

# Physiological Research Pre-Press Article

**Immunity – a significant pathogenic factor as well as an integral part of the psychoneuroendocrine-immune regulations**

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## **Summary**

Immunity plays an important role in the reactivity of the organism and, in this context, is an essential factor in the pathogenesis of many diseases. Basically, there is no system or organ in the body, whose dysfunction is not related to immunity consequences. In addition, there are also multisystem diseases simultaneously involving multiple body systems. They are not always caused by weak immunity, but also often by modified immune reactions known as overshooting. The essence of all these diseases is a change in the reactivity of the organism where immunity plays an important role. The immunity as such is then part of the systems of neuroendocrine-immune regulation, which have common mediators and receptors. The establishment of psychoneuroimmunology (PNI), a relatively new discipline in neuroscience, contributed to a detailed understanding of these mechanisms between central and peripheral NS, the endocrine system and the immune system. This research enabled the uncovering of the nature of stress-diseases and impact of other PNI-regulatory disturbances on the function of various body organs and systems of the organism as a whole. ~~It also showed the need for a comprehensive and individualized approach to the patient and the importance of both a targeted treatment and prevention.~~ The aim of this short review is to show complex interconnections of these relationships to better understand the human health and disease.

## **Key words**

Immunity, pathogenesis, psychoneuroimmunology, psychoneuroendocrine-immune regulations, stress diseases

## **Introduction**

Currently, there is no doubt that immunity plays a significant role in the pathogenesis of many diseases. Essentially, there is no system or organ in the body the impairment of which would not have immunity consequences. Additionally, there are other diseases named multisystem diseases that affect multiple systems in the body at the same time. Yet is it not always a matter of weak immunity, but also modified, often so-called overshooting immune responses that particularly are recently on the rise. Among them are various types of oversensitivities, such as allergies, atopies, anaphylaxes (pollen, food, etc.), where the body responds to allergens from the external environment in this manner.

However, aside from these, there are also autoimmune diseases, where abnormal immune reactions are directed toward the tissues of the body itself. The essence of all (not only) these diseases is a modified response of the body, in which immunity plays a significant role. Nonetheless, it must be emphasized that the mutual influence of both is two-directional. A compromised reactivity can thus be the consequence of immune changes, or affect immunity in its consequences. This points to the influences that are largely internally determined in the body, meaning mostly conditioned by heredity (constitutions, neuroendocrine relations, barrier functions, etc.), as well as by factors of the external environment that can be of various nature and intensity (for example physical, chemical, biological, as well as psychological and social).

The result of the effect of these factors upon a given body's reactivity is a various level of bodily prosperity, the determining factors of which are good health on one side or disease and possibly even death on the other. At the same time, all such internal and external factors and influences are mutually, functionally and multilaterally connected in order to best contribute (if possible) to the individual's good health. This is particularly a matter of sustaining stability of the internal environment, homeostasis. It was later completed with a term allostasis which means an additional process of reestablishing homeostasis under variable and changing conditions (Sterling, Eyer 1988). In the optimal case then is important to maintain the harmonious balance of both the homeostasis and allostasis with the influences of the external environment. In opposite situation when allostatic load (mainly in highly civilized society with increased demands in the nervous and mental sphere) is chronically high, then the allostatic overload develops together with various pathological consequences (Vožeh 1994, McEwen 1998b, 2008, McEwen and Wingfield 2003, Mašek et al. 2003) (Fig. 1).

## **Overview of current knowledge of psychoendocrine-immune relations**

Of the number of mechanisms that take place in sustaining normally functional immunity, as well as in cases of immune dysfunctions, it is appropriate to mention psychoneuro-endocrine relations and regulations. It is their knowledge that enables us to understand the changes of body responses, including immunity disorders caused, for example, by psychobiological stress, whether apparent through lower resistance against infections, various allergic reactions or weakened resistance against tumorous growth. Mutual relations between the neuroendocrine and immune systems are mediated through a number of ergones – neurohormones, neurotransmitters, as well as cytokines that are native to both these systems in which they are produced and where they are also actively taking effect (Blalock 1985, Blalock et al. 1985, Besedovsky et al. 1985, Besedovsky, del Rey 1988, Weigent et al. 1990, Ferenčík et al. 1998, Ganor and Levite 2014, Arreola 2016, Cacabelos 2016) (Table 1).

