STRESS & AUTOIMMUNE DISEASES

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Abstract: Incidences of autoimmune diseases are rising; the numbers of cases are tripled over the last few decades. There are more than eighty illnesses caused by autoimmunity. It has been estimated that autoimmune diseases are among the ten leading causes of death among women in all age groups up to 65 years. The etiology of autoimmune diseases is multifactorial: Genetic, hormonal, environmental, immunological factors, together with host susceptibility are all considered important in their development. The cause of this worldwide epidemic lies primarily in our environment and the toxic world in which we live, as various stressors have been implicated in the induction and perpetuation of many autoimmune diseases. Various stressors including physical, chemical, biological, and psychological have been shown to be responsible for this growing epidemic. Understanding the pathogenic modes of actions of various stressors e.g. molecular mimicry, role of cytokines, Toll-like receptors signaling pathways, role of stress proteins (heat shock proteins), role of reactive species, in addition to neuroendocrine immune systems interactions foster the advent in targeted therapeutic era. New strategies have been introduced and are being studied to overcome effects of oxidative stress at the cellular level for subsequent use as new therapies for autoimmune diseases e.g. targeting intracellular signaling pathways for various proinflammatory cytokines, DNA vaccines, anti-inflammatory neuropeptides, and more. The better understanding of these etiopathogenetic mechanisms can move us from the era of controlling or treating autoimmune diseases to a new era of preventing these diseases.

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1. Introduction

Autoimmune Disease (AIDx) is a condition in which the body immune system recognizes and attacks host tissues causing tissue destruction. It results from failure to sustain tolerance to self-molecules, i.e. a state of loss of immune tolerance (Bolon, 2012). It occurs when a self-antigen induces a specific adaptive immune response which the body cannot eliminate entirely, leading to chronic inflammation and tissue damage. Dozens of AIDx involving one or multiple organ systems afflict 3% or more of people worldwide (>75% women). It has been estimated that autoimmune diseases are among the ten leading causes of death among women in all age groups up to 65 years.

The etiology of autoimmune diseases is multifactorial; genetic, hormonal, environmental, immunological factors, together with host susceptibility are all considered important in their development (Ecrolini & Miller, 2009).

Genetic Factors: Many genes--over 20 different ones, each of which showed a small effect in contribution to susceptibility to autoimmune inflammatory diseases. However, genetic predisposition is only a minor risk factor; Low concordance rates were observed in monozygotic twins. In addition, geographic distribution was an additional risk factor for disease risk.

Hormonal Factors: Neuroendocrine hormones triggered during stress may lead to immune dysregulation, altered or amplified cytokine production, resulting in impaired host defense and autoimmune diseases. Blunting of the brain hormonal stress response is an important contributor to the development of autoimmune diseases. The reason for this is that chronic stress leads to impaired limbic-hypothalamic-pituitary-adrenal axis (LHPA) with reduced secretion of cortisol (this potent anti-inflammatory hormone that is released from the adrenal glands in response to stress); The LHPA axis becomes less responsive to stress potentially resulting

in an impaired capacity to cope with stressors. Several autoimmune diseases are mediated by neuroendocrine-immune (NEI) network dysregulation, including autoimmune rheumatic diseases: rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, as well as other autoimmune inflammatory diseases: Atherosclerosis, Graves' disease, type-I diabetes mellitus, among others (Butts & Sternberg, 2008).

Immunologic Factors: Autoreactive T cells i.e. reduced deletion or enhanced activation of autoreactive CD4+ T-helper (Th) lymphocytes; Defective immunomodulation by CD4+ regulatory (Treg) and CD8+ suppressor (Ts) T-lymphocytes; Autoreactive B cells & autoantibody production; Cytokine dysregulation i.e. dysregulated signaling (leading to a relative increase in pro-inflammatory cytokines); Role of complement.

Therefore, there were questions:

1) What is the cause of this growing epidemic?
2) Why is this number of cases tripled over the last few decades?
3) How does the toxic world in which we live cause the rates of autoimmune diseases to overshoot?

Top scientists in this field agree that the cause of this epidemic (which is worldwide) lies primarily in our environment, and in all the toxins, industrial fumes, heavy metals, chemicals, pesticides, infectious agents, as well as increasing psychological stress with long working hours, sleep deprivation, and unhealthy dieting and lifestyle

Stress is a stimulus or a succession of stimuli tending to disrupt the homeostasis of an organism. It is the response of the brain to unpleasant events. It is a ubiquitous and unavoidable experience of daily life, whether it arises from the external environment or from within the body (Butts & Sternberg, 2008).

