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Endocrinology: The Active Partner in PNI research

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Abstract

For the past two decades, research appearing in the pages of *Brain, Behavior, and Immunity (BBI)*, as well as other journals, has significantly deepened our understanding of the complexities of endocrine regulation of immunity in states of health and disease. This mini-review discusses contributions that endocrinology has made to the field of psychoneuroimmunology (PNI), as well as discoveries that PNI researchers have made of the pervasive interactions between the endocrine and immune systems. We highlight the endocrine-immune interface, emphasizing similarities between the immune and endocrine systems as well as hormone/cytokine interactions.

Differing endocrine-immune responses to acute and chronic psychosocial stress have been clarified during this time frame with the use of novel stress and endocrine sampling paradigms. Furthermore, investigations examining the role of cytokine involvement in acquired glucocorticoid resistance in illnesses like depression have expanded our understanding of the complexity of the endocrine-immune response to psychosocial stress. We have selected literature, with a focus on human studies, to illustrate these principals. We conclude with a discussion of the clinical relevance of endocrine-immune investigations and thoughts about the next decade of endocrine research in PNI.

Keywords

endocrinology; psychoneuroimmunology; stress; glucocorticoids; catecholamines; hormone resistance

Introduction

In 1967 it was reported that psychosocial influences could produce dramatic inhibition of growth in young children (Powell et al., 1967). This clinical entity, now called ‘emotional deprivation growth failure’, is multi-factorial in its origin but failure to secrete adequate amounts of growth hormone (GH) has been documented. When these children are removed from the adversity of their living environment, they often resume GH secretion and subsequent normal growth. More recently, similar finding have been documented in children from

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Romanian orphanages. Reports detailing possible associations between stress and the onset of Grave's disease with increased thyroid secretion and the development of Cushing's syndrome with excessive production of ACTH and cortisol also appeared in this same time frame. Both of these disease entities are associated with altered immune function. Grave's disease is a B and T lymphocyte mediated autoimmune disorder and Cushing's disease is associated with altered immune function as evidenced by the marked susceptibility to infection in these individuals. The field of PNI, while not yet directly examining these conditions, has greatly increased our understanding of how chronic psychosocial stress can induce a cascade of endocrine and immune events that are associated with numerous disease outcomes. Many of these papers have appeared in *BBI*.

This mini-review is organized into decades, beginning with 1987, the year *BBI* was first published. We review evolving concepts of the endocrine-immune interface and focus on how endocrine advances have informed as well as furthered PNI research. Our citations are highly selected and limited to forty articles to illustrate these advances. We conclude with a discussion of the clinical relevance of endocrine/immune investigations and suggestions for future endocrine research in PNI.

1987–1996: The Endocrine-Immune Interface and Stress

During this time period, one of the most important advances relevant to PNI was redefining our concepts of the endocrine-immune interface. Prior to this time the extensive bidirectional feedback regulation and shared secretory products of the endocrine and immune system had not been appreciated. It became apparent that the earlier concepts of what constituted the endocrine system were much too restrictive. Classic endocrine hormones, which were by definition to have a 'gland of origin' and be secreted into the circulation to their site of action, are now known to be secreted by other tissues, including immune cells. These findings have highlighted the complexity of the endocrine-immune interface and have reshaped the research and clinical questions that we are examining.

Endocrine/Cytokine Similarities and Interactions

The hypothalamus and pituitary were originally considered to be the only source of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), GH, prolactin and other hormones. The pioneering studies of Blalock and co-investigators demonstrated that immune cells could produce "pituitary hormones" (Weigent and Blalock, 1987). It is now clear that these 'hypothalamic' and 'pituitary' hormones can be synthesized by human immune cells in the thymus, tonsils, spleen, and lymph nodes and produce local biologic effects (Clark, 1997). For example, culture of human peripheral blood mononuclear cells in serum-free conditioned media release lymphocyte GH which augments the production of Interferon-gamma (INF)-γ (Malarkey et al., 2002). These cells also produce prolactin which can augment lymphocyte proliferation (Sabharwal et al., 1992). These 'immune system hormones' are secreted at very low levels and appear to exert most of their biologic effects through an autocrine (acting on the cell that secretes it) or paracrine (acting on nearby but dissimilar cell types) mechanism. Many of these 'lymphocyte hormone' studies did not have a psychosocial stress component. However, a study of lymphocytes in individuals with the chronic stress of caregiving for a spouse with Alzheimer's disease demonstrated a decrease of lymphocyte growth hormone synthesis in the caregivers (Malarkey et. al., 1996). This latter finding suggested that the lymphocyte pool of hormones may be responsive to stress and thereby influence cytokine biology.