The first empirical observations in this area were already conducted in previous centuries by entire generation of doctors beginning with the famous Galen (129-200 BC). Back then he had already stated that melancholic women more often suffer from cancer (Mašek et al. 2003). Also, time-tested and practice-tested truisms and sayings such as “a cheerful mind is one half of health” or “a healthy spirit dwells in a healthy body” should also be understood in this context.

Only in the last three decades of the 20<sup>th</sup> century was a systematic research initiated in this area, leading in the 1980s to the creation of the interdisciplinary field of psychoneuroimmunology (PNI). This originally produced random works, but later works that authors also began conducting systematically in regard to psychoneuroendocrine–immune interactions both in experiments on animals as well as human clinical studies. This is how, for example, behaviorally conditioned immunosuppression was described, as well as its significant role in the programming of neuroendocrine functions in mice (Ader and Cohen 1975, Pierpaoli and Besedovsky 1975). Structurally functional circuits responsible for neuroendocrine-immunity interactions were described, thanks to monitoring the effects of small brain electrolytic lesions on the immunoendocrine function of laboratory rats (Mašek et al. 1992, Petrovický et al. 1994). The impact of inherent cerebellum neurodegeneration on the adrenal glands, thymus and other parts of the lymphatic system of mutants was described, including a contribution from our research team (Beranová et al. 2002, Mandáková et al. 2005, Vožeh et al. 2014).

It must be said that certain stages are observable in regard to the overview of the key ergones shared by the immune and neuroendocrine systems (see Table 1). They were

particularly discovered over the course of the last decades of the 20<sup>th</sup> century, as well as subsequently until present times. First there were discoveries proving the connection of stress hormones with the HPA axis (hypothalamus –hypophysis – adrenal glands), but later also other peptides, derived from proopiomelanocortin (Blalock et al. 1985, Besedovsky et al. 1985, Smith et al. 1988, Besedovsky and del Rey 1988, Carr and Blalock 1988, Bauer 2005).

Shortly thereafter, receptors for these ligands were gradually found, again in both these systems, further confirming a functional two-way communication. The discoveries of this de facto molecular essence of the functional connection of both systems continued alongside exploration in the sense that cytokines native to immunity cells and tissues were identified in the nervous system, produced primarily by glia (Besedovsky and del Rey 1988, Weigent et al. 1990, Ferenčík et al. 1988, Kelley 2014, Holzer 2015, Hořejší 2017).

On the other hand, the role of lymphokines and monokines was found, mediating an inflow of information about the current condition of the immune system into the nervous and endocrine structures, which is absolutely indisputable and crucial for current immuno-regulation (Besedovsky and del Rey 1992, 2011, Haddad et al. 2002).

Subsequently, all of the above findings concerning neuroendocrine immunity interactions then logically led to the formulation of the concept of the immune system as a sixth sense within the further development of PNI. The essence of this concept lies both in peptides and non-peptides (for example gas neuromediators NO, CO, H<sub>2</sub>S) shared by both systems (Manusco et al. 2010) as well as cytokines (as ligands of the respective receptors of the immune system) that could form this sixth sense. Along with the classic five senses, this sixth sense is then able to detect various pathogens, tumorous cells or allergens with high sensitivity, as well as the ability to specify and differentiate those native only to the immune system. As a sixth sense, the immune system, together with shared signaling, is then capable of mobilizing the body to respond to specific triggers. All of the above mentioned mechanisms also likely play a role in the famous “placebo effect” (Blalock and Smith 2007).

The next stage of approach to a developing PNI particularly regards the role of psychology, stress and behavior factors which, as mentioned above, were already considered significant in the disease pathogenesis much earlier in history. However, a systematic research of these mechanisms and particularly scientific proofs concerning this are mostly a matter of the 21<sup>st</sup> century.

Although considered a threat these days, stress (or more precisely a stress response) is in essence a very useful ability in the adaptation of complex organisms, including humans and it can be stated with certainty that if this wasn't the case, many animals would have no chance

of surviving. On the other hand, if the stress is intense and long-term and, additionally, if this stress is of so-called psychobiological or psychosocial nature in the case of modern humans, which creates greater psychological than physical demands, than this “good servant turns into a bad master”. This then becomes a significant pathogenetic factor in the case of psychosomatic diseases, which could also be called stress diseases and disorders.