Stimuli acting as potential stressors are numerous, and include: physical stressors, chemical stressors, biological stressors, and psychological stressors. Over 1,400 physical and chemical reactions in conjunction with greater than 30 hormones and neurotransmitters are involved in body's stress response.

In recent years, much has been learned about the effect of various stressors on the immune function, and the role of the stress response in various autoimmune diseases. A large number of potential stressors have been implicated in the development of autoimmune disease (Cataldi, 2010).

4) How stress can cause or worsen disease?
5) How understanding the cross-talks between the brain and the immune system can help us structure our lives to help us heal?

Many retrospective studies found that a high proportion (up to 80%) of patients reported uncommon stress (physical, mental, emotional …etc.) before disease onset. Not only does stress cause disease, but the disease itself also causes significant stress in the patients, creating a vicious cycle. Thus, different stress reactions should be discussed with autoimmune patients, and obligatory questionnaires about trigger factors should include inquiries about common triggers; infection, trauma, psychological stress…etc. (Stojanovich & Marisavljevich, 2008).

Physical Stress: Various physical agents that may act as potential stressor include: Ionizing radiation, Non-physiological oxygen levels (hypoxia, hyperoxia), Ultraviolet rays (UVR), Heat exposure, strenuous physical activity and over exhaustion

Chemical Stress: Several environmental and occupational chemical exposures are considered as triggers for autoimmunity, including: Silica dust and lupus, use of permanent hair dyes in women was associated with a borderline increase in the risk of developing Systemic Lupus Erythematosus (SLE) in the CLU study (Cooper et al, 2001), Vinyl chloride and organic solvents in scleroderma, Mercury, gold or perchloroethylene in autoimmune kidney disease, and Polybrominated biphenyls in autoimmune thyroid disease.

Environmental chemicals may also contribute to autoimmune liver disease: non-alcoholic steato-hepatitis/ NASH). Not only foreign chemicals and agents have been associated with induction of autoimmunity, but also an intrinsic hormonal exposure, such as estrogens, which might explain the sexual dimorphism in autoimmunity. Better understanding of these environmental risk factors will likely lead to an explanation of the mechanisms of onset and progression of autoimmune diseases and may lead to effective preventive involvement in specific high-risk groups.

Psychological Stress: continued psychological stress (mental or emotional) can compromise brain function with impaired concentration, memory, and learning. It can damage the hippocampus responsible for pain predisposing to chronic pain & fatigue syndromes. It can result in immune dysfunction that results in autoimmune disease after frequent activation of the autonomic nervous system in the case of chronic stresses. Associations between psychological stress (mental or emotional stress) and depressive disorders as well as autoimmune disease have been established.

Many reviews discuss the possible role of psychological stress, and the major stress-related hormones, in the pathogenesis of various autoimmune diseases, and presume that the stress-triggered neuroendocrine hormones lead to immune dysregulation, which ultimately results in autoimmune disease by altering or amplifying cytokine production (Slavich & Irwin 2014; Stojanovich & Marisavljevic, 2008).

A retrospective cohort study of 15,357 adults has examined the effect of cumulative childhood stress and increased risk of developing autoimmune diseases in adults. Adverse Childhood Experiences (ACEs) included childhood physical, emotional, or sexual abuse, witnessing domestic violence, mental illness, or parental divorce.

The outcome was hospitalizations for any of 21 selected autoimmune diseases. Sixty-four percent (64%) reported at least one ACE.

First hospitalization for any autoimmune disease increased with increasing number of ACEs ($p < 0.05$). Persons with >2 ACEs compared to those with no ACEs showed a 70% increased risk for hospitalizations with Th1, 80% increased risk for Th2, and 100% increased risk for rheumatic diseases ($p < 0.05$).

This study concluded that childhood traumatic stresses increased the likelihood of hospitalization with a diagnosed autoimmune disease decades into adulthood. These findings are consistent with recent biological studies on the impact of early life stresses on subsequent inflammatory responses (Dube, 2009).

Biological Stress: Infectious agents and/or their products have been implicated in the pathogenesis of autoimmune diseases. Chronic bacterial and viral infections are associated with a variety of autoimmune diseases involving chronic inflammation, including rheumatic conditions as well as chronic fatigue syndromes. Possible mechanisms of bacterial & viral involvement as etiological agents or in the exacerbation of these diseases have been investigated intensively. An auto-regulatory loop might exist in the interaction of bacteria with the host and in pathogenic signal processing. These studies reveal potential therapeutic targets (Sherbet, 2009).

