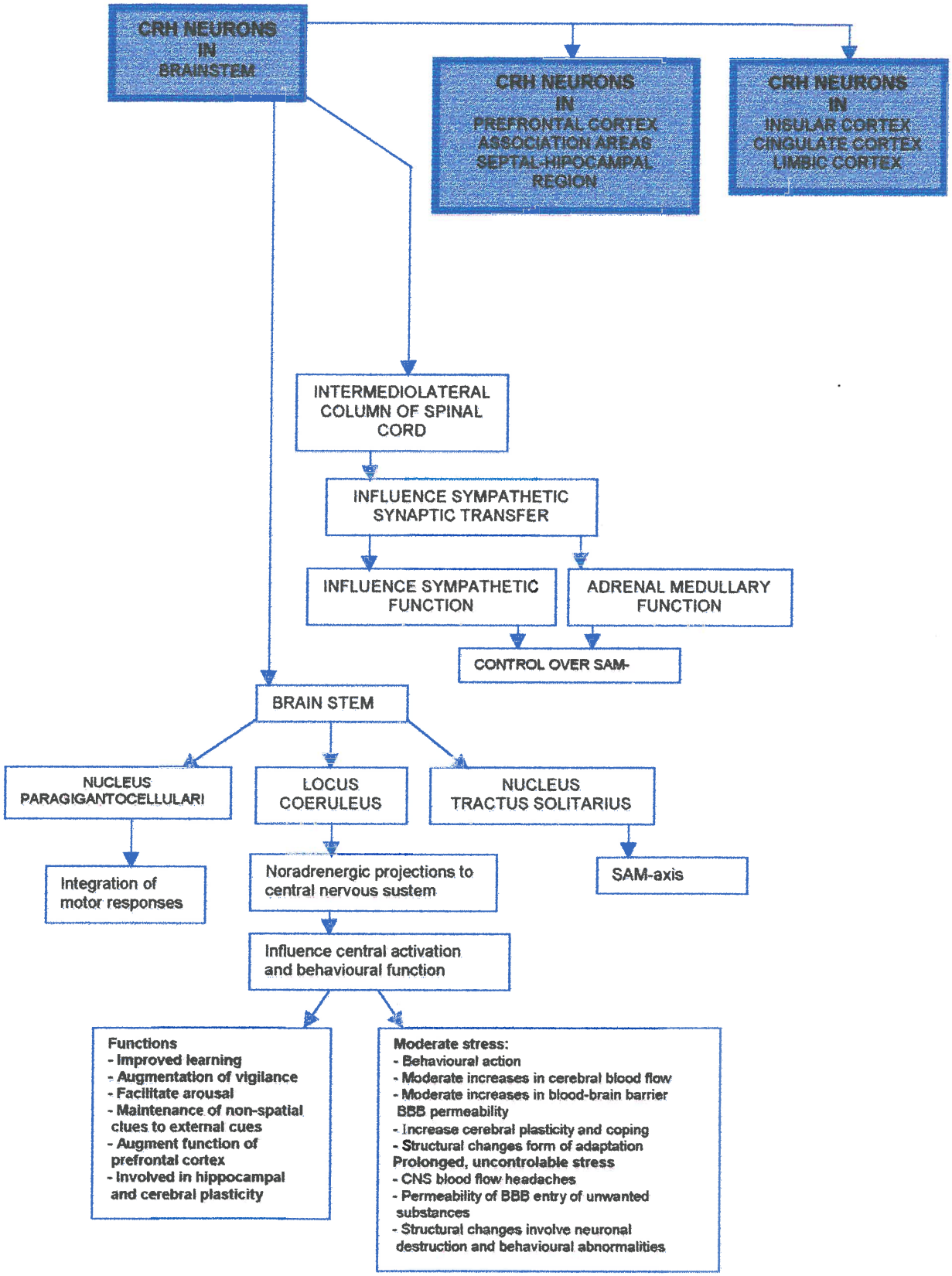


Figure 5.7: Distribution of CRH neurons in the brain stem and their projections

The major CRH neurons, with regard to the behavioural responses are found in the amygdala (54). These neurons are of great importance during the stress response where they play a role in the integration of autonomic, neuroendocrine, and behavioural responses to stress. The responses that occur upon stimulation of the amygdala are very similar to those seen upon central CRH injections. During conditions of emotional stress amygdalar CRH neurons are known to be stimulated to increase their CRH output and similar responses are seen in the amygdala upon central CRH injections (20,31,54). The appropriate part of Figure 5.1 showing amygdalar and other cerebral CRH nuclei is seen below as Figure 5.8. The discussion of Figure 5.8 follows on the next pages.

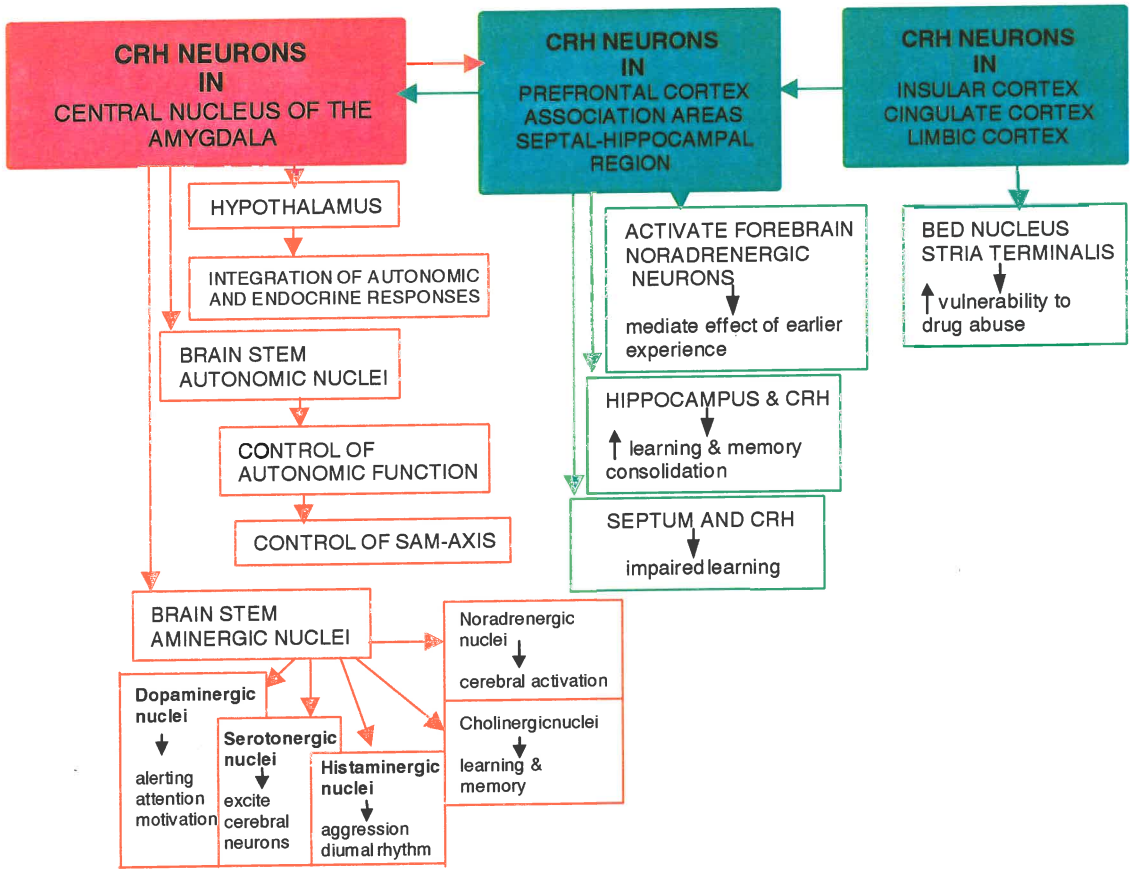


Figure 5.8: CRH neurons and their projections in the amygdala and other structures involved with emotional and cognitive processes