Unfortunately, these represent an ever-expanding number these days (Kemeny and Schedlowski 2007). The study of pathogenetic mechanisms of these diseases in relation to disturbed psychoneuroendocrine-immune regulations is particularly a matter of the last two decades and still continues. For example, the theory of Professor Charvát and his colleagues, published in 1964 (Charvat et al. 1964) and revolutionary in its day, was developed in detail, proving a causal relation between chronic mental stress and myocardial infarction. However, only recent studies have shown the participation of anti-inflammatory cytokines and this in relation to both acute and chronic ischaemic heart disease. The essential role of stress-related sleep disorders in relation to the release of these cytokines was also found in this relation. This proved the importance of quality sleep as a cardinal factor in development of both acute (myocardial infarction, acute cerebral stroke) and chronic circulatory diseases (Skinner et al. 2009, Motivala 2011).

Another significant area, where the research of psychoneuroendocrine-immune relations brought fundamental new findings, was the area of tumorous diseases. In this area, it has been a long-known fact that weakened immunity (for example due to long-term stress or other reasons, such as AIDS) is accompanied by a higher occurrence of tumors. However, only the research of the last few years specifically explained the participation of etiopathogenetic mechanisms within the psychoneuroendocrine-immune mechanisms in tumorigenesis, including a ratio of the individual anti-tumorous cytokines, the involvement of epiphysis, as well as two-way signaling between the tumor and the brain with subsequent modulation of neuroendocrine-immunity functions (Reiche et al., 2004, Ondicova and Mravec 2010, Lissoni 2012, Skřivanová et al. 2014,).

The continuing research also identified notable findings and consequences between compromised psychoneuroendocrine-immune relations in diseases belonging to the fields of psychiatry, skin and eye medicine.

In psychiatric diseases this specifically involves the relationship between depression and decreased immunity. Particularly depressions are evidently co-responsible, for example, for both the formation of tumors and the course of these diseases with a direct impact on the survival expectancy period. The same thing is true in case of infectious diseases, where it is

also a consequence of a depression-induced immunosuppression, as well as impairment of many multidirectional neuroendocrine-immunity interactions (Besedovsky et al. 1996, Irwin and Miller 2007, Smith 2015).

Surprising, although not greatly surprising, were also the recent discoveries in the pathogenesis of schizophrenia. Here, clear evidence proved a causal connection between anti-inflammatory cytokines found in increased amounts in the cerebrospinal fluid of the patients. Both the results of experiments on animal models and the epidemiological studies of humans proved a significant role of the early impairment of immunity for later increased immune reactivity. These studies showed that severe infections and autoimmune diseases could be risk factors for schizophrenia. Also, genetic research confirmed similar results in regard to this disease being “inflammatory”, identifying a connection between schizophrenia and chromosome 6p22.1 in an area that relates to the HLA system of human tissue antigens and other immune functions. This “inflammation” theory is also indirectly supported by the significant therapeutic effect of anti-inflammatory medications and antipsychotic medications with similar effect (Schubert 2014, Müller et al. 2015).

In relation to skin diseases, here the new discoveries reach all the way to the molecular level, confirming the well-known rule of ancient medical practitioners that “skin is the mirror of the body”, with the addition that the psychoneuroendocrine-immune subtext of the disease relates to psychosomatics. This was specifically proven in such skin diseases as atopic dermatitis, psoriasis, as well as malignant melanoma, the most frequent and continually increasing current diseases (Moynihan et al. 2010, Peters 2016).

And finally, although it is surprising, eye impairments also show etiopathogenetic consequences and have a continually and increasingly evident relation to psychoneuroendocrine-immune dysregulations. As shown by research focused in this direction, this subtext applies in the case of glaucoma, dry keratitis, atopic keratoconjunctivitis, uveitis, and the ever more frequent macular degeneration and eye malignancies (Ventura 2009). Also findings that re-evaluate and supplement the knowledge of the functional morphological substrate of these relations with the surprisingly significant role of enteric nervous system (ENS), known also as “gut brain” and colon microbiota, are among the latest significant discoveries in the PNI area, with an impact on many physical systems, as well as organs and actually on the organism as a whole. It is now without doubt that there is a two-way functional gut-brain axis to which both ENS and the rich colon immune system and microbiota contribute. Here should be also emphasized that the beginning of intestine colonization by useful bacteria in newborns starts with normal physiological mode of birth

and further then by prebiotics in maternal milk that positively affect function of the gut-brain axis (Rautava et al. 2012, Makino et al. 2013, Oliveros et al. 2015, Vazquez et al. 2016, Mittal et al. 2017).