Evidence of various Mycoplasma species infections has been strongly associated with Rheumatoid Arthritis (RA); there is often systemic infection of more than one species. Mycoplasma antigens induce both cell-mediated and humoral immune responses. Besides, H. influenzae, Bordatella, Yersinia, Chlamydia pneumoniae, Borrelia burgdorferi, Proteus mirabilis, & staphylococcal enterotoxins A & B represent possible infecting organisms as well.

Bacterial infections associated with other autoimmune conditions: Demyelinating diseases as Multiple sclerosis (MS), Landry-Guillain-Barre (LGB) syndrome …are possibly a consequence of autoimmune condition or infection by viral or bacterial agents with the resultant development of demyelinating plaques. LGB syndrome has been associated with Mycoplasma pneumoniae, Campylobacter jejuni & Haemophilus influenzae infection. Moreover, serology and PCR have provided ample evidence of Chlamydia pneumoniae, Borrelia burgdorferi, and Mycoplasma species, among others in MS, ALS, Alzheimer's and Parkinson's disease.

A tentative relationship between MS and streptococcal infection has been suggested (Sherbet, 2009; Casserly et al., 2007). Possible modes of pathogenic action of bacteria: the role of cytokines, Toll-like receptor signaling, interaction of heat shock proteins with the immune system, and role of reactive oxygen & nitrogen species (ROS/RNS)

Viral Infection: Various viral infections are sometimes associated with the initiation or exacerbation of autoimmune diseases. Viruses like Epstein-Barr virus (EBV), parvovirus, cytomegalo-virus, rotavirus, coxsackie B-1, hepatitis B & C virus, rubella, human herpesvirus-1, -6 and -7 and other viral infections showed association with several autoimmune diseases. EBV is known as an infamous viral agent that can encourage the initiation and perpetuation of different autoimmune diseases; systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, autoimmune thyroiditis, autoimmune hepatitis, and Kawasaki disease. Virus-like inclusions were found in the renal biopsy tissue of SLE patients. Various viral infections have been implicated in Type-I diabetes as well (Barzilai et al., 2007).

Possible modes of pathogenic action of viruses: Molecular mimicry between Epstein-Barr virus and human antigens: The involvement of HLA antigens in the pathogenesis of various autoimmune diseases has been suggested to be due to the molecular similarities between certain bacterial or viral antigens and HLA or other human antigens.

Viral persistence: Evidence that the human microbiota accumulates during a lifetime, and a variety of persistence mechanisms are coming to light. In one model, obstruction of VDR nuclear–receptor-transcription prevents the innate immune system from making key antimicrobials, allowing the microbes to persist. Genes from these microbes must necessarily impact disease progression. Recent efforts to decrease this VDR-perverting microbiota in patients with autoimmune disease have resulted in reversal of autoimmune processes. As the NIH Human Microbiome Project continues to better

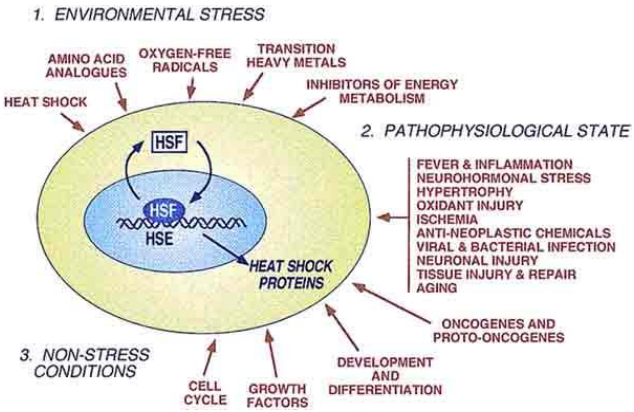
characterize the human metagenome, new insights into autoimmune pathogenesis are beginning to emerge (Proal et al., 2009).

Autoreactive T & B cells creating immortal cells by loss of apoptosis, production of autoantibodies, and role of cytokines: There is strong evidence that bacterial and viral antigens induce the synthesis of many pro-inflammatory cytokines with consequent implication in a wide range of autoimmune diseases.

Induction of Toll-like receptor (TLR) signaling: TLRs are transmembrane receptors that represent the first line of defense against microbial antigens, and can activate immune cell responses. They can recognize pathogen-associated molecular patterns (PAMPs) of infectious agents, including LPS, viral RNA, and unmethylated CpG-oligonucleotides. Exposure of cells to LPS or other toxins induces TLR signaling mechanisms with expression of different pro-inflammatory interleukins and interferons.

