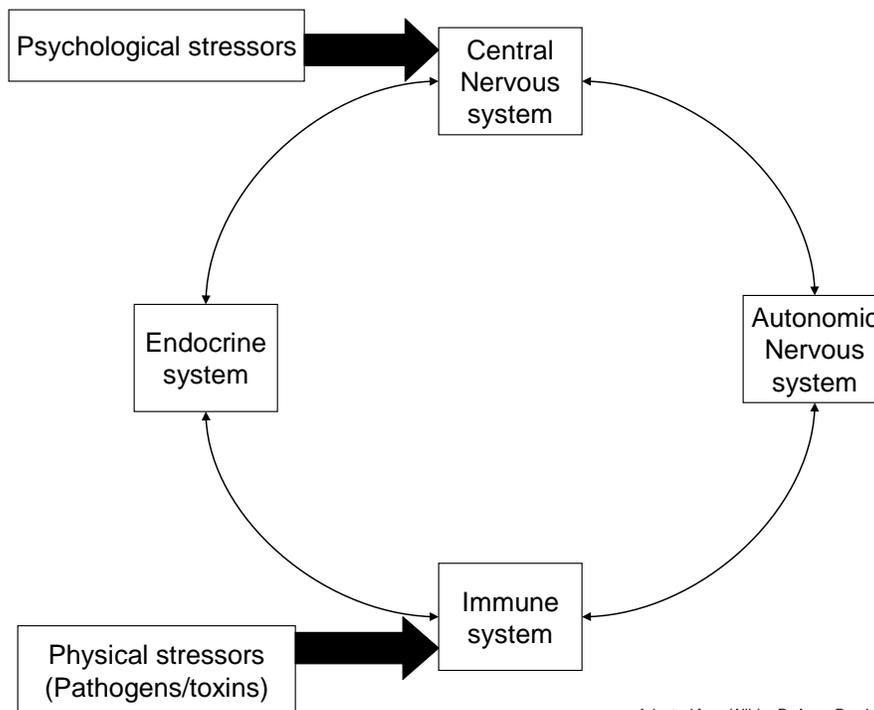


CHAPTER 34

PSYCHONEUROIMMUNOLOGY (NEUROENDOCRINEIMMUNOLOGY)

“The nervous system and immune system speak a common biochemical language and communicate via a complete bidirectional circuit involving shared ligands such as neurotransmitters, hormones and cytokines” (Blalock, 2005).



The term “Psychoneuroimmunology” (PNI) was first used in the 1970s. Other long terms have also been used to describe the interactions of various fields: psychology and the nervous, endocrine and immune systems.

A brief chapter is justified, as 1) these 4 fields have evolved separately and their interactions have not been widely described, and 2) the impact of immune system on these other system is not yet well covered in psychiatric textbooks.

“Stress” is the central issue and is defined as a general body response to initially threatening external or internal demands. Longer definitions mention disturbance of homeostasis, and much of this chapter deals with mechanism which work to restore homeostasis.

“Cytokines” are a category of “signaling molecules” which enable cellular communication. The distinction between cytokines and hormones is becoming less clear/important. Cytokines are produced by immune cells, particularly, monocytes and macrophages, (but also by brain neurons and glial elements; Breder et al, 1988).

“Circumventricular organs” (CVOs) are structures bordering the 3rd and 4th ventricles, regions of the brain in which the capillary bed does not form a blood brain barrier (BBB), but instead the vessels are leaky. They allow penetration of the barrier by hormones, neurotransmitters and cytokines.

“Sickness behavior” refers to the symptoms associated with inflammation (low mood, reduced appetite, increased fatigue and social withdrawal; Irwin and Cole, 2011). This follows penetration of the blood brain barrier and access to the hypothalamus by cytokines released from activated immune cells (and toxic products from bacterium cell walls).

Interestingly, many of these symptoms are shared with depressive disorder. Studies report 16-45% of patients treated with interferon (IFN)-alpha develop depressive symptoms during the course of therapy (Hauser et al, 2002). This is not to suggest that all depressive disorder is an immune response (although the case has been made that a sub-set of depression may be of immunological origin; Howren et al, 2009), but it alerts us to the difficulties which may be encountered when making psychiatric assessments of physically unwell patients.