Upon stressor-induced stimulation of the amygdala impulses are sent, as previously mentioned, to the paraventricular nucleus of the hypothalamus to increase the number of neurons that secrete both CRH and ADH. This will strengthen the CRH-induced ACTH-stimulating effect with an increase in cortisol and cortisol-related functions as well as the CRH-induced behavioural effects. During the central stress response integrated information from the amygdala is also sent, as shown in Figure 5.8, to areas of the hypothalamus, brain stem autonomic nuclei, brain stem aminergic nuclei, cerebral association areas, and limbic system, to coordinate the stress response. The importance of the CRH neurons of the amygdala in the coordination of the stress response is that the amygdala receives integrated information from the prefrontal cortex and limbic system, areas of great importance for analysis of incoming information, for the elaboration of thought and the development of perceptions. Information from the amygdala is subsequently sent to the brain stem and hypothalamus. Impulses from the hypothalamus and autonomic nuclei of the brain stem control almost all peripheral aspects of the stress response, while impulses from the aminergic nuclei of the brain stem control the activation state of the cerebral cortex and underlie most mood states (20,31,54). The CRH projections from the central nucleus of the amygdala go to the bed nucleus of the stria terminalis, the lateral hypothalamus, the midbrain central grey, the raphe nuclei, the parabrachial region and the nucleus tractus solitarius. Amygdaloid CRH neurons that project directly to dopaminergic, noradenergic, cholinergic, histaminergic and serotonergic neurons of the brain stem (54) are of great importance in setting the mood and activation state of the cerebral cortex during the stress response. The behavioural functions of the aminergic nuclei were shown in Figure 3.6 of the chapter which dealt with the psychoneurological interaction in terms of the central noradrenergic system, i.e., Chapter 3. To stress the importance of these CRH connections from the amygdala, a structure strongly associated with emotion and implicit memory, and the brain stem aminergic nuclei, it is perhaps necessary to recap some of the major functions of the aminergic nuclei. These nuclei project back to the higher brain centra and serve as major neuroendocrine regulators (55) in that

- the nigrostriatal dopaminergic system, which amongst others responds to aversive, as well as to appetitive information, is involved in attention, motivation and in alerting the individual.
- the raphe nuclei or brain stem serotonergic system, that increases the excitability of its target neurons which may explain why the system is often associated with depression.
- the basal nucleus of Meynert or acetyl cholinergic system, which is strongly associated with learning and memory.
- the tuberomammillary nucleus or histaminergic system, known to act asymetrically with regard to the hemispheres, and which is implicated in aggressive behaviour, circadian rhythms and abnormalities such as catalepsy

It is highly likely that CRH fibres from the amygdala also innervate CRH neurons in most of the areas to which they project, and that the CRH neurons of these areas project back to the amygdala (54). The amygdala is thus part of a network of brain nuclei that forms the basis of the stress response and that are interconnected by CRH neuronal pathways (54).

Indications are that major functional differences exist between the CRH neurons of the amygdala and that of the paraventricular nucleus. The paraventricular nucleus CRH neurons are under negative feedback control of the glucocorticoids, while in the case of the amygdalar CRH neurons, as well as those of the lateral bed nucleus of the stria terminalis, this is not the case and the regulation of CRH gene expression can be dissociated from that of the paraventricular nucleus (56). The CRH neurons of the amygdala are thought to be involved with fear and anxiety and in a number of clinical syndromes such as melancholic depression, excessive shyness and fearfulness in children, the posttraumatic stress syndrome, anticipatory anxiety, and self-administration of psychotropic drugs (56).

The prefrontal cortex, the cingulate cortex, the insular cortex, and other association areas, as well as the limbic system, also contain clusters of CRH neuronal cell bodies - in

addition to the CRH projections received from the brain stem and amygdala. These neurons, in turn, project, amongst other to the central nucleus of the amygdala. The association between these areas and the amygdala are important in the formation of emotional responses and in the appraisal of external events and internal sensations. CRH projections between the central nucleus of the amygdala, the lateral nucleus of the amygdala, the septum, the bed nucleus of the stria terminalis and the hippocampus help to integrate their individual contributions to the central stress response (20,31). The CRH neurons also activate forebrain noradrenergic activity, a pathway involved in the effect of early life experiences on adult behaviour (57). Another interesting collaboration between cortical/limbic system structures and CRH is that the effect of CRH on hippocampal neurons which would appear to be the enhancement of learning and memory consolidation – this is apparently accomplished through CRH1 receptors (58). In contrast to the effect on the hippocampus, the effect of CRH on the septum is to impair learning. At very high concentrations CRH will not only impair learning, but would cause severe anxiety. These effects are mediated via CRH2 receptors (58). When excessive CRH is associated with the development of anxiety it generally occurs when acting in collaboration with amygdaloid structures. It is, however, likely that some minimal level of preconditioned fear must be present for CRH to exert its anxiogenic effect (59). CRH, and its effects on cerebral structures involved in cognition and emotion, are implicated in a variety of abnormal behaviours. An in depth discussion of this would, however, require a thorough knowledge of the various CRH receptor type and their functions.

The preceding paragraphs showed the distribution of CRH neurons and their projections throughout the central nervous system, as well as their integrative functions. The next section will deal with the central corticotropin-releasing hormone/hypothalamo-pituitary-adrenocortical axis and immunity.

5.2 The neuroimmunological interaction in terms of the CRH/HPA-axis. The central role of CRH in the neurohormonal control of immunity

The influence of the hypothalamo-pituitary-adrenocortical (HPA) axis on the immune system is generally accepted. The knowledge of most people does, however, begins and ends with the effects of the final effector hormones, i.e., the glucocorticosteroids, on immunity. Even with regard to the effects of the glucocorticosteroids there are many misapprehensions. The most obvious mistake made is to see these steroid hormones only as immunosuppressive while, at basal physiological concentrations, they are necessary for normal immunocompetence. Another mistake is to see the glucocorticoid hormones as the only immunologically active substances of the CRH/HPA-axis.

The integrated scheme of CRH in immunological context was presented at the beginning of the chapter as Figure 5.2. The hormones of the HPA-axis consist of the hypothalamic-derived corticotropin-releasing hormone (CRH), which stimulates the release of pro-opiomelanocortin (POMC) from the anterior pituitary and other nuclei. POMC contains several hormones within its structure. Among the more important of these are β-endorphin, MSH and the adrenocorticotropic hormone or ACTH. ACTH, in turn, stimulates the release of the glucocorticoids from the adrenal cortex – the major glucocorticosteroid hormone in man being cortisol (60). The physiological-anatomical relationship of the HPA-axis can be seen in Figure 5.9 – a subdivision of Figure 5.2.

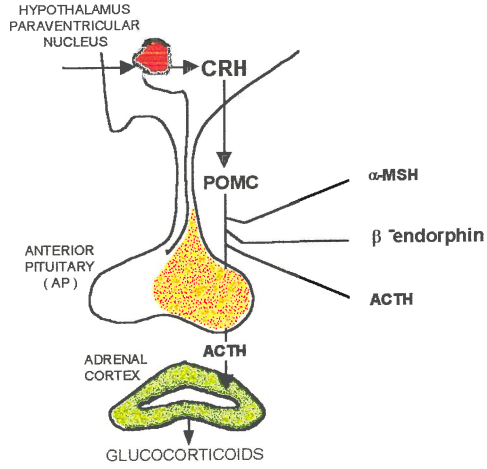


Figure 5.9: The CRH/HPA-axis

The aim of this section of the chapter is to demonstrate the influence of the CRH/HPA-axis on immunity, and more specifically the central neurohormonal role of CRH in immunological homeostasis. This was presented schematically in Figure 5.2. Before discussing this a few facts should be noted. The concept that the major stress axes, and in this case the CRH/HPA-axis, are generally immunosuppressive is, as was previously mentioned, evolutionary unsound and derived from experiments in which the effects of pharmacological dosages of steroids were tested and where synthetic steroids such as dexamethasone, rather than cortisol, were used. Cortisol has, in fact, immune-enhancing as well as immunosuppressive effects. It is, however, also important to remember that cortisol is just one of the CRH/HPA-axis hormones and that the ultimate influence of the CRH/HPA-axis is a function of the immunological effects of the total spectrum of hormones of the axis.