Phosphatidyl inositol-3-kinase (PI3K) is thought to participate in the TLR signaling pathway. PI3K activation is commonly observed after stimulation with various TLR ligands. The resultant activation of serine-threonine protein kinase Akt leads to increased expression of various proinflammatory cytokines including IL-12 & TNF. This provides a novel therapeutic approach (Hazeki et al., 2007).

Role of Heat-shock proteins (stress proteins):



6) What are Heat-Shock Proteins (HSPs)?

HSPs are a group of proteins that are present in all cells in all life forms, but are mostly known as stress proteins because their expression is increased when the cells undergo various types of environmental stresses.

They have a variety of functions for monitoring cell's proteins: Help new or distorted proteins fold into their correct shape, which essential for their function, act as 'chaperones,' is ensuring that the cell's proteins are in the right conformations and in the right place at the right time, transport old proteins to removal areas inside the cell, shuttle proteins from one compartment to another inside the cell (cell trafficking), play a role in the presentation of specific proteins sites or peptides to the cell surface to help the immune system recognize diseased cells.

Although HSPs represent an important initial line of defense against various stressors, they may represent immune-dominant antigens/ autoantigens that are presented to T cells bearing gamma delta receptors.

They have the ability to influence both innate and adaptive immune responses inducing the expression of various interleukins contributing to autoimmune disease. A growing body of evidence suggests that auto-reactivity in chronic inflammatory arthritis involves gamma delta cells, which recognize epitopes of the stress proteins. This supports the notion that HSPs actually play a role in autoimmune processes.

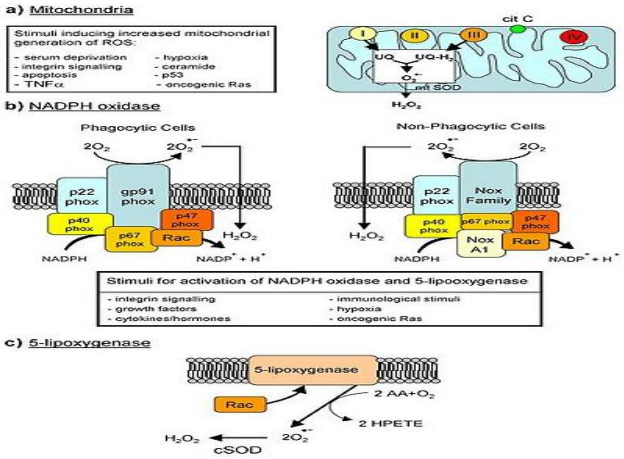
Alternate mechanisms for T cell stimulation by stress proteins is molecular mimicry of the DR susceptibility locus for RA by a stress protein epitope in gram-negative bacteria. The capacity of certain stress proteins to bind to multiple proteins in the nucleus and cytoplasm both physiologically and during stress or injury to cells, suggests that stress proteins may be important elements in the "immunogenic particle" concept of the origin of autoantibodies. Autoantibodies to a number of stress proteins have been identified in RA, AS, & SLE (Sherbet, 2009).

Role of Reactive Species (RS): Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), e.g. nitric oxide, [NO] are "two-faced" products. They are well recognized for playing a dual role as both beneficial and deleterious species. ROS and RNS are normally generated by tightly regulated enzymes; NADPH oxidase and NOS, respectively. Many of ROS-mediated responses protect cells against oxidative stress and maintain "redox homeostasis''.

Beneficial effects of ROS/RNS e.g. superoxide radical & nitric oxide occur at low/moderate concentrations where they act as molecular signals that regulate a series of physiological processes: Defense against infectious agents, Maintenance of vascular tone, Control of ventilation, Erythropoietin production, Cellular signaling pathways in various physiological processes, Induction of a mitogenic response (Coaccioli et al., 2010).

Normally in the organism, damage by ROS is counteracted with natural antioxidants: Enzymatic antioxidants: glutathione peroxidases, superoxide

dismutase (Cu-Zn SOD, Mn SOD), and catalase. Non-enzymatic antioxidants: thiol antioxidants (glutathione, thioredoxin), ubiquinol, uric acid, essential minerals (selenium, molybdenum,..) carotenoids, vitamin C, vitamin E (tocopherol), and flavonoids (Valko et al., 2007).



Reactive Oxygen Species ROS): Overproduction of ROS can be induced by various endogenous and exogenous factors and results in oxidative stress; a deleterious process that can be an important mediator of damage to cell structures, including lipids & membranes, proteins and DNA.

ROS act as second messenger by activating p38 mitogen-activated protein kinase (MAPK), activator protein-1 (AP-1), Nuclear Factor Kappa B (NFKB) with subsequent activation of transcription factors involved in the inflammatory cascade (Valko et al., 2006).