The neuroendocrine system

Hans Selye (1937) was the pioneer of “biological stress”. He demonstrated that a noxious stimulus (called a stressor) induces the release of adrenal cortical steroids. From early stress response investigations, neural and endocrine system interactions were noted, leading to the concept of the “neuroendocrine system”.

When stress impacts on the brain, there are two outflow pathways to the periphery. One is the hypothalamic-pituitary-adrenal (HPA) axis – traditionally termed part of the endocrine system – but here termed neuroendocrine because of the input from hypothalamic nuclei (particularly the paraventricular nucleus). Neuroendocrine cells receive neuronal input (neurotransmitter stimuli) and release hormones. Ultimately, glucocorticoids from the adrenal cortex.

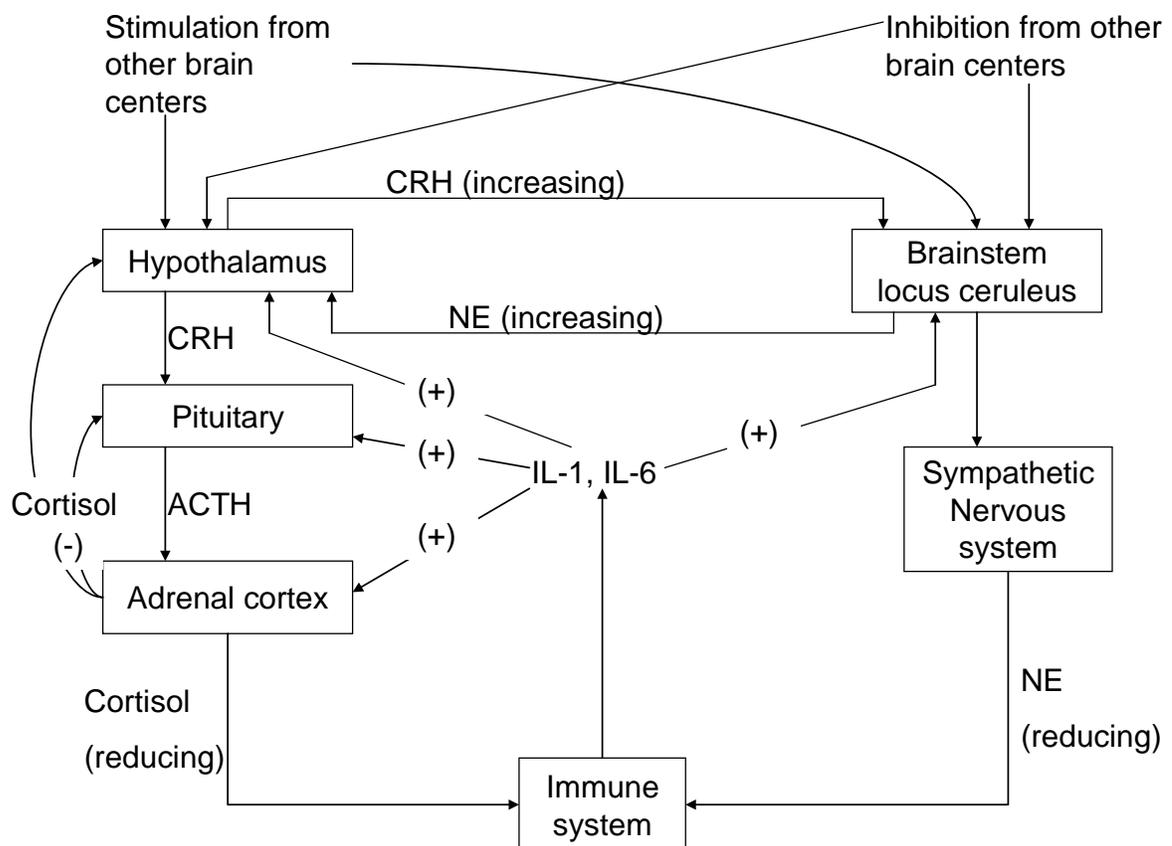
The other involves the sympathetic nervous system (commencing with corticotropin releasing hormone (CRH) stimulation of the locus ceruleus (LC) in the brain stem). It is conceptualized as having three parts. First, neural communication leading to release of epinephrine and norepinephrine from the adrenal medulla (Nicolaidis et al, 2015). Second, neural communication with cells and tissues with an immune function (liver, spleen, bone marrow, thymus, lymph nodes, skin and gastrointestinal system). And third, neural communication which directly prepares the body for action (dilating blood vessels to the muscles, constricting blood vessels to the skin, etc).