Based particularly on experimental research on “germ-free” rodents, colon microbiota is specifically attributed with the key role in the development of emotional behavior, stress and pain-modulating systems, as well as function of brain neurotransmitter systems. The above seemingly revolutionary findings are not as surprising if we consider the amount of bacteria in the colon (equal to the number of cells in the human body), the massive immune system (representing the largest amassing of this tissue in the body), as well as the amount of neurons (equal to their amount in the spinal chord – over 100 million). In any case these findings bring further understanding of diseases such as irritable bowel syndrome, autism, anxieties, depression, as well as neurodegeneration (for example Parkinson’s disease) (Collins et al. 2012, Bailey 2014, Borre et al. 2014, Lyte 2014, Mayer et al. 2015).

Aside from the above list of negative impact of psychoneuroendocrine-immune dysregulations, some of their positive influences should also be mentioned, as they are capable of preventively avoiding these impairments or subsequently mitigating them. This means that life should be harmonized in such way that stress situations are balanced with activities and experiences that positively influence both the body and the psyche. This is both quantitatively and qualitatively different for each individual, but the result should be a positive thinking and balanced optimistic world view (Steptoe et al. 2009, Boehm and Kubzansky 2012).

Despite the personality differences mentioned, here we can also find a common denominator, such as music – and not just any music. Regardless of the relatively individual approach to different styles of music, as a relaxation phenomena (increasing stress resistance, showing an evident positive impact on immunity), publications do differ and this holds true regarding specific composers. Mozart’s music is absolutely clearly preferred in this regard, given that the relaxation effect and particularly the positive impact on selected immunity parameters (certain cytokines and interferon-gama) was evidently more apparent than in the Beethoven and Schubert compositions (Kimata 2003, Okada et al. 2009, Fancourt et al. 2014).

## Conclusions

To conclude this paper, it must be stated that the etiopathogenesis of diseases is a far more complex matter than even the most significant representatives of modern medicine (even as late as the 20th century) could ever imagine. As mentioned in the introduction, the

occurrence of diseases is conditioned by the body's reaction under the influence of immunity and vice versa. All this is a close relation to the personality type that is conditioned genetically, as well as formed by other influences of the external and internal environment over the course of lifetime and in each given moment. This confirms all postulates regarding the unity of body and soul known from ancient history, but the scientific evidence concerning this was brought about by modern sciences, particularly through the formation of the PNI. This field finally proved the interconnectedness of the psychoneuroendocrine-immune relations and regulation in the sustenance of homeostasis of the organism, as well as the pathogenesis of practically all diseases related to its disruption.

This laid the foundations both for a correct understanding of an organism as a dynamic unit in health and illness and opened new possibilities of a complex approach to the prevention and treatment of diseases. On one hand, this means that we must continually see the patient's body as a whole and treat it in this manner. On the other hand, we must influence the respective known pathogenetic mechanisms of diseases on cellular, subcellular or even molecular levels in a sensitive and targeted manner.

At the same time, this points to the need to create an individualized medicine, tailor-made to the personality of the patient.

