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Conclusions

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The sphyngomyelin cascade signals the muse cerebral cortex and of thymocytes.

Stress releases cytokines (CTK) from both the CNS and immune system [1].

New signaling pathway is presented. Discussion of cytokines in stress. This is a nice paper.

Participation of orexin neurons in the processes of thermoregulation and in brain reactions to cold stress has been confirmed. The reactions of orexin-sensitive cells of the hypothalamus, midbrain, medulla, spinal cord and immune organs to antigen injections in different doses reflect changes in the function of orexinergic cells. These data highlight the role of orexin system in brain reaction to various kinds of stressors [2].

The authors used LPS, stapylococal enterotoxin and tetanus toxoid, all derived from bacterial products, which are known to activate the innate immune system via TLR? or by other innate antigen receptors [3]. The innate immune system developed receptors for pathogenic agents which are capable of activating the entire organism for host defense [4]. So acute febrile illness (APR) will develop after applying innate antigens to animals [5]. Naturally a systemic disease, such as APR is very complex indeed, and it activates multiple networks of regulatory centers/nuclei in the hypothalamus. Interestingly electric pain stimulation also activated the entire network. It is clear from these results that the hypothalamus handles stressful stimulation by activation of the hypothalamic regulatory network. The stronger is the stimulus the more centers/nuclei are activated in the hypothalamus. A commonly used antigen, bovine serum albumin (BSA) activated 2 out of 6 hypothalamic areas, which seems as a modest stimulation.

To date the the neurons containing both, orexin A and B were shown to be involved in brain response to stress. Here we review new experimental data about the involvement of orexin neurons in brain reactions to stressors (hunger, hypoglycemia, immobilization, pain, etc.). Recent evidence shows that the release of orexin A and B may affect hormone secretion of the hypothalamic-pituitary-adrenal axis hormones in response to stressors. Hypothalamic orexin-containing neuron groups depend for activation on applied stimulation. The patterns of morphological and functional changes of orexin-containing neurons, which are localized in various hypothalamic structures, were analyzed after application of various stressors (eg. restraint stress, cold stress, antigen application). Our own results, in agreement with data in the literature, suggest certain functional identity of orexin-containing neurons in the perifornical part of hypothalamus. The reactions of orexin-sensitive cells of the hypothalamus, midbrain, medulla, spinal cord and immune organs to antigen injections in different doses reflect changes in the functional of orexinergic cells. These data indicate the participation of orexin system in brain reaction to various kinds of stressors [6].

Oexin is a new neuropetidee, which is also found in the immune system. So, here is another shared mediator to deal with.

In chronic stress the HPA axis and SNS may not be the major players. GC sensitivity is altered and GC resistance may develop. The organism has the ability to fine-tune sensitivity to hormonal signals at the level of the target tissue. Low GC sensitivity may predict PTSD. Reduced HPA axis activity is frequently found in conditions and disorders characterized by increased systemic low-grade inflammation.

It has been found that catecholamine (CAT) sensitivity inversely related with plasma C-reactive protein (CRP) (but not IL-6) concentrations, indicating that a lower CAT sensitivity is related with higher peripheral inflammation. It is anticipated that the autonomic nervous system takes over immunoregulation during chronic inflammatory disease. However,

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more studies are required to elucidate this problem [7].

The question is what could happen after the acute stress response is over? In most instances vasopressin takes over and leads the organism to healing and recovery. What if the condition keeps going on? It is stated in this paper that a so called *chronic inflammatory disease* will develop. The observations that there is GC resistance, and the HPA axis also inhibited make perfect sense, after all, these regulatory pathways failed to protect the host. That catecholamines (CAT) and acethilcholine (ACH) would do the job is a logical assumption. CAT is known to be immunostimulatory and supports the APR. Acethylchline suppress immune function [8]. In this paper CAT was suggested to act against chronic inflammatory reactions. So ACH may be available as well. One question remains. What if the suppression of GC and ACH also develops? We must keep in mind that the innate immune system possesses tremendous potential for autonomy. So it could work alone and provide defense by maintaining chronic inflammation. So ultimately regulation would be done by stimulatory and suppressor cytokines produced within the system of innate immunity [9]. The long inflammatory process is undesirable, mainly for its high metabolic request, but still it is a defense reaction and may lead to recovery.