The immune system

The immune system responds to physical assault (in the form of pathogenic micro-organisms and tumor cells). [However, recently it has been demonstrated that social stressors can also trigger immune system activity (Lacy et al, 2013).]

The immune system is complicated, with components including an intact skin through to specialized cells (Killer T cells) and specific molecules called antigens.

Of particular interest in the current chapter (which attempts to integrate the immune and neuroendocrine systems) are chemicals (neurotransmitters, hormones and cytokines) which are released by the cells of one system and impact on the cells of the other. (The notion that there is more than one system, is of course, arbitrary, and reflects the history of scientific discovery.)



Modulation

A comprehensive account of the bi-directional modulation of these systems is beyond the expertise of the current author. Instead, some examples are offered, which support the notion that these systems are highly integrated. Future research can be expected to provide additional details and open new therapeutic avenues.

The immune modulating the neuroendocrine system: examples

1. Cytokines, interleukin-1 (IL-1), IL-2, IL-6, tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma) pass through the circumventricular organs and impact on the hypothalamus, leading to fever and sickness behavior.
2. Cytokines impacting on the HPA lead to cortisol release from the adrenal cortex (Chowers et al, 1996; Dunn et al, 1999).
3. Immune cells synthesize IFN which passes the blood brain barrier, impacts on brain and may cause "depression" (Hauser et al, 2002).
4. Elevated levels of C-reactive protein and IL-6 in children are associated with behavior problems (Slopen et al, 2013).
5. Lymphocytes synthesize hormones including ACTH, prolactin and growth hormone (Wilder, 1995).
6. Peripheral cytokines stimulate afferent pathways such as the vagus nerve which leads to the release of cytokine and stimulation of brain cells (McCusker and Kelley, 2013).
7. Cytokines reduce the efficiency of glucocorticoid receptors (resistance) which reduce the negative feedback (which may have a role in depression) (Pace and Miller, 2009).
8. Acetylcholine and adrenaline neurotransmitters, and hormones [recently, melatonin] are endogenously produced in the immune system (Blalock, 2005).

For (simplified) details, see the following list:

<u>Source</u>	<u>Hormone/neurotransmitters</u>
Lymphocytes	Acetylcholine, melatonin
T Lymphocytes	ACTH, endorphins
B Lymphocytes	ACTH, endorphins
Macrophages	ACTH, endorphins
Splenocytes	Adrenalin, CRH,
Megakaryocytes	Neuropeptide Y

The neuroendocrine modulating the immune system: examples

1. Sympathetic/noradrenergic nerve fibers innervate important organs and systems related to the immune system, including the liver, spleen, thymus, bone marrow, lymph nodes, skin, and digestive tract and respiratory apparatus (Montoro et al, 2009; Irwin and Cole, 2011).
2. Adrenergic receptors are located on lymphocytes (Hadden et al, 1970).

3. Catecholamines and corticoids suppress the production of IL-12 by immune cells (Elenkov and Chrousos, 1999).
4. Increased cortisol suppresses immune function (McEwen et al, 1997).
5. Cortical steroids directly affect immune cells, increasing the production of IL-4, 10 and 13 (DeKruyff et al, 1998).
6. Neuropeptide, neurotransmitter and neuroendocrine hormone receptors are located on immune cells (Blalock, 2005).
7. Neurotransmitters (acetylcholine, noradrenaline, serotonin, histamine, glutamic acid, GABA), neuropeptides (ACTH, Prolactin, Vasopressin, Bradykinin, Somatostatin, VIP, SP, Neuropeptide Y, enkephalin, endorphin), neurological growth factors (NGF) and hormones (adrenalin and corticoids) modulate immune function (Montoro et al, 2009).
8. Neurons synthesize IL-1 and other cytokines (Breder, 1988).
9. Parental separation results in higher levels of C-reactive protein in the adult (Lacy et al, 2013).
10. Exogenous administration of CRH and ACTH produce a substantial increase in IL-6 in the adrenal glands (Hueston and Deak, 2014).
11. Marital distress has long-term immune consequences (Jaremka et al, 2013).

