Chapter

Psychoneuroimmunology and Genetics

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Abstract

Psychoneuroimmunology is a study that investigates the interaction between human emotions and the immune system, which is mediated by the endocrine and nervous systems. The nervous and immune systems maintain extensive communication, including communication to lymphoid organs from deep-rooted sympathetic and parasympathetic nerves. Genetic factors are responsible for individual variation in emotional reactivity, and neuroendocrine stress responses were shown by earlier studies in humans. Several gene-environment studies have shown that long-term effects of stress are being moderated by genetic variations in the hypothalamic-pituitary-adrenal (HPA) axis. There is a large interindividual variability of HPA axis stress reactivity on variants of the glucocorticoid (GR) or mineralocorticoid receptor genes, and it documents a sex-specific association between different GR gene polymorphisms and salivary cortisol responses to acute psychosocial stress. In conclusion, many kinds of mind-body behavioral interventions are effective in improving mood, quality of life, reducing stress, and anxiety, thereby altering neuroendocrine and immune functions, and ultimately altering the genetic aberrations. However, the question remains as to whether these latter effects are sufficiently large or last long enough to contribute to health benefits, or if they are even relevant to the development of a disease.

Keywords: psychoneuroimmunology, immunology and genetics, emotional stress, genetic factors involved in stress, epigenetics involved in stress

1. Psychoneuroimmunology

Psychoneuroimmunology is an area that examines the interaction between human emotions and the immune system, which is mediated by the endocrine and nervous system. The brain controls the immune system by hardwiring sympathetic and parasympathetic nerves to lymphoid organs. Further neuroendocrine hormones such as a corticotropin-releasing hormone or substance P regulate cytokine balance. The immune system controls some brain activities such as sleep and body temperature. Based on anatomical and a close functional connection, the nervous and immune systems act in a very mutual way. Over recent decades, reasonable evidence has emerged that these brain-to-immune interactions are highly modulated by psychological factors which influence immunity and immune system-mediated disease [1].

The nervous and immune systems maintain extensive communication, including communication to lymphoid organs from deep-rooted sympathetic and

parasympathetic nerves. Acetylcholine, norepinephrine, vasoactive intestinal peptide, substance P, and histamine such as neurotransmitters modulate immune activity. Corticotropin-releasing factor, leptin, and alpha-melanocyte-stimulating hormone such neuroendocrine hormones regulate cytokine balance. The brain activity mainly body temperature, sleep, and feeding behavior is influenced by the immune system. The major histocompatibility complex directs T cells to immunogenic molecules held in its cleft and also controls the development of neuronal connections. Neurobiologists and immunologists are exploring common ideas like the synapse to understand properties such as memory which is shared between these two systems [2].

Both neuronal (direct sympathetic innervation of the lymphoid organ) and neuroendocrine (hypothalamic-pituitary-adrenal axis) pathways are involved in the control of the humoral and cellular immune responses. There is a recent evidence on the immunosuppressive effect of acetylcholine-secreting neurons of the parasympathetic nervous system which influences the central nervous system primarily through cytokines. Neuroimmune signal molecules such as hormones, neurotransmitters, neuropeptides, cytokines, or their receptors enable mutual neuroimmune communication. Subcellular and molecular mechanisms of cytokine-neuropeptide/neurotransmitter interactions were extensively investigated. At the neuroanatomical level, neuroimmune communication in the role of discrete brain areas related to emotionality has been established. Immuno-enhancement, including the antitumor cytotoxic activity and antiviral activity, related to the "brain reward system," limbic structures, and neocortex, offers a new direction for therapy in immune disorders [3].

2. Immunology and genetics

Genetic predisposition is important for this immune function. Stress-mediated inflammation is a common feature of many hereditary disorders, due to the proteotoxic effects of mutant proteins. Harmful mutant proteins can induce dysregulated IL-1β production and inflammation. Depressive disorders are often accompanied by profound changes in immunity. Clinical observations in depression disorders showed that immune dysfunction is the main cause of increased risks in other oncological, inflammatory, and infectious diseases. Immunological reactions in psychoemotional stress play an important role. Studying Antidepressant-Sensitive Catalepsy (ASC) in mice showed a decrease in IgM immune responses and sensitivity to the administration of antidepressants. Unlike their non-depressive parental CBA strains, ASC lines show the difference in T-lymphocyte distribution and changes in IgG and IgM immune responses, low antibody production, abnormal CD4+ T-cell content in blood and spleen, and variations in CD4+/CD8+ T-cell ratio [4].