The *adaptive immune system (ADIM)* involves the bone marrow that produce bone marrow derived (B) lymphocytes, and also release precursor cells for thymus derived (T) lymphocytes. B cells produce antibodies and regulate antibody formation. T cells mediate cellular immunity by killer T cells, and T cells mediating delayed type hypersensitivity. During an ADIM response, T and B lymphocytes proliferate, and their receptors undergo somatic mutation and clonal selection in order to generate highly specific antigen receptors. Seven to ten days needed for an adaptive immune response to develop. Antigen presenting cells (APC) initiate the ADIM response.

Innate immunity (INIM) protects us for life. Innate antigen receptors are germ line coded, constant and polyspecific. The bone marrow produses monocyte/macrophages which recognize antigen. CD5+ B lymphocytes producing polyreactive natural antibodies, and polymorhonuclear granulocytes which are phagocytic cells. Natural killer, NK and NKT cells, and suppressor/regulatory T (Ts/r) cells are thymus derived. Cytokines are produced by monocytee/macrophages, NK, NKT Ts/r cells. The liver produces acute phase proteins (APP). Complement, properdin, defensins, scavenger receptors, enzymes and numerous other substances function as APP. The INIM system is capable for instantaneous defense at any time even under adverse conditions it will protect the host.

During *homeostasis* both the adaptive and innate immune systems are regulated by vasopressin (VP) and everything works in harmony. During *acute illness* immune derived cytokines induce the *acute phase response,* which is an emergency defense reaction against life threatening insults. During APR the INIM system is stimulated rapidly (maximum $\sim$ 1000 times, within 24–48 hours) and take over host defense as the ADIM system is not capable for a rapid response, and it is suppressed. Major endocrine, metabolic, and immune alterations take place. The HPA axis, sympathetic nervous system, glucocorticoids, catecholamines, pro-inflammatory cytokines, the brain, liver and white blood cells mediate APR. Fever and catabolism are hallmarks of APR.

APR is the last effort by the organism to survive a life threatening event. In the overwhelming majority, febrile illness will be followed by recovery, which indicates the efficiency of this reaction. As a rule acute febrile illness will subside and chronic inflammatory disease will follow. During chronic inflammation VP becomes the regulator of hypothalamic function of the inflammatory process. Recovery will follow in most instances. The neuroendocrine, metabolic and immune abnormalities will be normalized and VP will serve as the hypothalamic factor regulating immunity and bodily functions during homeostasis.

In cases when chronic stress does not subside, the INIM system will remain activated, and because of the excess energy requirement by this system, *cachexia* may develop, which may be a lethal condition [10].

The hypothalamo-pituitary-adrenal axis (HPA) harmonize immune response to inflammatory stressors. Cytokines and other humoral factors play particularly important roles in this communication. Cytokines act as major feedback regulators of the vertebrate immune response. *Acute stress* can compromise the activation of the HPA axis and activate the innate immune system for defense, redirecting leukocytes from the circulation to the environment-organism interface. During the initial phase of stress ($\sim$24 hrs) the innate immune system goes to the site of infection/insult and rapidly recognizes innate antigen associated homologous epitopes (homotopes) [11] in most instances resolves the problem and leads to recovery.

Rarely the acute response may be followed by HPA activation and continuation of the stress response. *Chronic stress* leads to chronic immune arousal and

subsequent sterile, low-grade inflammation, which has been identified in most "stress-related or "civilized" disorders in humans.

The pituitary-gonadal axis leads to gender difference in the activation of HPA axis. Corticotropin-releasing hormone (CRH) and its receptors (CRF-R1 and CRF-R2), melanocortin peptides, glucocorticoids or pro-inflammatory cytokines can also act as immunoregulators, since their receptors is present in lymphoid organs, also in peripheral blood and organs that are enhanced under inflammatory conditions.