Clinical aspects

The Holy Grail

The Holy Grail of PNI is around the question of whether psychological factors (presumably modifiable) can be employed to moderate the immune system and influence the onset and outcome of physical diseases.

Diseases of particular interest include infections (such as hepatitis and AIDS), autoimmune diseases (such as rheumatoid arthritis and multiple sclerosis) and cancer.

Possible psychological interventions include the talking and relaxation/hypnosis therapies and in the broader context, social engineering to reduce loneliness, isolation and poverty.

Earlier findings were encouraging:

1. Healthy students under examination stress manifest a decrease in indicators of cellular immune response (Glaser et al, 1986).
2. Stressful life events can play a part in the onset and exacerbation of auto-immune diseases (Homo-Delarche et al, 1991; Nakata, 2012).
3. Cognitive-behavioral interventions have been associated with improved physical symptoms of some auto-immune disorders (Radojevic, 1992).
4. Some studies involving education and psychological treatment have demonstrated increased cancer survival (Spiegel et al, 1989; Fawzy et al, 1993).

More recent work continues to promise benefits from psychological therapy for physical disease (Armaiz-Pena, 2009), but progress has been slow. An important review (Miller and Cohen, 2001) somewhat unexpectedly, found that the immune system shows little response to psychological intervention, and another (Montoro et al, 2009) did not find chronic stress to be an intrinsic cause of allergy. Nevertheless, beneficial effects of social support and connectedness on the immune system continues to be anticipated (Audet et al, 2014).

While psychological therapy improves the outcomes in certain physical disorders, it is not yet established that this is attributable to alterations in the immune system (that is, the benefits of reduced distress, relaxation and increased confidence may simply enable individuals to deal better with their disorder).

Factors associated with the nervous, endocrine and immune systems have been proposed as the explanation of the poor health status associated with poverty and low social status (Littell, 2008; Kemeny 2009). While some such elements may be involved, much work is needed before definitive conclusions can be made on this topic.

Non-Holy Grail stuff

1. Should a sub-section of depression prove to be due to immune dysregulation (Eisenberger et al, 2010; Jarcho et al, 2013), a new avenue for treatment (for this sub-section, at least) will be opened. There is already a suggestion that the augmentation of antidepressants with anti-inflammatory agents (aspirin, celecoxib) can be beneficial (Blume et al, 2011).
2. Complicated grief – similar in many ways to depression – appears to be associated with dysregulation of the immune system (O'Connor, 2012).
3. Anxiety has also been associated with dysregulation of the immune system (Salim et al, 2012).
4. Unsurprisingly, PTSD has disturbed psychoneuroimmunological features (Pace & Heim, 2011).
5. Some evidence suggests cognitive decline and dementia may also be associated with “over-expressed cytokines” (McAfoose and Baume, 2009).
6. A role for the immune system in the etiology of schizophrenia (Tomasik et al, 2014) and bipolar disorder (Barbosa et al, 2014) has been discussed.
7. Epigenetics is a most exciting new field which has given us a biological mechanism by which “psychosocial world” can modify our neurological-endocrinological-immunological inner world (Mathews & Janusek, 2011).

Conclusion

“There is increasing evidence of a strong interconnectivity between genetic disposition, epigenetic processes, stress-related hormonal systems and immune parameters in all forms of (mal)-adjustment to adverse living conditions”
(Ehlert, 2013).

Close integration and bi-directional communication between the neuroendocrine and immune systems has been demonstrated. Work reviewed in this chapter provides possible mechanisms by which such disease prevention and improved outcomes might be achieved.

Evidence indicates that psychological therapy may improve the outcome of physical disorders. However, it is not yet proven that such improvements are the result of alterations in immune function (although at least in some cases, this is probable).

Depression, schizophrenia, bipolar disorder, anxiety, PTSD, dementia and other disorders may have unexpected roots, and new therapies may be quite close. And, epigenetics, at last, provides a mechanism to bridge the psychological-physical divide.

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