Stress-induced inflammation is a key pathogenic factor in inherited diseases and autoinflammatory syndromes. The stress contributes severity of the symptoms in these diseases. A study showed the correlation among basal stress, disease severity, and antioxidant response in two different cryopyrin-associated periodic syndrome (CAPS) patients sharing same nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 3 (NLRP3) mutation [5]. Hence, similar stress-related mechanisms may operate in other genetic diseases, where inflammation causes disease progression and mutant protein present in monocytes. Improving the responses to stress represents a promising therapeutic opportunity for this kind of serious diseases, while considering the genetic factor (individual tolerance levels) may play a major role.

3. Molecular mechanisms of emotional stress

Identification of mechanisms underlying a dysregulation of major components of the stress response system is a very challenging task as it involves complex cellular interactions at the level of different organs and systems. One of the main features of the stress response is the activation of the hypothalamic-pituitary-adrenal axis (HPA) [6]. The main regions of the brain that shows stress response are hippocampus, amygdala, and prefrontal cortex. Decreased activity and neuronal atrophy in the hippocampus and in the prefrontal cortex, as well as increased activity and neuronal growth in the amygdala, are involved in post-traumatic stress disorder (PTSD) [6]. The changes that stress induces mainly affect the levels of cortisol and catecholamines (epinephrine, norepinephrine, dopamine). Catecholamines are released shortly after stress onset and go back to normal levels upon stress termination. Glucocorticoids act by binding to two types of receptors—mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). Molecular mechanisms involving this stress response are genetic, epigenetic, and immunological nature.

4. Hormonal and immunological factors in stress response

The primary hormonal end product of the HPA axis is cortisol. A longitudinal study of 358 Dutch adolescents with a mean age of 15 years over 3 years showed that cortisol awakening response (CAR) moderated the effects of depressive symptoms on violent adult outcomes. The results showed that depressive symptoms were positively associated with violent outcomes when CAR levels are low [7].

Mental and physical stress can suppress the immune system in both humans and animals. Chronic stress-induced alterations in immune responses could result from increased cell death and apoptosis or decreased cell proliferation. It is well known that exhausting physical activity and mental stress lead to immunosuppression of the immune system by steroid hormone regulation. Chronic stress significantly enhances corticosterone production and induces lymphocyte apoptosis [8, 9]. Stress hormones like cortisol play a fundamental role in regulating immune responses and the balance of T helper (Th) 1 and Th2 cytokines, thereby modulating the susceptibility of various immune-related disorders. Toll-like receptors (TLRs) play a key role in modulating immune responses, cell apoptosis, and cell survival. Among 11 known TLRs in mammals, TLR9 plays a major role in chronic stress-induced immune suppression by modulating corticosteroid levels [10].

Psychosocial stressors increase peripheral cytokine production, a potentially important factor in the development of depression or anxiety [11, 12]. Subsets of patients with the major depressive disorder (MDD) and post-traumatic stress disorder have higher levels of multiple inflammatory markers, including the cytokine interleukin 6 (IL-6) [11, 13]. Preexisting differences in the sensitivity of an individual's peripheral immune system like cytokine interleukin 6 (IL-6) dictates their subsequent vulnerability or resilience to social stress [14].

5. Genetic factors involved in stress

Molecular studies of the stress phenomenon have found some genes which are differentially expressed in stressed individuals and control subjects. Studies

involving effect at individual genes as well as genome-wide studies at cellular, tissue, and individual levels are reported.

A study of DNA microarray from circulating leucocytes showed that the stress causes some genes upregulated and some other genes downregulated. The downregulated genes are mainly related to apoptosis, cell cycle inhibitors, NF-KB inhibitor (Apo J), and antiproliferative cytokines. The upregulated genes are involved in cell cycle activation, and enzymes involved in nucleic acid biosynthesis and proteins. Other upregulated genes are transcription factors that control chromatin structure and cell growth [15]. The transcription factor that controls many of these genes is NF-KB. Hence, NF-KB plays a key role in the cellular stress response.

Researchers have attempted to attribute genetic variation among individuals to their neuroendocrine responsiveness to environmental stimuli like stress by studying how the immune system interacts with the nervous and endocrine systems and, together, how they impact upon the course and outcome of disease [16]. As early as 1992, Gatz et al. studied the importance of genes and environments on the symptoms of depression [17].

Genetic factors are responsible for individual variation in emotional reactivity, and neuroendocrine stress responses were shown by family and twin studies in humans and by the study of inbred strains and selection experiments in animals [18]. A twin study revealed the significant genetic impact on the cortisol awakening response with heritability estimates between 0.40 and 0.48 for the mean cortisol increase after awakening and the area under the curve, respectively [19]. An increased cortisol awakening response in individuals reporting chronic stress includes social stress and lack of social recognition [19].