This redox imbalance can initiate a wide range of toxic oxidative reactions in the cell including: Initiation of lipid peroxidation, Oxidations of amino acids in proteins, direct inhibition of mitochondrial respiratory chain enzymes, Inactivation of specific enzymes by oxidation of co-factors, Inhibition of membrane sodium/potassium ATPase activity, Inactivation of membrane sodium channels, Damage of DNA, Oxidative cellular stress induced by environmental factors, such as cigarette smoke, UV or ionizing radiation, bacterial or viral infection, or any number of oxidizing xenobiotic compounds, triggers a wide range of pro inflammatory cellular responses. ROS are capable of initiating DNA single strand breakage, with subsequent activation of the nuclear enzyme Poly ADP Ribose Synthase (PARS), leading to eventual severe energy depletion of the cells, and necrotic-type cell death.

Excessive increase in Reactive Species (RS) production has been implicated in the pathogenesis of various autoimmune, demyelinating, and chronic inflammatory disorders: atherosclerosis, cardio-vascular diseases, hypertension, diabetes mellitus, RA, ischemia/reperfusion injury, and ageing by activating specific signaling pathways which lead to transcription of genes involved in production of proinflammatory cytokines and other inflammatory mediators hence perpetuating the inflammatory cascade (Moroni et al., 2010).

Various studies have evaluated the oxidative stress in various autoimmune rheumatic diseases; RA, SLE, APS, PsA as well as other autoimmune diseases, and found significantly higher levels of Serum Hydroperoxide Concentration (SHC) with significant reduction in Total Antioxidant Capacity (TAC) and Thiolic Capacity (TC), concluding etiopathogenic role for RS in these diseases (Coaccioli et al., 2010; Moroni et al., 2010)

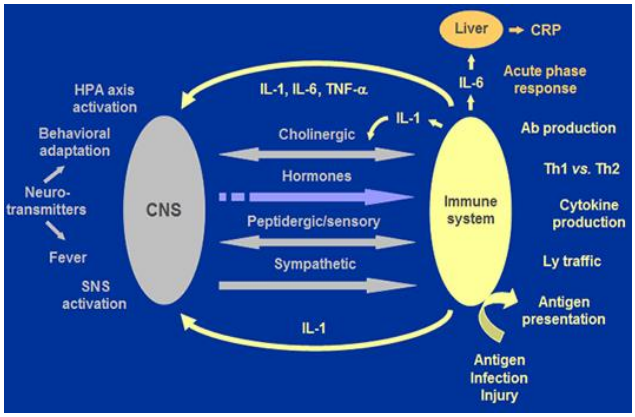
Reactive Nitrogen Species (RNS): Nitric oxide (NO) is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS). Two constitutive NOS isoforms [endothelial NOS (eNOS) and neuronal NOS (nNOS)] are formed and play important roles in the regulation of vascular tone and homeostasis. Cytokine-inducible NOS (iNOS) generates excessive amounts of NO. This is required for bacterial clearance during infection. The general and overall effects would be bactericidal /cytotoxic in nature. iNOS exerts deleterious effects and has been implicated in the pathogenesis of a number of autoimmune, inflammatory, neurodegenerative diseases: RA, SLE, MS among others; all show associated synthesis of NO and their toxic products. Up-regulation of the iNOS has an important role in the expression of pro-inflammatory mediators in inflammation, and can be responsible for sustained inflammation, and as a cytotoxic molecule with a pivotal role in apoptosis at the joints of RA patients (Predonzani et al., 2015).

Neuro - Endocrine - Immune System Interactions: Inflammatory responses are modulated by a bidirectional communication between the Neuro-Endocrine System (NES) & Immune System (IS). Many lines of research have established the numerous routes by which the Immune System (IS) and the Central Nervous System (CNS) communicate.