In spite of series of experimental data, the role of CRH and other members of its family, as well as its receptors in inflammation are still controversial [12].

In several countries, work is considered not only source of income, but also represents well-being and social identity, provides social relations, regular daily activity and planning of life. Job stress may derive from environmental conditions, not necessarily related to the working activities, but to additional conditions such as low social support, repetitive work, gratification and shifts. Moreover, perception of job insecurity today affects also the workers with stable employment because of the global economic crisis. Stress job conditions or situations of job insecurity may influence the life style, including smoking habit, healthy dietary habits and mental health status; they are considered serious stressful situations which may induce emotional disorders. Job strain and/or insecurity may thus affect both neuroendocrine and immune systems: reduced immune reactivity to mitogens and/or decreased blood NK cytotoxic activity was reported either in unemployed workers or in those with a high perception of job insecurity and/or job stress. It is also known that stress play an important role in autoimmune diseases. Although genetic factors have a key role in the pathogenesis of autoimmune disorders, occupational stress (as in night shifts) was also reported association to an increased incidence of autoimmune disorders [13].

This paper properly points out that stress is multifactorial in nature. The sensitivity of the individual, which is genetically controlled, counts a lot when it comes to the adverse reaction to stress. We must keep in mind that the primary function of the stress response is host defense. However, the brain has the capacity to *anticipate danger,* which in turn will turn on the CNS-HPA-ACTH-ADR-INIM axis, when danger is anticipated. In other worlds the CNS replaces the stress event and gets the innate immune system going. This is fantastic if it helps to eliminate the stressor. However, if INIM cannot eliminate the problem, because it is job related? This is when the problem comes in. The activated INIM will drain the resources of the body without stopping the problem. In this situation disease may follow. In serious cases cachexia and death may develop [5].

The evidence indicating that immune reactions, which are based on lymphocyte proliferation, are regulated by mechanisms that are involved in the growth control of all cells in higher animals is reviewed. Growth and lactogenic hormones (GLH) or type I cytokines (TICTK) are required for the development and function of the immune system. It is suggested, that GLH/TICTK deliver the first signal to cells, including lymphocytes, that prepares them for proliferation, differentiation and function. This signal is designated as the *competence signal.* It is required for the growth of animal cells in general and for lymphocyte growth, and is obligatory for the maintenance of immunocompetence. The second group of signals, that control cell growth, are delivered by cell-to-cell and cell-to-matrix signaling and are designated as *stromal or adherence signals.* Adhesion molecules, tissue bound hormones, cytokines and matrix components mediate these signals. The antigen receptor belongs to the Immunoglobulin Family of adhesion molecules. Hence the antigen signal is capable to activate the immune response, it can inhibit it also. Within the immune system antigen presentation represents such a signal for which cell-to-cell interaction is obligatory. Adhesion molecules are fundamental to the organization of multi-cellular organisms and the signals delivered by them serve the basis of species, organ and tissue specific recognition. This recognition system has been perfected during evolution from self-recognition to individually specific antigen recognition. This system also plays a role in the elimination of degenerated and neoplastic cells. Cell-to-cell signaling has a dominant power over other signals to commit the cell to proliferation. The cell cycle is then completed after the delivery of *cytokine signals.* Cytokines are tissue hormones which are usually, but not always, secreted by the same cells that deliver the second signal. The nature and combination of these three groups of signals will determine the fate of each cell, which may be survival, proliferation, differentiation and function or alternately apoptosis. Hormones and neurotransmitters, that alter signal delivery, modulate further this basic pattern of animal cell growth. It is reasonable to conclude on the basis of current evidence that GLH/TICTK maintain immunocompetence, which enables the immune system to respond to specific antigenic and mitogenic stimuli [14].