Co-localization of hormones and cytokines in endocrine glands has also been reported. The human pituitary and other endocrine tissues contain cytokines such as interleukins where they can act in an autocrine or paracrine fashion to influence endocrine secretion. An example of

this phenomenon would be the human adrenal gland production of IL-6 and TNF-α where they may be involved in local control of synthesis of cortisol and other adrenal steroids (Judd et al., 2000). This local cytokine regulation of adrenal cortisol secretion may help explain why some studies have shown increased ACTH levels but not cortisol levels following some psychosocial stressors. Some of these tissue cytokines can also enter the peripheral circulation and function like a hormone by acting on a target tissue at a distance from the cell of origin.

How have these observations just discussed affected basic and clinical research? First of all, the discussion of endocrine and cytokine co-localization has been greatly influenced by the names which were originally assigned to these agents. Their names were reflections of the first biologic test system which was used to evaluate their function. If, for example, IL-6 had been first tested for its in vivo influences on the hypothalamic-pituitary axis (HPA), the observation that it could increase cortisol secretion may have led investigators to name it 'cortisol releasing factor'. There are numerous examples where a delay in finding important functions of certain hormones and cytokines occurred because of the narrow functional name it was originally assigned. An example of this phenomenon is the hormone leptin, which was originally thought to only regulate food intake but is now known to have other important functions such as involvement in initiating menses and modulating T lymphocyte cytokine production (Welt et. al., 2004; Lord et. al., 1998).

Much of the work in PNI has focused on hormones influencing cytokine production through hormone/receptor interactions on immune cells and subsequent regulation of transcription factors like the pro-inflammatory cytokine transcription factor NF kappa B. In contrast, it has also become clear that the regulatory relationship of hormones and cytokines is bidirectional. For example, proinflammatory cytokines like TNF-α can alter the glucocorticoid receptor and induce glucocorticoid resistance (Lewis-Tuffin and Cidlowski, 2006). Furthermore, TNF-α, at low physiologic concentrations has been shown to reduce Insulin-like growth factor-1 (IGF-1) responses in murine neurons, myoblasts, and human epithelial cells. TNF-α produces this inhibition of IGF-1 action by inhibiting its post receptor signaling activities. Likewise, IL-6 reduces plasma IGF-1 levels, suppresses its anabolic activity, and reduces expression of hepatic GH receptors, which leads to a GH receptor resistance (Kelly, 2004). These investigations of the endocrine-immune interface have provided insight into the complex interactions of these systems following psychosocial stress.

Endocrine Measurement Issues

A problem for the design of human PNI studies has been timing the collection of endocrine and immune measures in order to see if they are interrelated as the influence of one on another is frequently not seen on simultaneously acquired samples. Furthermore, short hormone half-lives and diurnal variation make frequent endocrine sampling critical when trying to find significant endocrine changes with stress protocols.

A significant advance in approaching this problem was provided by the use of salivary cortisol testing (Kirschbaum and Hellhammer, 1992). This technology has markedly improved endocrine research in PNI studies concerning the HPA axis in humans replacing user unfriendly 24 hour urine collections and/or frequent blood sampling. In a naturalistic setting with multiple sampling time points throughout the day, which are easy to perform with the salivary cortisol method, researchers can achieve a variety of assessments of HPA axis function. These evaluations have included approximating the mean daytime secretion, the cortisol response to awakening, the response to a lunch challenge (cortisol is increased by the carbohydrate content of the meal), sensitivity to inhibition of cortisol by dexamethasone, and the diurnal variation of daily cortisol secretion. One or more of these cortisol sampling paradigms has been used in most human studies where the HPA axis has been evaluated using saliva. Furthermore, the

salivary cortisol levels reflect the serum non-protein bound free fraction of cortisol available for transport into cells.

In contrast to cortisol, salivary catecholamines and sex steroids are rarely reported in PNI articles. The catecholamine norepinephrine in saliva is a poor index of acute changes in sympathetic activity (Kennedy et al., 2001). Furthermore, salivary hormone concentrations are quite low when compared to serum or plasma levels and this can cause problems with assay accuracy.