CRH is the first hormone of the cascade and as such the main regulator of the secretion of all other hormones of the CRH/HPA-axis, including the POMC-derived β-endorphin, MSH and the adrenocorticotropic hormone or ACTH, as well as the adrenocortex-derived cortisol. CRH, as well as the hormones derived from the mother compound POMC, are immunological active in their own right. CRH, the first hormone of the HPA-axis, can, as seen in the first section, underlie the total central stress response, i.e., it has a regulatory influence on virtually all neurohormonal factors that form part of the response. Neurohormonal substances that form part of the central stress response include the gonadotropins, thyroid hormones, noradrenaline, serotonin, acetyl choline, dopamine, β-endorphins, and other opioids, growth hormone, insulin, and others. All of these substances have immunological effects (61,62). Thus, as major regulator of the central stress response, including the activity of the CNA/SAM-axis and the CRH/HPA-axis, CRH can influence the immune system

- directly, through what appears to be mainly its pro-inflammatory actions
- indirectly, by changing the activity-level of the hormones of the HPA-axis
- indirectly, by its control over the SAM-axis. (Chapter 4 dealt exclusively with SAM-axis immune function.)

- indirectly, due to its control over a wide spectrum of neurohormonal factors that form part of the central stress response – each of them known to have immune-related effects.

It is therefore warranted to ascribe a central role to CRH in the immunological adaptation of the stress response.

The previous paragraph summarised the central role of CRH in the neurohormonal control of the immune system. In the following paragraphs the roles of the individual neurohormonal factors mentioned are briefly touched upon. This is done merely to substantiate the claim made that CRH fulfills a central role in stress-induced neuroendocrine regulation of immune function.

5.2.1 Cortisol as immunological regulator

As cortisol is generally seen as the major, and by some less informed individuals, as the only, immunologically active substance of the HPA-axis, it will be the first hormone to be addressed. Cortisol is well known for its immunosuppressive effects and is often assumed to be only immunosuppressive. The reason why cortisol is, in an immunological sense, the best known hormone of the HPA-axis is that it belongs to a class of steroids often used, in pharmacological dosages, for immune suppression after organ transplantation and in chronic inflammatory conditions such as rheumatoid arthritis. This idea of cortisol being only immune suppressive is again one of the major misconceptions about the HPA-axis and its effects on immune function – a misconception that can have seriously deleterious effects in its therapeutic applications. Cortisol is, in fact, necessary for normal immunocompetence and it is would appear to be immune suppressive mainly at pharmacological levels and at the levels seen in chronic aversive stress situations. Several good reviews on the immune modulating (63,64) and immunoenhancing (65) influences of cortisol can be found and this will not be discussed here in any great detail.

The overall effects of cortisol (glucocorticoids) were presented in Figure 5.1 and the relevant section of Figure 5.2 is presented below as Figure 5.10.

GLUCOCORTICOIDS

Immunological effects of glucocorticoids (cortisol)

Primary lymphoid tissue

Role in thymic cell development, T-cell selection, apoptosis of cells in thymus (2).

Secondary lymphoid tissue

Role in splenic T-cell selection – peripheral T-cell selection through clonal depletion and expansion (2). Necessary for initial antigen-specific response (2) in secondary lymphoid tissue.

Total in vivo immune response

Generally anti-inflammatory at pharmacological levels – immune modulatory at physiological levels. Biphasic response – dose-dependent and exposure time-dependent. May be a prerequisite for the coordinated immune response (5).
Plays a role in maintaining the appropriate balance between the effectors and inhibitors of apoptosis of cells (12).
Basal physiological and low acute stress levels, in a time-, dosage- and cytokine-dependent manner, can enhance almost all aspects of immune function (normal regulation).
During infections: Excessive pro-inflammatory cytokine production will stimulate HPA-axis to increase cortisol release to immune inhibitory levels (protection of body against infection, systemic inflammatory response, self-damage and autoimmune processes).
Pharmacological dosages: Generally immune suppressive, with a shift from pro-inflammatory to anti-inflammatory cytokine production. Allergic reactions to corticosteroids may develop (14).

Mechanisms

Acute stress: Increased circulating neutrophils; decreased circulating lymphocytes (Th, Tc, B-cells, NKCs,) and monocytes. Represent redistribution of leukocytes rather than destruction (17).
Long acute to chronic stress: Decreased total leukocyte numbers. Modulation of immunological effects (differentiation, proliferation, inflammatory and immune responses) of peptide hormones, metalloproteinases and cytokines by interfering with the activity of other transcription factors such as CREB, AP-1 and NKκB (3). Inhibits antigen presentation by macrophages, as well as their production of IL-1, IL-2, IL-6, IFNγ (18).
Arrests lymphocyte proliferation in stage G0 and G1 (18).
Suppresses the differentiation of monocytes to macrophages (18).
Important role in Th1/Th2 response: Favours the shift to a Th2 cytokine response (autoimmunity linked to Th-1 responses; allergy and asthma linked linked to Th-2 responses) (2).
Upregulation of certain cytokine receptors and enhancement of related responses (2).
Induction of acute phase responses – including behaviour (2).
Stimulatory effect on B-cell responses (Th-2 responses) (2).
The type 1 GC receptor/cortisol complex acts as functional antagonist of the type 2 receptor which means that cortisol can have opposing effects (20).
The affinity of GC receptors are determined by genetic polymorphism, associations with immunophilins, and by various cytokines (20).

Immunological effects of glucocorticoids (cortisol) - continued

In inflammation

Inhibits the immediate inflammatory response to injury by suppression of vascular leakage (6). Many of the anti-inflammatory effects are mediated through a combination of the up-regulation of anti-inflammatory mediators and the down-regulation of pro-inflammatory mediators. Binds to GRE on glucocorticoid responsive genes and increases the transcription of genes coding for anti-inflammatory proteins (lipocortin-1, IL-10, IL-1receptor antagonist and neutral peptidases) (7).
Inhibits the expression of multiple inflammatory genes (pro-inflammatory cytokines, enzymes, receptors, adhesion molecules) through direct inhibitory interaction between activated GC receptors and activated transcription factors (7).
Can suppress gene expression in immune-related substances by changing chromatin structure (7).
Stimulates lipocortin-1 that in turn inhibits phospholipase A2 activity with a resultant decrease in the production of inflammatory mediators such as prostaglandins and leukotrienes (18).
Stimulates the secretion of neutrophil-derived lipocortin-1which inhibits extravasation in response to chemotactic stimuli (9).
Decreases the expression of the gene that codes for cyclo-oxygenase 2, thus further suppresses the production of inflammatory prostaglandins (18).
Controls local inflammation through lipocortin-induced detachment of neutrophils from post-capillary venules (4). Inhibits the gene that encodes for nitric oxide synthase (18).
Stabilises lysosomal membranes, thus reducing local release of proteolytic enzymes and hyaluronidase (18).
Inhibits the differentiation and proliferation of mast cells (18). Suppresses the proliferation of fibroblasts, as well as their synthesis and deposition of fibrils (18). Not only does GC regulate cytokine secretion, but cytokines modulate the function and expression of GC receptors (13).
Mediates the production of thymosin-β-sulfoxide by monocytes that inhibits neutrophil chemotaxis, lowers neutrophil adhesion to endothelial cells and causes neutrophil dispersion (10).
Mediates expression of adhesion molecules (glucocorticoid-induced adhesion match) through stimulation of the production of cytokines and lipocortins that control adhesion molecule expression (18).