Corticotropin releasing hormone (CRH) and Vasopressin (VP) are the hypothalamic immunoregulators. The CRH – adrenocorticotropic hormone (ACTH) – glucocorticoid (GC) and catecholamine (CAT) axis, jointly with VP, stimulate innate immunity (INIM). During acute illness CRH activates the HPA-GC-CAT axis and INIM will be amplified up to 1000 times in 24–48 hours. GC and CAT stimulate directly INIM and also generate suppressor/regulatory T cells (Ts/r) which inhibit adaptive immune (ADIM) function. The acute phase response (APR) is a complex metabolic, endocrine and immune response which leads to a systemic inflammatory response. This is the last attempt to save the host organism from life threatening disease/injury. In most cases healing and recovery will follow, so APR is a very effective in host defense [15].

Vasopressin has emerged in recent years as a very important immunoregulatory peptide of the hypothalamus. Vasopressin is capable of maintaining immune function, both innate and adaptive immunity. This is due to the ability of vasopressin to stimulate both the hypothalamus-pituitary-adrenal axis and also prolactin. The hypothalamus-pituitary-adrenal axis is important for innate immune function, whereas prolactin and growth hormone maintain adaptive immunocompetence. Recent results show that vasopressin also has a direct regulatory effect on cytokines.

During acute illness vasopressin will rise along with corticotrophin releasing hormone. In this case corticotrophin releasing hormone regulates the inflammatory process, and vasopressin supports this role. Innate immunity is amplified by glucoicorticoids and catecholamines whereas adaptive immune function is suppressed.

During chronic inflammation corticotrophin releasing hormone is repressed and vasopressin becomes the primary hypothalamic immunoregulator. Vasopressin gradually restores homeostasis by maintaining both the hypothalamus-pituitary-adrenal axis and prolactin secretion in balance and hence restores normal immune function and leads to healing and recovery of the organism.

Therefore, the two hypothalamic immunoregulatory peptides, corticotrophin releasing hormone and vasopressin have different functions. Corticotrophin releasing hormone plays an important function in acute phase response, whereas vasopressin supports the acute phase response, but it is really the hypothalamic regulator of healing and of physiological immune regulation [16].

Natural antibodies are those antibodies present in the circulation of vertebrates that have not been previously exposed to specific antigens. The best characterized and studied natural antibodies are those directed against blood group substances; it was not known that blood group substances contain epitopes shared with microorganisms living in the gut of the individuals. Using more sensitive methods it has been established that natural antibodies are present in the sera/plasma of normal healthy individuals and that these antibodies may have a physiological role connecting the immune system and may participate in the removal of aging cells, miss folded proteins, etc.

Some characteristics of natural antibodies have been described over the years. Most natural antibodies are the IgM isotype, although other isotypes, such as IgG and IgA, are also present. Natural antibodies are germ line encoded, meaning that under normal circumstances they do not contain mutations in their variable regions. Natural antibodies have polyreactive binding sites, which imply that these antibodies may bind different epitopes with different structure/conformation. Due to their polyreactivity, natural antibodies often bind with low to medium affinity (10^5–10^7 M^{-1}). As mentioned above, the specificity of these antibodies is directed against normal microbiota, but some clearly recognize self-antigens. Natural antibodies may also have a role in protection against invading microorganisms [17].

The B cells producing natural antibodies (Nab) belong to the *innate immune system*; hence they rely on germline genes to develop their immmunoglobulins. The epitopes such antibodies recognize are evolutionarily highly preserved, crossreactive antigens of pathogenic microorganisms. This explains the polyspecificity of such antibodies. As pointed out, these B cells are activated by microorganisms in the gut and elsewhere. LPS would activate innate B ells. Throughout evolution the innate antigen receptor system has evolved to recognize highly conserved crossreactive epitopes on pathogenic microorganisms. Innate immune cells are fully mature and are ready to respond instantaneously, without delay when the pathogenic agent presents itself to innate immune cells [9]. The value of innate antibodies is illustrated by the therapeutic value of normal immunoglobulins on patients suffering from diverse diseases [18].