Prolactin, GH/IGF-1 and the Hypothalamic-Pituitary Gonadal Axis

Human prolactin and GH are pituitary hormones that have pulsatile secretory patterns during the day and night with almost two thirds of their secretion occurring during sleep. This normal yet erratic pulsatile GH secretory pattern, where levels can change within minutes from 0.3 ng/ml to 5 ng/ml, has made it difficult to distinguish secretory changes produced by stress from those secondary to normal pulsatile release. Prolactin has much less daytime secretory variability and therefore it's secretory changes during a stress protocol are easier to interpret. Urinary GH determinations have been used by some investigators to evaluate the marked nocturnal secretion of GH, but the reliability of urinary GH assays has been controversial. The more stable marker of GH secretion is IGF-1 which is primarily produced by the liver after stimulation by GH and is responsible for most of the biologic effects of GH.

During this decade prolactin and GH where shown in a variety of animal studies to have a potentially important role in immune regulation. Several of these studies appeared in *BBI* suggesting a modulatory role for prolactin in humoral and cell mediated immunity. In humans, other than a report that mycobacterialla cell killing by human monocytes was enhanced by prolactin in serum of individuals with elevated prolactin levels, and that human lymphocyte prolactin has a lymphoproiferative autocrine effect in cultured cells (Sabharwal et al., 1992), an important influence of prolactin on cellular and humoral immunity had not been demonstrated. Recently, however, a *BBI* paper indicated that prolactin when added to human blood increased TNF-α and INF-γ producing CD4+ and CD8+ cells and interleukin-2 (IL-2) producing CD8+ cells (Dimitrov et al., 2004). Arguing against a significant immune modulatory role for prolactin in humans, however, is the absence of any immune observed sequelae in individuals with low prolactin levels or with markedly elevated levels for months to years from pituitary tumors that produce prolactin levels 100 to 1000 times above normal.

A recent paper in *BBI* reviews the evidence concerning the role of GH and IGF-1 on thymus growth, reversing age-related loss of cells in the thymus and bone marrow, priming leukocytes to secrete free radicals, and reducing mortality following infection with S. typimurium (Kelley, 2004). In humans, however, the role of GH on humoral and cellular immunity is not well defined. A recent report suggested that physiologic concentrations of GH added to human peripheral blood mononuclear cells could increase the number of INF-γ CD4+ cells (Dimitrov et. al., 2004). Similar to the prolactin story however, individuals with either marked increases in GH or IGF-1 from pituitary tumors or acquired GH deficiencies from a variety of disease processes are not prone to infectious illness, autoimmune disease, asthma, allergies or other cellular or humoral immune defects. It is possible, however, that in humans the immune effects that GH and IGF-1 induce can be handled by redundant control mechanisms in the face of moderate or even severe GH deficiency.

Human studies evaluating the hypothalamic-pituitary-gonadal axis have been absent from most PNI research and *BBI* articles. This trend may be changing with the increased emphasis on evaluating the influence of stress on cytokine production in difficult pregnancies. CRH inhibits gonadotropin-releasing hormone secretion whereas glucocorticoids suppress pituitary lutinizing hormone (LH) and ovarian estrogen and progesterone secretion and produce target

tissue resistance to estradiol (Chrousos et al., 1998). In addition, the proinflammatory cytokines IL-1 and TNF-α inhibit secretion of gonadotropin-releasing hormone from the hypothalamus and LH from the pituitary with a subsequent decrease in estrogen in women and testosterone in men (Straub and Cutolo, 2001). Generally androgens are immunosuppressive and estrogens can both inhibit and stimulate the immune response. This complex interaction of the pituitary gonadal axis, proinflammatory cytokines, cortisol, and catecholamines has been evaluated in individuals with rheumatoid arthritis (Straub and Cutolo, 2001).

Stress Research

As the pages of *BBI* readily reveal, a mainstay of research during this decade was devoted to mapping out the effects of stressors on immune cells and the respective contributions of the HPA hormones ACTH and cortisol and the sympathetic-adrenal-medullary (SAM) axis hormones epinephrine and norepinephrine. There are several reasons why catecholamines and/or cortisol have routinely been included in stress studies in PNI, including that their immunomodulatory properties were already well established and that they respond relatively quickly to stressors.