Figure 5.10: The role of cortisol in the neurohormonal control of immunity

A number of immunological effects of stress-induced cortisol secretion should be mentioned as these facts are of importance for any individual who attempts to understand the influence of the psychological disposition on the immune system. This is especially important as acute and chronic emotional stress may have direct opposite influences on the immune system. It should, however, be remembered that the *in vivo* effects are often a reflection of the combined action of both major stress axes – a fact that is perhaps of lesser importance as the SAM-axis is under strong CRH influence, as was discussed in the first section of this chapter.

The first aspect to be addressed is the significant decrease in numbers of almost all circulating leucocytes with acute stressor application. This was previously seen as immune suppressive. It is, however, now realised that it merely represent a functional redistribution of these cells from the circulation to organs such as lymphoid tissues, mucosal sites and the skin. This is, in other words, an adaptative mechanism of physiological significance where immunocompetent cells are directed to areas of defense and immunosurveillance. Upon the disappearance of the acute stressor these cells return to the circulation and it is mostly only with chronic stress, where the glucocorticosteroid levels remain above basal levels for a significant amount of time, that glucocorticosteroid-induced apoptosis with an absolute reduction in cell numbers will occur (66). Research on these aspects has even solved the riddle of how these cells are transiently removed from the circulation and sequestered in distant organs and structures through the expression of cytokine-induced expression of adherence molecules. This aspect would, however not further be addressed here. In addition to cellular redistribution, the immuno-enhancement of innate immune functions has further been verified by reports of the glucocorticoid's ability to increase the expression of pro-infammatory cytokines (IL-6, TNF, IL-6, MIF) receptors, the induction of acute phase proteins, serum amyloid A-3 mRNA levels, certain complement fractions and a decrease in the endogenous IL-1 receptor antagonist. A link between the effect of cortisol on acute phase proteins and psychological conditions such as depression has also been shown by several groups (67), but would be addressed at a later stage.

The second aspect to be mentioned is the immune-enhancing effect of cortisol on both cellular and humoral immune function by acute stress-induced activity of the HPA-axis. In addition to the functional cellular redistribution during acute stress it is now becoming evident that many immune functions are enhanced by acute stressors, including delayed type skin hypersensitivity reactions, the primary and at times even the secondary immune responses, mitogen and anti-T cell receptor-induced proliferation of splenocytes, as well as secretion of nitric oxide, IL-1β and TNF-α (68). A very clear indication that the glucocorticoids could be immune enhancing is the fact that low levels of cortisol is necessary for antibody production in *in vitro* cell cultures, and that the variability of the cortisol concentration in different batches of serum may give rise to *in vitro* variability in antibody production (69). One of the more interesting effects of glucocorticoids on the enhancement of immune function is its synergistic action with cytokines. These effects would not be described here but it is of importance to remember when, at a later stage the behavioural-cytokine interaction is discussed as both cortisol and cytokines have several behavioural effects.

The immune-enhancing effects of the glucocorticoids are probably best illustrated by practical examples such as the fact that administration of physiological dosages of glucorticoids reduces the number of respiratory infection in patients with adrenocortical insufficiency, reduces the symptoms of respiratory illness when introduced at the onset of the disease, increases the resistance to influenza virus, can be effective in cases of mononucleosis and can sometimes exacerbate inflammatory responses (67). The functional implications of the stress-induced enhancement of immunoreactivity could obviously also include beneficial effects in conditions such as cancer and infection. However, it could have seriously deleterious effects during autoimmune and chronic inflammatory conditions. A typical case of the latter is the negative effects of day-to-day acute stressors on rheumatoid arthritis (70), and on the onset and exarcerbation of psoriasis and perhaps in multiple sclerosis (71).

In contrast to the just mentioned immune-enhancing effects, the immunosuppressive effects of glucocorticoids are much better known – mainly because glucocorticoid

hormones are, in pharmacological dosages, widely used as immunosuppressive agents. The immunosuppressive effects of pharmacological administered glucocorticoids are widely reviewed and described in textbooks. Some of the effects include suppression of the synthesis or secretion of immunoglobulins, prostaglandins, leukotriens, histamine, cytokines, reactive oxygen species, as well as suppression of almost all macrophage functions, mitogen and antigen lymphocyte proliferation, NK cell activity and leukocyte migration and activation (67). Perhaps of more importance is the fact that variations in the physiological levels, specially increases above the normal physiological levels, can also have immune suppressive effects. These changes in physiological levels of endogenous glucocorticoids usually have protective effects such as a) the containment of ongoing immune responses to prevent tissue damage (72), b) helping to control the inflammatory response in order to prevent development of the systemic inflammatory response or even septic shock (the latter function mediated through the inhibition of toxin-induced increases in the production of pro-inflammatory cytokines such as IL-1 and TNF, and the inhibition of the production of eicosanoids and other inflammatory substances (67), and c) the prevention of autoimmune disease. Hypoactivity of the HPA-axis has, in fact, in the past been seen as a predictor of the development of certain autoimmune disorders (73). This protective effect against the development of autoimmune disease is mediated partially by shifting the immune response to a Th2 cytokine reponse. Of interest is the fact that individuals with a strong HPA-axis response to environmental stressors may be more resistant to the development of autoimmune disorders and there are suggestions that these individuals may perhaps be more susceptible to infections or the development of cancer. Cancer-associated personality types have been described in Chapter 2. The fact that chronic stress-induced hyperactivation of the immune system would lead to immune suppression and can be deleterious to health is indisputable. The reason why it could increase the susceptibility to infections and cancer but ameliorate autoimmune disorders and chronic inflammatory conditions is self-evident. Several good reviews on the immune suppressive effects of chronic stress are available (74,75,76).

From a psychological point of view it is important to mention that cortisol influences the type of cytokines to be produced by immune and other cells. This will not only determine the direction of the immune response but will also largely be responsible for the type of immunologically-induced behavioural adaptations of the stress response. The effect of immune-derived cytokines on behaviour will be addressed in Chapter 6. Suffice at this stage to say that cortisol favours the production of Th2 cell cytokines such as IL-4, IL-5, IL-10 and IL-13 and tends to suppress Th1 associated cytokines (76).

Many paradoxical reports and observations still exist with regard to the interaction between psychologically stress-induced glucocorticoid secretion and the immune system. A reasonable model of this interaction has been proposed by Dhabhar and McEwen (67). An adaptation of this model is seen in Figure 5.3, as presented at the beginning of the chapter. In looking at Figure 5.3 it is important to understand the difference between the effects of periods of chronic and of acute stress on the immune system. The reason is that it may very well explain the paradoxical immune-related differences in behavioural and psychosomatic symptoms seen during conditions of aversive emotional experiences.

5.2.2 Other hormones of the HPA-axis as immune regulators

CRH stimulates the release of POMC from the anterior pituitary and arcuate nucleus. Within POMC are contained several immunoregulatory hormones which, when released from the mother molecule through proteolytic processes, can exert immunological effects. The more important of these are ACTH, β-endorphin and α-melanocyte stimulating hormone. Some effects can be seen in Figure 5.1. Suffice to say that ACTH can exert both inhibitory and stimulatory influences and that, β-endorphin and α-melanocyte stimulating hormone are at present generally seen to be immune suppressive.