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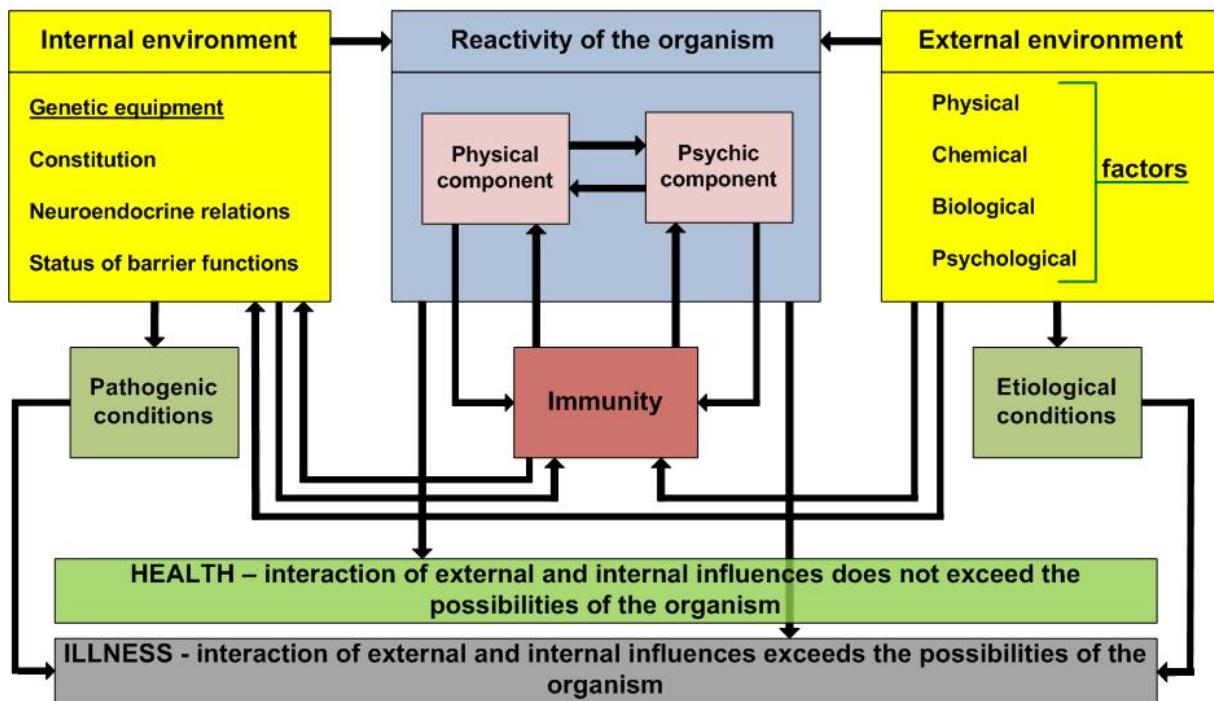
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## Immunity – a significant part of reactivity of the organism



**Fig1. Immunity - a significant part of reactivity and their interconnectivity with other factors in the context of the whole organism**

**Tab. 1: Joint mediators of the neuroendocrine and immune system**

Pituitary hormones	Neuropeptides
Adrenocorticotropic hormone (ACTH)	(Met) enkephalin
Endorphins	Arginine vasopressin (AVP)
Thyroid-stimulating hormone (TSH)	Oxytocin
Chorionic gonadotrophin (HCG)	Neuropeptide Y
Luteinizing hormone (LH)	Vasoactive intestinal peptide (VIP)
Follicle-stimulating hormone (FSH)	Somatostatin (SST)
Prolactin (PRL)	Insulin-like growth factor 1 (IGF - 1)
Somatotrophic hormone (STH)	
Hypothalamic releasing factors	Cytokines formed by some types of glia and neurons
Corticotropin-releasing hormone (CRH)	Interleukins IL 1, 6, 10
Somatotropin releasing hormone (SRH)	Interferons IFN $\alpha$ , $\beta$ , $\gamma$
Luteinizing hormone releasing hormone (LH-RH)	Tumor necrosis factor TNF- $\alpha$ Transforming growth factor TGF $\beta$ Transforming growth factor TGF $\beta$ Granulocyte macrophage colony stimulating factor (GM-CSF) Monocyte chemoattractant protein MCP-1
Gaseous mediators	
<b>Nitric oxide (NO)</b> gas	neuro immuno-modulator and general biological messenger acting on the nervous (synaptic transmission, cognition), immune and vascular system
<b>Hydrogen sulphide (H<sub>2</sub>S)</b> gas	in a neurotransmitter significant induction of hippocampal LTP, nociception, in the periphery is involved in relaxation of smooth-muscle
<b>Carbon monoxide (CO)</b> gas	is a general neuromodulator acting both in the peripheral and central NS (synaptic plasticity, brain stress control)
<b>All these gases are involved in the regulation of the HPA stress axis in the hypothalamus</b>	