Using stressors as endocrine probes in PNI research was a natural extension of the earliest research examining hormone effects on the immune system, which started in the early 1900's with observations that injections of adrenaline increased circulating white blood cells. Research progressed steadily over the decades, with the discovery that norepinephrine elicited immune responses, and that cortisol suppressed immunity. Among the several disciplines that have examined these issues, it could be argued that PNI has been at the forefront demonstrating that psychogenic challenges lead to changes in levels of circulating hormones that yield observable immune effects. Within the repertoire of human experimental methodologies that PNI has had at its disposal, laboratory and naturalistic stressor studies have been used successfully to map out many complex relationships between hormone levels and immune parameters. Over the years, investigators expanded acute stress research protocols to include mathematics tasks, public speech stressors, video and role playing games, academic examinations, exercise challenges, heat stress, marital interaction paradigms and parachute jumping. Chronic stressors have included perceived life stress, socioeconomic stress, trauma and post traumatic stress disorder (PTSD), and other major life events including bereavement and caregiving. In addition to the changing landscape of stressors, immune measures too changed over the years, starting with simple counts of immune cells in early studies, to examining the cytotoxicity of natural killer cells, immune cell proliferation, cytokine and antibody production, differentiating T-helper cell subsets, effects on anti-viral immunity, tumor metastasis, expression of selectin and integrin adhesion molecules, and actual adhesion phenomena.

Furthermore, publications in *BBI* have differentiated a multitude of diverse factors that influence stress-induced endocrine/immune responses, including the effects of acute versus chronic stress, mild versus severe stress, controllable versus uncontrollable stress, continuous versus intermittent stress, optimism versus pessimism, effects of anticipation of a stressor, anxiety, worry, depression, social standing and social support, aging, the menstrual cycle, fitness, spaceflight, insomnia, diurnal rhythms, acupuncture, and relaxation. In addition, other important inter-individual factors, including positive affect, resiliency, loneliness, and availability of respite for caregivers have been found to be important. Throughout many of these studies, the consistency of underlying HPA and SAM hormones and their receptors on immune endpoints has been remarkable. For example, the magnitude of the immune cell trafficking response to acute stress is dependent on a combination of the pre-stress level of circulating norepinephrine, the sensitivity and/or density of the $ß_2$-adrenergic receptors being expressed on the immune cells, and the size of the stress-induced increase in norepinephrine (Mills et al., 1995). The magnitude of the increase in circulating levels of proinflammatory

cytokines in response to acute stress is influenced by the size of the cortisol response (Kunz-Ebrecht et al., 2003).

Acute stress research should continue towards determining the clinical relevance of reactivity phenomenon. There is a large literature, including several reviews, demonstrating that high levels of chronic psychological stress are associated with a reduced antibody response to vaccination. Fewer studies in humans have examined endocrine mechanisms of acute psychological stress on antibody responses to vaccinations. Edwards et al. (2006) recently showed in *BBI* that individuals who performed either a mental arithmetic or a cycle ergometer task immediately prior to receiving influenza vaccine had significantly enhanced antibody responses at 4 and 20 weeks post vaccination. In addition, IL-6 but not cortisol responses to the tasks predicted subsequent antibody responses. Other studies published in *BBI* suggest that individuals who tend towards greater SAM and HPA responses to acute stressors are at increased risk for illnesses when exposed to a stressor (Cohen and Hamrick, 2003).

1997 – 2006: Hormone Resistance, Diurnal Variation, Chronic HPA and SAM Activation

Hormone Resistance

Familial—The phenomenon of hormone resistance received increasing attention in PNI research during this decade. In humans, classic hormone resistance syndromes such as familial thyroid and glucocorticoid resistance are rare (Chrousos et al., 1993). Individuals with thyroid hormone resistance have elevated thyroid hormone and pituitary TSH levels and a goiter. They are, however, without symptoms from their thyroid excess as elevated thyroid levels are able to compensate for their cellular thyroid resistance. Likewise, familial generalized glucocorticoid resistance in humans has also been described in individuals with elevated ACTH and cortisol levels which resist suppression by glucocorticoids. However, these individuals have few if any manifestations of deficient cortisol secretion because this generalized resistance is compensated for by an increase in circulating cortisol which then supports normal cellular activities.