The relevant part of Figure 5.2, is reproduced here as Figure 5.11 in order to show some of the immunological effects of the hormones just mentioned.

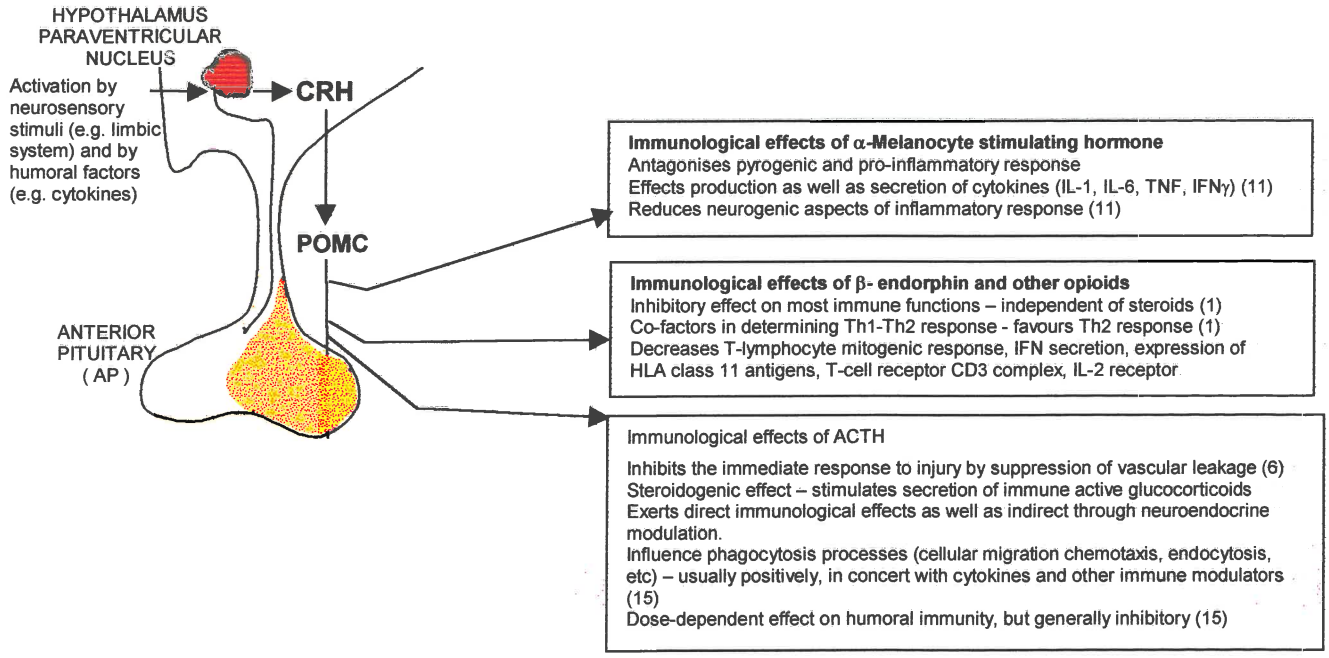


Figure 5.11: Immunological effects of other POMC-derived hormones of the HPA-axis

5.2.3 Corticotropin-releasing hormone (CRH) as direct immunoregulator

As already mentioned, CRH can influence the immune system through its regulatory influence on the HPA-axis, especially cortisol, as well as by controlling the total central neurohormonal stress response – including the CNA/SAM-axis. However, CRH has, in itself, immunoregulatory properties. These effects would in general appear to be pro-inflammatory. Nervous system derived CRH secretion is stimulated by stress-induced limbic system and other neurosecretory signals, and by humoral factors such as TNFα, IL-1 and IL-6. CRH can however, also be secreted by immunocompetent cells. Whether of neurosecretory origin or derived from immune cells involved in the inflammatory process, CRH can act as direct immunomodulatory autocrine or paracrine mediator of inflammation. It has, in fact been shown that immune cell hypersecretion of CRH may play a role in human autoimmune inflammatory diseases such as rheumatoid arthritis and

Hashimoto thyroiditis (77). These conditions of disturbed immunological homeostasis are known to be accompanied by behavioural alterations.

Some pro-inflammatory actions of CRH were shown in Figure 5.2 and for convenience sake reproduced below in Figure 5.12.

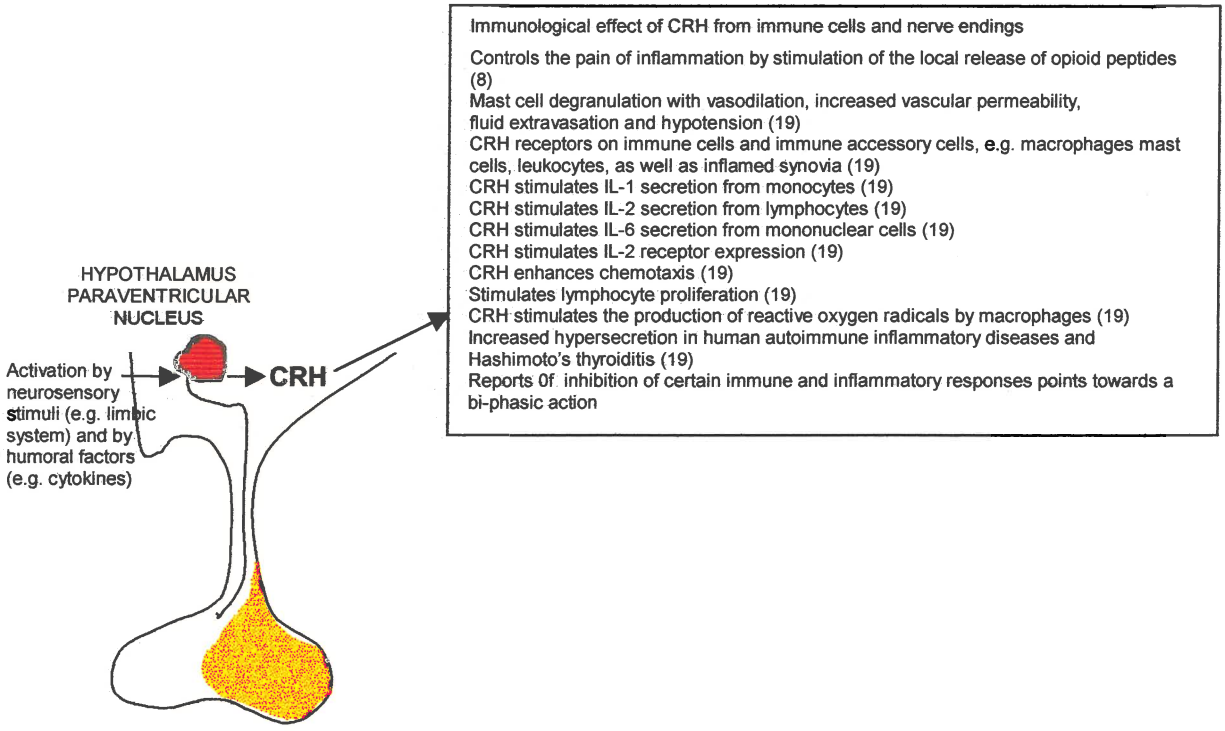


Figure 5.12: The pro-inflammatory effects of CRH

It is suggested that CRH, released from peripheral nerves, participate in an axon reflex loop with immune cells where the secreted CRH would stimulate the immune cells and immune accessory cells to initiate the immune response. This process has been implicated in stress-induced diseases such as asthma and eczema, as well as in the development of stress-induced migraine (77).