The authors analyzed the effects of short synthetic peptides and native DNA preparations on the function of the immune and neuroendocrine systems under various stress conditions. These preparations of peptides and nucleotides are known to be effective modulators of the immune and neuroendocrine systems. Here we discuss a new concept, which suggests that endogenous

short peptides and their synthetic analogs bind to specific sequences of nucleotides in DNA strands. These site-specific peptide-DNA interactions modulate cellular genetic functions and form the basis of molecular-genetics of stress-protective short synthetic peptides. Protective action of nucleotide preparations on impaired functions of the immune and neuroendocrine systems was shown. It seems that these effects are based on the ability of nucleotides to penetrate cells and subsequently splitting into nucleotides, which, after releasing from the cell, bind to purinergic P2 receptors. The results indicate that short synthetic peptides and native DNA preparations are capable of correcting stress induced impairment of neuroimmune function [19].

This is a highly original paper on a little known subject. Who would think that protein and nucleic acid break-down products would modulate the stress response? But it is happening; the results to prove it are in our hands. This is incredible! The body made use of tissue brake down products to regulate the stress response! Such products are in ample supply if tissue injury is associated with stress. But even if there is no tissue injury these materials are available during normal metabolism, I suppose, so no investment is required for specific synthesis. They are available and may be used for regulating the stress response. The perfection of other Mother Nature is admirable!

Chronic fatigue syndrome (CFS) is a disorder diagnosed following at least 6 months of disabling, unexplained mental and physical fatigue accompanied by other physical and psychological symptoms. Fibromyalgia (FM) is a chronic pain syndrome of unknown etiology characterized by diffuse pain and tender points, which must be present for more than 3 months. These patients have the path similarity in psycho-neuro-endocrino-immunological system [20].

This paper is about differential diagnosis of CSF and FM, which is regarded as different entities but frequently appear together. But what about the pathomechanism?

A recent paper states: "We conclude that CFS is accompanied by a relative resistance of the immune system to regulation by the neuroendocrine system. Based on these data, we suggest CFS should be viewed as a disease of deficient neuroendocrine-immune communication" [21].

If the neuroendocrine system cannot communicate with the immune system it is not life threatening, the INIM system defends the host. However, there is no neural input which would bring in the ability of immune reactions to adapt to environmental and other, even internal, demands of the organism. Fatigue and exhaustion indicates that the body survives, but is not capable to function in the real world. This disease is the perfect example to illustrate the significance of the Neuroendocrine system in immunoregulation. Without such regulation, the immune system works blindly, without knowing what is happening in the outside world. *Could this be the final stage of the stress sydromes?* One may assume that it would go like this: *Acute Stress-Stress –healing...Chronic inflammatory disease . . . chronic fatigue syndrome...Cachexia . . . Exit??* More work is required to elucidate the correct answers to these questions.

The brain and immune system being the two principal adaptive systems in the body permanently share information both in the form of neural impulses and soluble mediators. The CNS differs from other organs due to several peculiarities that affect local immune surveillance. The brain, which is separated from the rest of the body by blood-brain-barrier (BBB), produces the cytokines by itself and the latter along with other neurotransmitters regulate various brain functions including cognition, memory, and neuronal differentiation. The stress of different origin increases the serum cytokine levels and disrupts BBB. As a result peripheral cytokines penetrate into the brain where they begin to perform new functions. Long-term stress as well as physiological aging result in hormonal disturbance, first of all in the form of HPA axis depletion and dehydroepiandrosterone (DHEA) decrease. Thus, the changes observed in stressed subject form a picture typical of the aging brain. The concept of stressful cognitive dysfunction, which is under consideration in this review, allows picking out several therapeutic targets [22].

But what about *successful ageing*? [23] Some studies done on very old people revealed that they do maintain their endocrine and immune parameters within normal levels! So how could we prevent such deleterious effects of chronic stress and of ageing? Apparently there are examples that this could be resolved. Perhaps we will find this out later . . .

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