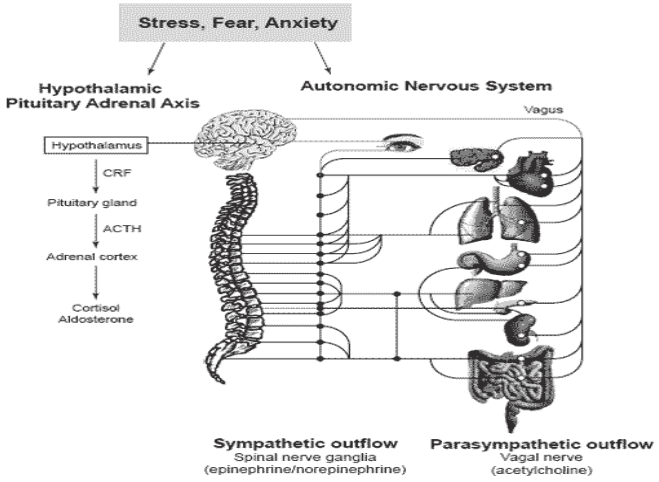
The immune system signals the Central Nervous System (CNS) through immune mediators and cytokines that can cross the blood-brain barrier, or signal indirectly through the vagus nerve or second messengers. The CNS signals the immune system through hormonal pathways, including the Limbic - Hypothalamic - Pituitary - Adrenal axis (LHPA) and the hormones of the neuroendocrine stress response, and through neuronal pathways, including the Autonomic Nervous System (ANS). Interactions between the CNS and IS play an important role in

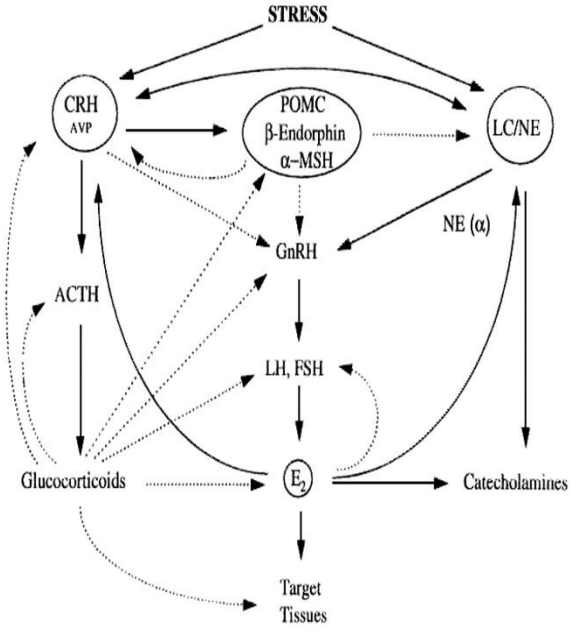
modulating host susceptibility or resistance to inflammatory diseases.

NES produces neuropeptides and hormones which can modulate the activity of the immune system. It also secretes proinflammatory cytokines (IL-1β, IL-6, & TNFα). On the other hand, the IS produces cytokines, which can modulate the neuroendocrine system. It produces neuropeptides (CRH, ACTH, AVP, POMC, PRL, & GH). Therefore, both systems can modulate the activity of one another (Marques-Deak et al., 2005).



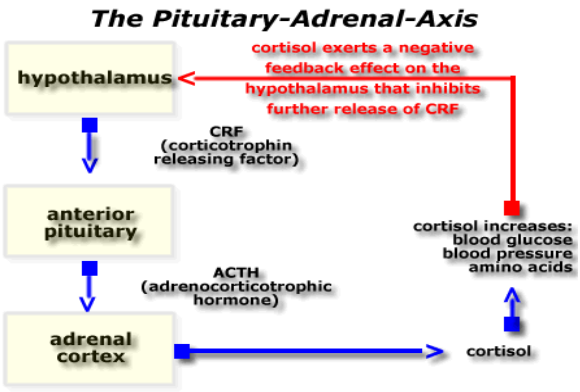
Adaptive response to various stress stimuli involves activation of: Limbic-Hypothalamus-Pituitary-Adrenal (LHPA) axis and Sympathetic autonomic nervous system (SANS).





The Limbic-Hypothalamus-Pituitary-Adrenal (LHPA) axis: Whenever a person is subjected to acute stress, whether an internal or external stressor, the limbic system of the brain triggers the hypothalamus to secrete Corticotropin-Releasing Hormone (CRH). In the hypothalamus, cytokines (IL-1β, IL-6, &TNFα) activate the production of CRH & AVP which are stimulatory factors for adrenocorticotrophic hormone (ACTH) release in the pituitary gland, and consequent cortisol production in the adrenal cortex. Cortisol will in turn inhibit the production of CRH & AVP in the hypothalamus as well as ACTH in the pituitary gland. The released glucocorticoids have anti-inflammatory and immunomodulatory effect, causing a shift in patterns of cytokine production from a TH1- to a TH2-type pattern.

When cortisol blood levels become excessive, this turns off CRH release in a negative feedback loop. CRH also stimulates the production of a pituitary-derived cytokine: Macrophage Migration Inhibitory Factor (MIF) which counteracts the immunosuppressive effects of cortisol on T cells and macrophages with consequent production of IL-1β, TNFα, IL-6 promoting inflammatory response. Moreover, local production of CRH, AVP, & PRL has shown to contribute to chronic inflammation (Eskandari et al., 2003).