Immune cell-derived CRH is of importance in the initiation, propagation and regulation of inflammatory responses by enhancing pro-inflammatory actions such as vasodilation, increased vascular permeability, mast cell degranulation and increased chemotaxis, and by stimulating lymphocyte proliferation, pro-inflammatory cytokine secretion and

cytokine receptor expression (77). The paracrine pro-inflammatory actions of immune cell-derived CRH are mediated mainly through CRH-1 and CRH-2 receptors on neighbouring immune cells. A good review by De Souza is available on CRH receptors, their physiology, pharmacology, biochemistry and role in the immune system, as well as in the central nervous system (78). In view of the indications of a role for the inflammatory process in certain mental disorders referred to in Chapter 2, the wide distribution of CRH neurons within cerebral structures involved in the behavioural processes (referred to in section 1 of this chapter) and the pro-inflammatory role of CRH in immune regulation, it is tempting to speculate about a role for the CRH pro-inflammatory function in mental disturbances.

5.2.4 Indirect effects of CRH on immune regulation through its regulatory effects on neurohormonal substances which form part of the central stress response

As was be seen in the first section of this chapter, CRH is the main integrator and regulator of the stress response and, as such, exerts a major influence on the secretion of most neurohormonal substances. Most of these neurohormonal factors are able to influence the immune system and several of them are, in fact, also secreted by immunocompetent cells. Neurohormonal substances, involved in the stress response, of which the secretion are, to a greater or lesser degree, influenced by CRH, include noradrenaline, adrenaline, dopamine, serotonin, acetyl choline, histamine, thyroid hormones, growth hormone, prolactin, gonadotrophins and most other steroid hormones, endorphins, enkephalins, antidiuretic hormone, oxytocin, insulin, glucagon and a host other neurohormonal factors. All of these substances have immunomodulating functions – some immune-enhancing and other immunosuppressive – that act in concert to orchestrate the behavioural influences on immunity. The regulatory influence of CRH on these factors and their effects on the immune system will not be discussed here, but can freely be found in literature (61,79,80,81).

From a psychological point of view it is important to mention the stress spectrum hypothesis of Dhabhar and McEwen (82). The stress spectrum hypothesis states that one section of the stress spectrum is characterized by eustress, i.e., acute short duration stress

or controllable stress that would most probably result in immunopreparatory or immunoenhancing effects. This section of the stress spectrum is marked by a quick physiological stress system activation in the presence of the stressor, followed by a quick termination of the stress response once the stressor is removed. The opposite end of the stress spectrum is characterized by distress, i.e., chronic repeated or physiologically exhausting stress. This could very well be equated with uncontrollable stress and would generally lead to immune suppression. Distress is generally characterized by either persistence of the physiological stress response long after the stressor had been removed or by repeated activation of the stress response – sometimes without returning of the physiological mechanisms of the stress response to baseline values. This condition of repeated or continuous exposure to high activation of the physiological stress response, with its concomitant wear and tear on the psychophysiology, is often referred to as the allostatic load (83), and generally results in immune suppression. A third section of the stress spectrum, i.e., resilience, falls between the eustress and distress sections and is defined as the ability of the person to cope and survive for extended periods of time under conditions of increasing stress. This must surely be dependent on the coping skills of the individual and on his perception of controllability or uncontrollability of the situation. In this third section of the stress spectrum it is feasible to suspect immune function to be a product of the balance between all stress hormones – with CRH as main determinant.

Section 5.1 and Figure 5.1 demonstrated the distribution and central integrating role of CRH neurons and their projections in the nervous system. In section 5.2, Figure 5.2 and Figure 5.3, the central role of CRH in the neurohormonal control of the immune system was briefly illustrated. In these two sections it was seen that CRH performs a central role in psychoneuroimmunology in terms of the CRH/HPA-axis. Figure 5.4 (p5.11) presents an outline of this central role.

The next section will argue that *psychoneuroimmunology in terms of the two main stress axes* can, in fact, be translated into *psychoneuroimmunology in terms of CRH*.

5.3 Psychoneuroimmunology in terms of the two main stress axes.

5.3.1 The central role of corticotropin-releasing hormone.

This section, in integrating the information from sections one and two, argues that CRH does not only play a central role in the psychoneuroimmunological interactions of the CRH/HPA-axis, but also in that of the CNA/SAM-axis. The section therefore illustrates the central role of CRH in psychoneuroimmunology in terms of the two major stress axes. It requires very little explanatory text as the descriptions and references with regard to the CRH/HPA-axis were provided in the previous sections and that of the CNA/SAM-axis in Chapters 3 and 4. Figure 5.13 presents the concept in a simple diagram.

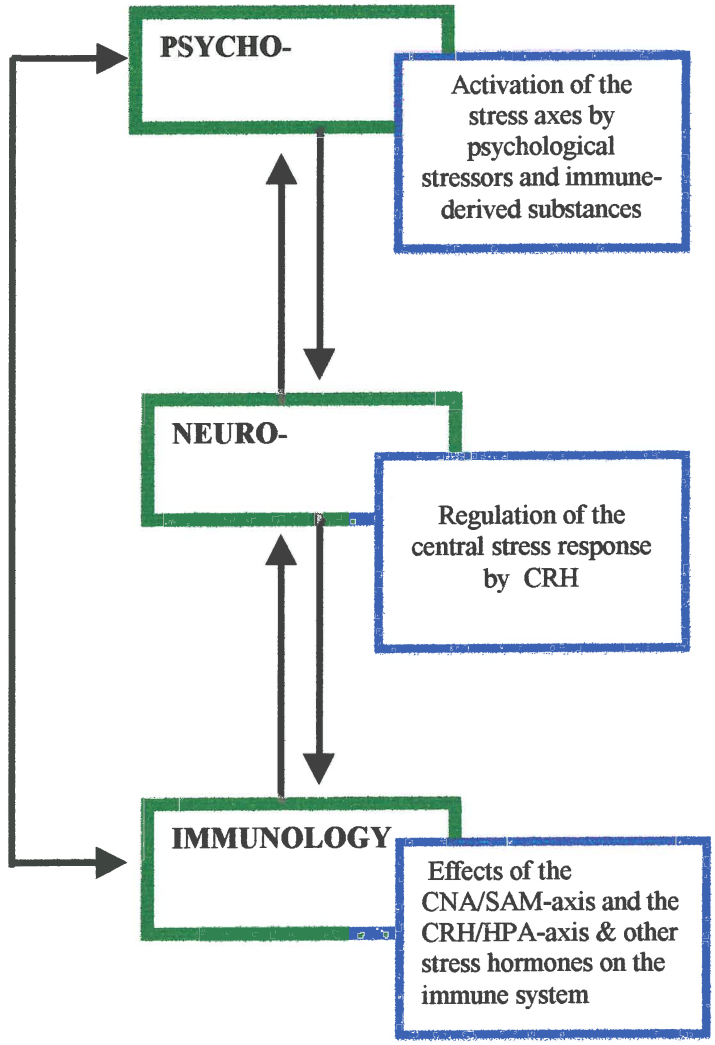


Figure 5.13 A heuristic diagram of psychoneuroimmunology in terms of the two main stress axes

An integrated full scale model with details CRH is presented as Figure 5.15 on page .

In order to see CRH as the central factor in the psychoneuroimmunological interactions of the two main stress axes it must be able to influence both the central nervous system (CNS) and peripheral functions of the two main stress axes. The question whether CRH can influence the central noradrenergic (CNA) system, or not, has already been answered in Chapter 3 where a reverberating positive feedback cycle was shown to operate between the CRH neurons and the (CNA) neurons. In addition, if CRH can influence the behavioural functions of the CNA system there should be some kind of correspondence between the behavioural effects of noradrenaline and CRH. The CNS noradrenergic functions and psychopathology associated with abnormal CNA activity were described in Chapter 3. Some of the functions and effects of the CRH system are touched upon in the next couple of paragraphs in order to show the correspondence.