Several gene-environment studies have shown that long-term effects of stress are being moderated by genetic variations in the hypothalamic-pituitary-adrenal (HPA) axis. Studies by Wust et al. investigated contribution of large interindividual variability of HPA axis stress reactivity on variants of the glucocorticoid or mineralocorticoid receptor genes and documented a sex-specific association between different GR gene polymorphisms and salivary cortisol responses to acute psychosocial stress [20]. Single-nucleotide polymorphisms (SNPs) associated with stress vulnerability and resilience are found in the GR (e.g., through regulation by the FK506 binding protein 5 [FKBP5]), the corticotropin-releasing hormone factor receptor 1 (CRHR1), and the MR genes [21].

The genetic component is often complex in these studies and involves several genes and, hence, should study the quantitative trait loci (QTL). It is easy to study QTL in plants and animals where you can easily get the inbred lines where the genetic makeup is similar among individuals. Quantitative genetic analysis to behavioral responses to environmental challenges like stress in humans is done mainly on the large cohorts of families and twins.

Another approach is the utilization of genome-wide association studies (GWAS) that would facilitate identification of new genes involved in stress development and elucidate the molecular pathways which are dysregulated. In contrast to candidate gene studies that are based on prior biological knowledge, in GWASs common variants across the whole genome are screened concerning the contributing genes. GWASs for human stress-related phenotypes are rare [21]. A meta-analysis on plasma cortisol levels in 12,597 participants found a genome-wide association of SNPs in the SERPINA6/SERPINA1 locus. GWAS and individual gene studies are often underpowered owing to smaller sample sizes. There is a need to test whether the identified candidate genes appear to be nominally significant in the GWASs in larger samples [21].

6. Epigenetics involved in stress

Even though genome is the blueprint for biological activity, the epigenome adds another layer on top of the genome and serves to modulate gene expression in response to environmental cues. Epigenetic modification induced by environmental factors could influence the development of chronic pain by modulating genomic expression of one or more biological systems associated with pain and psychological stressors. Recent studies demonstrate that adverse psychosocial environments like stress can affect gene expression by altering the epigenetic pattern of DNA methylation, chromatin structure by histone modifications, and noncoding RNA expression [22].

Most of the epigenetic studies employ animal models at early life experiences that demonstrate epigenetic modification that occurs in response to stressors, which alter the developing epigenome in the hippocampus. Some studies evaluate epigenetic modification using adult models of stress and depression as well as consideration of the role of epigenetics in resilient versus susceptible phenotypes. Adverse events such as stress or maltreatment at early stages of development can more readily trigger epigenetic alterations which can adversely affect physiological function and behavior in adult life. Studies involving human samples from different models like suicide victims with and without child abuse, prenatal depression, and post-traumatic stress disorder showed altered DNA methylation patterns at the glucocorticoid receptor gene (NR3C1) [22]. The salivary cortisol response which in turn leads to altered central regulation of the HPA axis consequent to maternal depressed mood. Epigenetic changes due to stress affected the gene expression of several genes including estrogen receptor alpha (ER-A), trichostatin (TSA), N-methyl-D-aspartate (NMDA), nerve growth factor-inducible protein-A (NGFI-A), arginine vasopressin (AVP), brain-derived neurotrophic factor (BDNF), and cyclic-AMP response element-binding protein (CREB) [22]. Telomere shortening is one of the molecular indicators as an epigenetic effect on stress and chronic pain [23].

7. Biomarkers for diagnosis and treatment of stress

The hypothalamus-pituitary-adrenal axis (HPA axis) is a vital part of the human stress response system. The endocrine marker cortisol is a useful index of HPA axis activity, and it shows good intraindividual stability across time and appears to uncover subtle changes in HPA regulation. Cortisol activity and the response are important biological indicators of emotional and behavioral responses to environmental stressors. Low cortisol activity is hypothesized to be linked to antisocial behaviors [24]. Several studies demonstrated the role of age and gender; endogenous and exogenous sex steroid levels; pregnancy, lactation, and breastfeeding; smoking, coffee, and alcohol consumption; as well as dietary energy supply in salivary cortisol responses to acute stress [25]. Salivary cortisol levels are a reliable measure of HPA axis adaptation to stress and hence are a useful and valid biomarker in stress research [26].

The knowledge of the molecular bases of genetic variability points to the biochemical pathways responsible for the differences in stress responses will allow the development of new therapeutic strategies for pathological conditions [18]. Interventions aimed at manipulating the epigenome are a real and promising possibility to circumvent the stress-related psychoneuroimmunology disorders. Epigenetic and telomere changes may offer an array of targets that can be exploited for prevention and treatment interventions [27].

In conclusion, many kinds of mind-body behavioral interventions are effective in improving mood, quality of life, reducing stress, and anxiety, thereby altering neuroendocrine and immune functions, and ultimately altering the genetic aberrations. However, the question remains as to whether these latter effects are sufficiently large or last long enough to contribute to health benefits or if they are even relevant to the development of a disease. Unfortunately, there is no strong body of evidence that supports the clinical correlation between psychoneuroimmunology and genetics and reaping the health benefits through behavioral interventions.

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