The most common form of hormone resistance that occurs is acquired. Insulin resistance and its associated metabolic syndrome components are commonly seen instances of this phenomenon. These individuals have elevated insulin levels but a decreased ability of insulin to move glucose into cells.

Acquired CNS Glucocorticoid Resistance—Another form of hormone resistance is acquired glucocorticoid resistance, which has been found in the CNS and immune system following psychosocial stress. Acquired CNS glucocorticoid resistance has been found in women with chronic stress-induced functional hypothalamic amenorrhea (Brundu et al., 2006). They are found to have elevated cerebrospinal fluid (CSF) cortisol levels with normal CSF CRH levels. These findings suggested a CNS resistance of CRH to inhibition by cortisol.

Extensive research concerning acquired CNS glucocorticoid sensitivity has been performed in depressed individuals. Increased levels of cortisol have been found in patients with major depression and they demonstrate a resistance of the HPA axis to suppression by dexamethaxone (Holsboer 2000). The most sensitive neuroendocrine secretory test combines dexamethasone suppression with CRH stimulation of ACTH. The amount of ACTH and cortisol released is higher in individuals with depression. There is a significant correlation between normalization of the cortisol response to dexamethasone and clinical improvement of the depression (Holsboer 2000). Clinical sequelae of this persistent increase in cortisol include osteoporosis and cognitive impairment which will be discussed in more detail later in this article.

Acquired CNS glucocorticoid resistance may also be associated with events occurring in the first week of life (Weaver et al., 2004). In these rodent studies the absence of maternal pup licking, grooming, and arched-backed nursing behaviors altered DNA methylation and histone acetylation and thus decreased transcription factor binding to the glucocorticoid receptor gene promoter in hippocampal tissue. This epigenetic event inhibited synthesis of the glucocorticoid receptor thus altering feedback inhibition of glucocorticoid secretion leading to CNS glucocorticoid resistance (Weaver et al., 2004). When stressed, the animals deficient in maternal care hypersecreted corticosterone. The authors suggest that environmental programming by maternal behavior can produce sustained altered gene expression and function over a lifetime.

Acquired immune glucocorticoid resistance—Immune acquired glucocorticoid resistance is seen in various disease settings, including steroid resistant asthma, inflammatory bowel disease (ulcerative colitis/Crohn's disease), rheumatoid arthritis and the acute respiratory distress syndrome, as well as in young healthy individuals (Chriguer et al., 2005). Futhermore, several studies have reported acquired immune glucocorticoid resistance following psychosocial stress. The stress of social disorganization in rodents has been shown to produce acquired immune glucocorticoid resistance (Stark et al., 2001) and it has also been observed in depression and chronically stressed parents of cancer patients (Miller et al., 2002).

In individuals with acquired immune glucocorticoid resistance the ability of dexamethasone to inhibit in vitro LPS stimulated cytokine release from peripheral mononuclear cells is impaired. Recent research suggests that cytokines and the signaling elements they induce alter glucocorticoid receptor function and expression which may then lead to glucocorticoid resistance. For example, proinflammatory cytokines can alter glucocorticoid receptor gene expression leading to an increase in cellular NF-kappa B activity and a subsequent increase in proinflammatory cytokine production. It appears that when the hGR-alpha to hGR-beta isoform ratio is decreased in immune cells glucocorticoid resistance occurs (Lewis-Tuffin and Cidlowski, 2006). Stated another way, the glucocorticoid receptor beta isoform is antagonistic to glucocorticoid action. Furthermore, there are other intracellular glucocorticoid receptor pathways that can be altered in glucocorticoid resistant states (Holsboer 2000).

Therefore, in PNI research the measurement of serum ACTH and cortisol following psychosocial stress opens the door to understanding the possible contributions of the HPA axis on immune function and other cellular systems. However, target tissue resistance or even heightened responses to cortisol, as seen with certain glucocorticoid receptor polymorphisms, also have to be considered before concluding that cortisol dysregulation is not involved in the immune pathophysiology being evaluated.

Diurnal Variation

In humans, as in other organisms, there is an endogenous pacemaker of circadian (about 24 hours) clock genes located in the suprachiasmatic nucleus of the hypothalamus that generates a circadian rhythm. The regulation of endocrine secretion is among those processes but it also includes immune, metabolic, blood pressure, and other physiologic functions. The timing of the circadian rhythm is synchronized to the solar day-light by dark-light periods, which normally regulate the sleep-wake cycle.