5.3.2 Neurobehavioural effects of CRH

The neurobehavioural effects of CRH are summarized in Figure 5.14, and expanded on in

Behavioural functions and effects of CRH

- Most important is the regulation and integration of neuroendocrine, autonomic, immunological and behavioural aspects, especially during the stress response.
- As a result of the above, a regulatory function in almost all physiological and psychological processes.
- Acute, moderate increases in CRH generally leads to adaptational responses to stressors (increased alertness, controlled emotional and cognitive activation, decreased reflex time, moderare decreases in appetite and libido).
- Very high or chronic increases have negative physiological and psychological effects (anxiety and anxiety-related disorders, negative cognitive and emotional states, hyperresponsitivity to sensory stimuli, anorexia nervosa and sexual impotence).
- Pharmacological levels result in:
    - o Suppression of exploratory behaviour in strange environments
    - o Increased activity in familiar environment
    - o Decreased operant conflict reponses
    - o Changes in memory and learning
    - o Place and taste aversion
    - o Behavioural sensitization
    - o Enhanced stress-induced freezing
    - o Induction of seizures at very high levels
    - o Facilitation of acoustic startle
    - o Induction of conditioned fear
- Several mental disorders are known to be accompanied by high CRH (certain affective disorders, anorexia nervosa, obsessive-compulsive disorder, vulnerability to chronic drug abuse, the PMS syndrome), as well as by low CRH levels (seasonal depression, chronic fatigue syndrome, fibromyalgia, post traumatic stress syndrome).

Figure 5.14: The behavioural effects of central nervous system CRH

the pages to follow.

Corticotropin-releasing factor plays a role in a wide variety of behavioural and other functions, including sleep, arousal, motor function, feeding, reproduction, immunology, circadian rhythmicity, metabolism, as well as coping and learning behaviour (84,85,86). The CNA system was seen to be involved in all of the above (Chapter 3).

Stress-induced behavioural effects of CRH, as gleaned from the effects of the administration CRH agonists (87) further include

- Suppression of exploration of strange environments
- Increases in activity in familiar environments
- Decreased operant conflict responding
- Changes in learning and memory retrieval
- Place and taste aversion
- Behavioural sensitisation
- Enhanced stress-induced freezing
- Seizure inducement at very high dosages
- Facilitation of acoustic startle
- Induction of conditioned fear
- Suppressed sexual behaviour
- Suppressed feeding behaviour
- Increased grooming

Most of the above has been verified by attenuation of similar stress-induced behaviour by CRH antagonists. Many similar effects have been recorded with stress-induced increases in CNA/SAM-axis activity (Chapter 3).

It is important to remember that acute and moderate increases in CRH generally facilitate adaptation to adverse conditions, while chronic or very high acute levels of CRH have negative psychological, as well as physiological effects. Moderate increases in central nervous system CRH activity lead to increased alertness, controlled cognitive and

emotional activation, a decrease in reflex time, a moderate decrease in appetite and a decreased libido. However, with prolonged, high CRH activity the alertness will turn to anxiety and may even result in anxiety-related disorders, the cognitive and emotional activation turning into negative emotional states, the decreased reflex times being exacerbated to hyperresponsivity to sensory stimuli, the decreased appetite becoming anorexia nervosa and the suppressed libido sexual impotence (39,81). Similar biphasic effects are seen with activation of the central noradrenergic system (Chapter 3).

High CRH levels have been reported in several mental disorders including melancholic depression (88) anorexia nervosa (89), panic disorder, obsessive compulsive disorders, chronic alcoholism and alcohol withdrawal symptoms (90,91), exercise dependence, malnutrition and the PMS syndrome (39,81). It is also said to play a role in the vulnerability to addictions such as cocaine dependence (92). In contrast, subnormal levels are reported for conditions such as seasonal depression, chronic fatigue syndrome (93) posttraumatic stress syndrome and nicotine withdrawal (39,94). The mental disturbances associated with CNA abnormalities were recorded in Table 3.3 where high CNA activity was seen to be found in melancholic depression, eating disorders, obsessive-compulsive disorders, panic disorder, alcohol dependence, aggression, and others. Clear evidence exists that variations in basal CRH levels and CRH receptor density are associated with differences in stress adaptation (95). It is also clear that the stress pathology associated with either hyper- or hyposecretion of CRH can only be properly understood when the type of CRH receptor, the distribution as well as the density of these receptors are taken into consideration as receptor alterations are often the basis of changes in stress vulnerability and may predispose to mental disorders (95).

The most important function of CRH, and probably the one that forms the basis of most of its behavioural, as well as physical effects is the fact that CRH constitutes the principal neuropeptide in the regulation of the stress response (20,88). As can be seen in the middle section of the final integrated scheme at the end of the chapter (Figure 5.15), CRH neurons not only coordinate the central behavioural, but also the autonomic, endocrine, and motor function stress responses (84). It would, however, appear that different groups

of CRH neurons constitute the major mediators in the peripheral as opposed to the central behavioural stress response, with the PVN CRH neurons predominantly involved in controlling the peripheral, and the amygdalar CRH neurons in the behavioural responses. The amygdala is, however, important for the integration of these two modalities of the stress response as it sends information to both the brain stem and the hypothalamus. The brain stem, which receives processed information from the amygdala, also plays an important dual role as it is involved in the regulation of the peripheral SAM-axis, as well as in the regulation of the cerebral activation state and development of emotions by the brain. The CRH neurons of the brain stem are in a bidirectional communication with that of the amygdala and can in this way modulate the peripheral as well as behavioural stress effects. (20,31).The hypothalamus, in receiving information from the amygdala coordinates the autonomic and endocrine responses and by implication also the cortisol-associated behavioural functions. CRH, therefore, is indirectly in control of the behavioural effects of cortisol.

Most of the behavioural changes seen in association with abnormal CRH levels are mediated in conjunction with the effects of the central noradrenergic system, the glucocorticoids and the amygdala. However, CRH neurons in the hippocampus (explicit memory retrieval), the prefrontal cortex (important for fully formed concepts of awareness and elaboration of thoughts), as well as in other association and cortical areas, that help to do appraisals, to form perceptions and to weigh such perceptions up against sources of coping, are important for delivering pre-analysed, context-related information to the amygdala. The amygdala is known to a) receive information from virtually all neocortical sites (including highly processed information from the prefrontal cortex), b) to give meaning to processed information by analysing it against the backdrop of previous experiences, and c) to be the major structure involved in implicit memory. It is therefore an ideal structure for such involvement in the behavioural functions. As previously mentioned, the amygdala forms part of a network of brain nuclei interconnected by CRH neurons. The amygdala, being the origin of the major CRH projections throughout the emotional brain, sends CRH axons to the bed nucleus of the stria terminalis, the hypothalamus, the midbrain central grey, the autonomic nuclei of the

brain stem and to the aminergic nuclei of the brain stem – all structures intimately involved with behavioural and autonomic functions (20,31,54,87). A very important interaction between the CRH, the amygdala and the glucocorticoids is seen in the development of anticipatory anxiety (96). The amygdala is known to be involved in the anticipation of fearful and anxiety-producing events. It is, in fact, said that the activation of amygdaloid CRH mRNA by glucocorticoids may be responsible for the conditioned chronic expectation of negative events, and perhaps also in chronic arousal pathology (96). It has to be remembered that the amygdala, in contrast to the PVN, increases its CRH output when stimulated by cortisol (20). The implications of the development of anticipatory angst and chronic arousal in the young speaks for itself with regard to future adult mental and physical health. The importance of the CNA system in fear and anxiety-related disorders was dealt with in Table 3.2 and elsewhere in Chapter 3.