Sympathetic Autonomic Nervous System (SANS): Sympathetic noradrenergic and peptidergic fibers innervate lymphoid organs. This provides an additional physical link to neural modulation of the immune response. Neutrophils, macrophages, Natural killer cells, T & B lymphocytes were found to express adrenergic receptors on their surfaces.

Acute stress: If the stresses in our life are only occasional, and we take adequate time for rest, relaxation and sleep to restore LHPA equilibrium, then occasional stress cortisol release will not be a problem, i.e. some cortisol is essential for life.

Excessive stress: When the body is subject to excessive stress that exceeds the body capability of healing, circumstances of stress, overcome the negative feedback regulation of the LHPA axis, together with SNS overstimulation with excessive production of stress hormones (cortisol, epinephrine & norepinephrine), i.e. excessive cortisol is equally damaging.

Chronic stress: Prolonged unresolved stress can result in defective LHPA axis response which can be one of the factors responsible for a shift from acute to chronic phase of inflammation, and can be an important contributor to the development of various autoimmune diseases. As a consequence of this LHPA axis dysfunction, there is a lower diurnal cortisol level in RA patients, and lower cortisol response to surgical stress.

Many autoimmune diseases and disease states of chronic inflammation are accompanied by alterations in the complex interactions between the endocrine, nervous and immune systems (Silverman & Sternberg, 2008).

Thus, treatment of autoimmune diseases needs multidisciplinary care interventions that target patients' disease symptoms and help them cope with their illness; it should include stress management and behavioral intervention to prevent stress-related immune imbalance (Stojanovich & Marisavijevich, 2008).

In an ideal world, we would make lifelong stress management an integral part of our daily life. We would: Sleep eight to nine hours nightly, Take relaxing breaks during the day, Take frequent mini-vacations from work to restore LHPA & SANS equilibrium, Utilize stress reduction techniques such as meditation, quiet prayer, massage, relaxation techniques…etc., Have regular aerobic exercise: take brisk 30-to-60-minute walks daily in the open air, Live in quiet homes without chronic noise stress from loud TVs, stereos, traffic…etc., Follow healthy eating habits: Eat only nutritious foods: fresh fruits & vegetables, fish, poultry, whole grain, and low fat, take a multivitamin supplement daily to boost the immune system, our air and water should be clean, Avoid tobacco, alcohol, Avoid stimulants such as pseudoephedrine, Avoid chemical stressors such as heavy metals: lead, mercury, pesticides….. Etc., and pharmacologic management of anxiety.

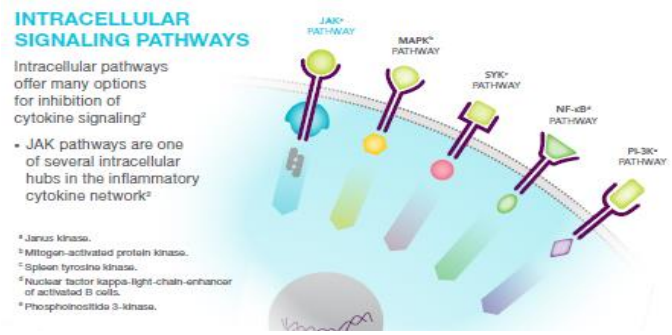
Antioxidants: Antioxidants can help reduce the oxidative damage to our cells by capturing damaging free radicals: Vitamin A, C, and E (tocopherol) supplements. Trace elements: Cu, Zn, Mn, Se, molybdenum. Pharmacological preparations that provide the proper nutrients needed to promote the body's own ability to manufacture and absorb glutathione (GSH). The depletion of glutathione and the cofactors to recycle glutathione between its oxidized and reduced states may play a key role in the loss of self and chemical tolerance. There is some evidence that glutathione depletion activates iNOS which in turn promotes T lymphocyte activation i.e. increased iNOS activity promotes lymphocyte activation. Inducible NO synthase (iNOS) can be expressed in macrophages and is able to induce NO production. Ultimately, Treg failure and barrier breakdown. Others supports the production and function of superoxide dismutase (SOD) and catalase (CAT); two vital antioxidants produced by the body to fight the potent free radical superoxide.