Chronic psychosocial stressors may cause disruption of circadian rhythms of neuroendocrine stress response systems. Several *BBI* papers have discussed disruption of HPA axis rhythms in depression, PTSD, the financial stress of unemployment, fibromyalgia, and cancer (Sephton and Spiegel, 2003; Crofford et al., 2004). The most common diurnal rhythm abnormality for cortisol is a decrease in the am cortisol peak level and an increase in the pm nadir leading to a

flattening of the diurnal secretion of cortisol. The normal diurnal cortisol pattern is disrupted in night shift workers and has also been reported to be predictive of increased mortality in women with breast cancer (Sephton and Spiegel, 2003). Whether this cortisol rhythm is involved in influencing the biology of the tumor or is just a marker of disease burden and progression is not clear. Most hormones and many cytokines have some degree of diurnal variation and future PNI investigations should help further clarify how important disruptions of circadian rhythm of hormones and cytokines are as predictors and/or mediators of disease processes.

Immune Consequences of Cortisol and Catecholamine Elevations

Cortisol and catecholamines have profound effects on the innate and adaptive immune systems. They tend to inhibit the production of proinflammatory cytokines such as IL-12 and TNF-α as well as TH-1 cytokines, IL-2 and INF-γ whereas they tend to stimulate the production of TH-2 cytokines such as IL-10 and IL-4. Thus, when stress produces excessive immune stimulation these stress related hormones are available to dampen this response and produce a change in TH-1/TH-2 balance. Numerous articles in PNI research suggest that deficient or excessive cortisol or catecholamine responses to stress produce a shift in this balance and make one susceptible to differing disease processes (Elenkov and Chrousos, 2002). For example, individuals with a robust cortisol response to stress would have a decreased TH-1/TH-2 ratio and be more susceptible to infections (from a reduced cellular immune TH-1 response) and with the corresponding increase in TH-2 humoral immune response they would be at more risk for allergies or asthma. Conversely, a deficient cortisol response to stress might lead to an increase in the TH-1/TH-2 ratio with an associated increased risk for rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus, autoimmune thyroid disease, and Crohn's disease.

In contrast, hormones released following acute stress may meditate immuno-enhancement. It's been reported that a short duration stressor significantly enhanced skin delayed-type hypersensitivity and that this enhanced immune response was dependant on corticosterone and epinephrine (Dhabhar and McEwen, 1999). Following both acute and chronic stress, cytokine and hormonal receptor genetic polymorphisms can modify endocrine/immune responses which may dampen or enhance the associated immune response.

What about excessive catecholamine secretion and disease outcomes? One area of focus has been reactivity studies where heightened catecholamine responses to stress is thought to play a role in the future onset of hypertension or surgery-induced experimental pulmonary tumor metastasis (Melamed et al., 2005).

Also, the increase in catecholamine release after acute emotional stress can precipitate severe cardiac decompensation. This was recently described in a group of 19 individuals, of whom 95% were women, with a clinical presentation that included chest pain, pulmonary edema, cardiogenic shock, EKG abnormalities, and severe left ventricular dysfunction, without myocardial infarction (Wittstein et al., 2005). News of an unexpected death precipitated cardiac dysfunction in about half the individuals while the remainder experienced a variety of other events which produced emotional stress. In these individuals plasma catecholamine levels were 7 to 34 times higher than found in normal individuals and remained markedly elevated one week later. The catecholamine levels were thought to be causing vascular spasm or direct myocardial injury. These individuals experienced gradual clinical improvement, but what would have been the immune consequences of this acute stress? Based on our previous discussion, they would have been dramatic.

A recent paper in BBI extensively reviews what is known about norepinephrine, the ß-adrenergic receptor, and immunity in humans (Sanders and Straub, 2002). The authors conclude that the human data are not sufficient to provide any clear pattern of change in immune

parameters that would be predictive of a change in sympathetic tone or health changes that would derive from the reported immune findings. They provide suggestions, however, for studies that could provide clarity in these areas.

2007: Clinical Relevance and Future Directions

The endocrine system plays a major role in the cascade of biological events that occur in response to stimuli such as the light-dark cycle, stress and disease. Disease outcomes are far downstream from numerous preceding endocrine and immune events and timing disease onset can be somewhat arbitrary. Does a person have non-disease a month before a diagnosis of coronary disease, rheumatoid arthritis or diabetes? The more easily addressed question is if perturbations of the endocrine/immune interface from psychosocial stressors produce measurable intermediate biologic endpoints in the ‘gap’ between disease initiation and diagnosis that are known risk factors for various disease processes. In approaching this question, PNI and other fields of research are providing some answers.