5.3.3 In conclusion

The ubiquitous distribution of CRH neurons and projections throughout the central nervous system enables the CRH system to influence and control a wide variety of functions. This makes it an ideal substance to be involved in psychoneuroimmunological integration. Its pervasive influence on the behavioural functions can probably be ascribed to the fact that CRH neurons and projections are present in all central nervous system areas involved in cognitive and emotive functions. In addition, CRH can directly as well as indirectly control immunological activity. Indirect effects include CRH's regulatory influence over other immunocompetent neurohormonal factors such as ACTH, β-endorphin, α-MSH, cortisol, as well as over hormones of the stress response. The fact that CRH from the paraventricular nucleus is in control of the HPA-axis is a well-known fact. However, CRH neurons from other brain centers such as the amygdala may also exert an influence on the HPA-axis. CRH would, however, also appear to be in control of the other stress axis, i.e., the CNA/SAM-axis. There can be no doubt that the CNA functions are strongly dependent on CRH activity. The most important pathway of the CRH control over central noradrenergic function is probably mediated via CRH projections from the central nucleus of the amygdala to the brain stem noradrenergic nuclei. With regard to the argument that the peripheral part of the CNA/SAM-axis, i.e.,

the sympathoadrenomedullary system is to a large extent under control of CRH, there can also be no doubt. In section two of this chapter it was shown that the activity of the SAM-axis is controlled by CRH neurons, not only at the level of the brain stem, but also at the level of the intermediolateral column of the spinal cord, the hypothalamus and the amygdala. (20,31). Some post-ganglionic sympathetic nervous system fibres have even been shown to be CRH-secreting fibres. The control of CRH over the SAM-axis was diagrammatically shown in Figure 5.1 and is incorporated into the final scheme of psychoneuroimmunology in terms of the major stress axes (Figure 5.15). In view of the central role of CRH in the control of the HPA-axis and in that of the CNA/SAM-axis it can by right be said that *psychoneuroimmunology in terms of the two major stress axes* can be equated with *psychoneuroimmunology in terms of CRH.*

In line with the title of the thesis the final full-scale version of *psychoneuroimmunology in terms of the two main stress axes* can be seen on the following page (Figure 5.15).

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Behavioural functions and effects of CRH

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  - Place and taste aversion
  - Behavioural sensitization
  - Enhanced stress-induced freezing
  - Induction of seizures- very high levels
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  - Induction of conditioned fear
- Several mental disorders are known to be accompanied by high CRH (certain affective disorders, anorexia nervosa, obsessive-compulsive disorder, vulnerability to chronic drug abuse, the PMS syndrome), as well as by low CRH levels (seasonal depression, chronic fatigue syndrome, fibromyalgia, post traumatic stress syndrome)

ENVIRONMENTAL EVENT
APPRAISAL
Cognitively planned or conditioned
IGNORE
PERCEPTION
Non-threatening/ irrelevant
PRIMARY APPRAISALS
Believes & commitments
PERCEPTION
Threat or challenge
SECONDARY APPRAISALS
Resources, options, controllability
ACTIVATION OF CENTRAL STRESS RESPONSE
COPING BEHAVIOURS
Problem or emotion focused

PSYCHO -
Stress-induced CRH secretion

NEURO -
Neuronal-derived CRH
Integrates and coordinates
Autonomic, endocrine, motor, immunological, and behavioural responses

CRH NEURONS IN CENTRAL NUCLEUS OF THE AMYGDALA
HYPOTHALAMUS
INTEGRATION OF AUTONOMIC AND ENDOCRINE RESPONSES
Control of peripheral stress response
BRAIN STEM AUTONOMIC NUCLEI
CONTROL OF AUTONOMIC FUNCTION
CONTROL OF SAM-AXIS
Control autonomic stress response
BRAIN STEM AND AMINERGIC NUCLEI
Noradrenergic nuclei → cerebral activation
Cholinergic nuclei → learning & memory
Dopaminergic nuclei → alerting attention motivation
Serotonergic nuclei → excite cerebral neurons
Histaminergic nuclei → aggression diumal rhythm
Control central behavioural stress response
Integrated emotional and cognitive control

CRH NEURONS IN BRAINSTEM
N. Paragigantocellularis
Control of motor responses
+ SEROTONIN
- Acetyl choline
- β ENDORPHIN
- Dynorphin
- GABA
Control central behavioural stress response
Integrated emotional and cognitive control
Projection to brain stem N. tractus solitarius and to intermediolateral column of spinal cord
Locus coeruleus Noradrenaline (NA)
Control SAM-axis
Projections to CNS:
Cerebral activation
↑ NA: ↑ cerebral plasticity
(= behavioural adaptations)
↑↑↑ NA: cerebral damage & abnormal cognitive and emotional behaviour
Control cerntral activation

- IMMUNOLOGY
CRH effects
Pro-inflammatory response
CRH
Control of central stress response
Secretion of immunologically active stress hormones
NORADRENALINE
Necessary for immunocompetence
↑↑ levels: Immunosuppressive and anti-inflammatory
POMC
ACTH Immune effect
β-ENDORPHIN Immune effect
α-MSH Immune effect
ACTH
CORTISOL
Necessary for immunocompetence
↑↑ levels: Immunosuppressive and anti-inflammatory

CRH NEURONS IN HYPOTHALMUS (PVN) CRH
CNA-axis
Psychological stressor input from amydala
Cytokines
ANTERIOR PITUITARY
POMC
ACTH
β-ENDORPHIN
Stress buffer
β-endorphin Behavioural functions
INHIBITION
ADRENAL CORTEX CORTISOL
CORTISOL
Hippocampus Normal levels:negative feedback High levels: hippocampal damage and behavioural impairment
Hippocampus Diurnal rhyhms
Amygdala Stimulates CRH and ADH secretion by hypothalamus
Permissive actions Normal: metabolic regulation Abnormal levels: stress pathology
Control metabolic stress responses
Immunological effects Normal: immune enhancement Above normal: immune suppression
Control + integrate immune response
Behavioural effects of cortisol
- Stress adaptation - new homeostasis
- Warning signals of adversity
- Emotional and cognitive adaptational changes with chronic overproduction and chronic underproduction

Control behavioural adaptation

CRH NEURONS IN THE INTERMEDIOLATERAL COLUM OF THE SPINAL CORD
ACT ASPREGANGIOLIC FIBRES OF SYMPATHETIC SYSTEM
CONTROL AUTONOMIC STRESS RESPONSE

PREFRONTAL, INSULAR & CINGULATE CORTICES
CRH neurons help to integrate emotions into the CNS's formulation of the behavioural & physiological stress responses
Control and integrate working memory with rest of stress response

Figure 5.15 Psychoneuroimmunology in terms of the two main stress areas. The central role of corticotropin-releasing hormone.

Legend to Figure 5.15

Figure 5.15: Psychoneuroimmunology in terms of the two main stress axes. The central role of corticotropin-releasing hormone.

[The psychoneuroimmunological integration is shown in three layers with the top horisontal layer representing the *psycho-*, the middle layer the *neuro-* and the bottom layer the *immunological aspects*. This figure is a summary of the text and other figures of Chapter 5.]

This chapter dealt with the CRH/HPA-axis, firstly in terms of the psychoneurological interactions where the central nervous system CRH neuron distribution, the functions, and the interactions were illustrated, and secondly with the neuroimmunological interactions where the central role of CRH in neuroendocrine control of the immune system was demonstrated. The last section discussed the psychoneuroimmunological interaction in terms of the two major stress axes, i.e., the CRH/HPA-axis and the CNA/SAM-axis and showed that psychoneuroimmunology in terms of the major stress axes can translate into psychoneuroimmunology in terms of CRH. In order to understand the practical implications of psychoneuroimmunology it is necessary to know how immune-related events can influence behaviour. The next chapter will deal with the mechanisms through which the immune system can influence behaviour.

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