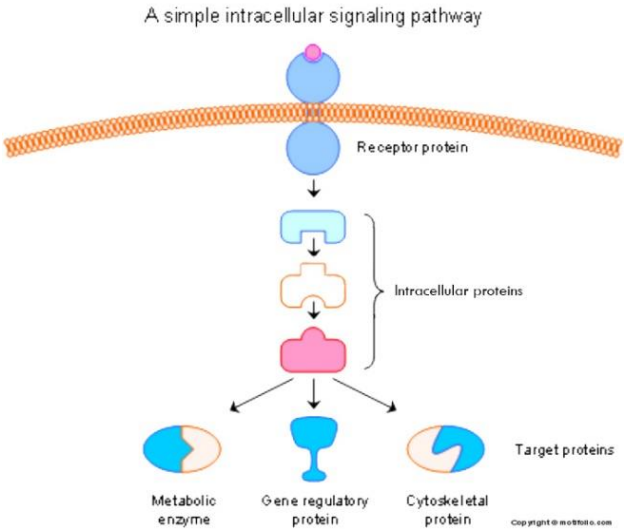
Flavonoids: Evidence suggests that flavonoids have potential neuroprotective effects controlling neuro-inflammatory processes contributing to the cascade of events culminating in the neuronal damage in neurodegenerative disorders; Parkinson's and Alzheimer's disease. They have been shown to be highly effective in preventing age-related cognitive decline and neurodegeneration, and that they may express such ability through a multitude of physiological functions, including an ability to modulate the brains immune system. They also show potential to inhibit neuro-inflammation through an attenuation of microglial activation and associated cytokine release, iNOS expression, nitric oxide production and NADPH oxidase activity.

Current evidence indicates that the regulation of these immune events appear to be mediated by their actions on intracellular signaling pathways, including the nuclear factor-κB (NF-κB) cascade and mitogen-activated protein kinase (MAPK) pathway.

Novel Therapeutic Targets: Advances in our understanding of the cellular and molecular mechanisms in rheumatic disease fostered the advent of targeted therapeutics era: Targeting stress proteins /Heat Shock Proteins (HSPs), anti-inflammatory neuropeptides/ neuro-hormones, Inhibitors of iNOS, and inhibitors of intracellular cell signaling pathways e.g. p38 MAPK (mitogen-activated protein kinase), ERK (extra-cellular regulating kinase), JNK (c-Jun-N-terminal kinase), Phosphatidylinositol 3-kinases (PI3K) Jak-Stat (Janus kinase & signal transducer & activator of transcription).

Controlling Cell Signaling: Every cell in an organism is exposed to hundreds of different signals from its environment. The cell can respond to these signals in a variety of ways, and does so independently. However, all of these independent actions come together in a very complex and interconnected pathway of communication that governs basic cellular activities and coordinates cell actions. The ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis. Errors in cellular information processing can be responsible for diseases such as cancer, autoimmunity, and diabetes. By understanding the fundamentals of cell signaling, researchers hope to be able to develop new drugs and treat them selectively and effectively. As intracellular signaling pathways transmit environmental information to the cytoplasm and subsequently to the nucleus, where they regulate cellular responses and gene transcription and as various intracellular signaling pathways are involved in the initiation & persistence of inflammation, Small molecules can be designed to block intracellular enzymes that control these cell signaling pathways, hence abolishing related effects of inflammation & tissue damage.





Targeting Stress Protein /Heat Shock Proteins: Targeting stress proteins through the engineering of DNA vaccines containing the heat-shock protein gene from mycobacteria in order to intervene in autoimmune processes. Instrumental HSPs include HSP 90, 70, 65, 60, 40 and 27 (Santos et al., 2009).

Anti-Inflammatory Neuropeptides: Resolution of inflammation and re-establishment of immune homeostasis and maintenance of tolerance: Vasoactive intestinal peptide (VIP), Urocortin (UC), Adrenomedullin (AM), Alpha melanocyte stimulating hormone (αMSH), Cortistatin, and Ghrelin (Delgado & Ganea, 2008).

iNOS inhibitors: Recently it has been demonstrated that treatment with NG-monomethyl L-arginine (L-NMMA); an inducible Nitric Oxide Synthase (iNOS) inhibitor prevents the activation of Poly ADP Ribose Synthase (PARS), and prevents the organ injury associated with inflammation. It has been shown to reduce urinary markers of systemic oxidant stress in proliferative lupus nephritis.

2. Conclusion:

To sum up, with more understanding of the etiology and trigger factors of autoimmune and chronic inflammatory diseases, as well as different pathogenetic mechanisms more therapeutic targets can be identified that can offer novel treatments or even preventive measures for the rising epidemic of autoimmune and chronic inflammatory diseases. With continuous serious efforts in the field the best is yet to come.

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