We will use the example of Cushing’s syndrome to discuss this issue of the gap between disease initiation and diagnosis. Cushing’s syndrome, a classic endocrine disease associated with excessive cortisol secretion usually from a primary defect in either the pituitary gland or the adrenal, possesses several suitable characteristics for such a discussion. Typical findings in individuals with Cushing’s disease related to increased cortisol levels include abdominal obesity, fatigue, skin fragility, depression, memory defects, osteoporosis, decreased wound healing, and frequent infections. Some of these findings in Cushing’s syndrome related to excessive cortisol secretion have also been seen in individuals under chronic stress and most have been the subject of PNI research.

We can then ask whether cortisol levels that are increased for the individual but still within the normal population range (as referenced by the clinical laboratory) produce findings less dramatic but similar to Cushing’s syndrome? There is suggestive evidence that this may occur. For example, excessive secretion of cortisol following chronic stress, but without any indication of Cushing’s syndrome, has been associated with osteopenia (the precursor of osteoporosis), decreased wound healing, and memory defects (Cizza et al., 2001; Glaser et al., 1999; Lupien et al., 1998).

What about the finding in Cushing’s syndrome of an increase in abdominal fat which is associated with features of the metabolic syndrome? In individuals with increased perceived stress, laboratory stressors often produce an increase in cortisol secretion compared to control subjects with less perceived stress. Chronic stress also produces overeating and sleep deprivation which increases the hormones that further encourage eating behaviors (Spiegel et al., 2004). It has been suggested from studies in rats that chronic stress and the glucocorticoid corticosterone can increase food intake and lead to a specific increase in abdominal fat deposition (Dallman et al., 2003). In humans with abdominal obesity, stressors accentuate cortisol secretion compared to lean controls (Epel et al., 2000) which would further aggravate the central deposition of fat if repetitive stress occurs in these individuals. This chronic stress induced elevation in cortisol secretion could also have immune consequences including increased susceptibility to infection and decreased wound healing,

These are examples of the power of PNI research in examining the relationship between various biopsychosocial measures and early disease markers. It is these ‘signs and symptoms without a diagnosis' which cause many people to seek out a health professional. Gaining clarity in regards to the underlying endocrine/immune mechanisms would probably help in developing new strategies for their clinical management.

What research articles would an endocrinologist like to see appear in *BBI* in 2007 and beyond? As noted earlier, most hormones exhibit diurnal variation and future PNI studies should delineate whether disruptions of endocrine circadian rhythms alter immune function, worsen disease outcomes, or are just markers of underlying diseases processes. Furthermore, frequent endocrine sampling protocols adds complexity to a research design but is often needed to determine the relationship between endocrine changes and corresponding immune responses. More attention will probably be given to the role of selective acquired endocrine resistance in evaluating immune function in a variety of psychosocial settings which could be expanded beyond acquired glucocorticoid resistance to include other endocrine/immune interactions. The influence of genetic polymorphisms on endocrine and cytokine responses to stress, as well as the impact of individual psychosocial resilience factors in modifying these responses, will also be more fully explored.

In addition to these directions, it is time for PNI researchers to increase their presence in the clinical arena to explore the endocrine/immune consequences of stress in situations such as cancer chemotherapy. Although numerous PNI studies have been conducted in patient groups (including systemic lupus erythematosus, multiple sclerosis, chronic fatigue, HIV, diabetes mellitus, cancer, arthritis, asthma, and heart failure) studies should examine how the endocrine and immune issues which we have presented influence therapeutic outcomes.

Evidence continues to be published that stress-endocrine-immune interactions and their associations with chronic inflammation are involved in the pathogenesis of infections and depression, as well as cardiovascular, rheumatologic, and gastrointestinal disorders. If one goes through the lexicon of common human symptoms and diseases it is apparent to most PNI investigators that chronic stress and its subsequent biologic cascade will be found to be involved in their pathogenesis and continued clinical course. The next twenty years of research into stress-endocrine-immune-genetic interactions will add plenty of opportunities, challenges and excitement as their roles in human disease are explored.

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