## THE ANALYSIS OF THE IMMUNE AND NEUROENDOCRINE SYSTEMS CO-REGULATION IN CONDITIONS OF RISK FACTOR EXPOSURE<sup>1</sup>

## D. Lanin

Federal State Research Institution "Federal Research Center for Medical and Preventative Technologies of Public Health Risk Management", Perm, Russia

**Abstract.** The author analyzes the literature data on co-regulation of the immune and endocrine systems and its change under chemical exposure. The article outlines the approaches to identifying effect markers to assess dysfunction of the regulatory systems under exposure to various risk factors. **Key words:** chemical factors, immune system, neuroendocrine system

The triad regulatory "metasystem" [2, 9, 15] is currently a generally accepted concept that includes neuroendocrine and immune circuits; here, various regulatory mechanisms (nervous, endocrine, and immune regulation) exert reciprocal regulatory effects [1, 10, 11, 21, 31]. On the other hand, the effect of risk factors including chemical environmental and workplace factors on individual regulatory circuits [5, 6, 7, 16, 24] is well established. This report provides an overview of the co-regulatory effects of the immune and endocrine systems and the publications that reflect the change in individual components of the regulatory function of those systems under exposure to chemical risk factors.

The possibility of neuroendocrine impact on the immune system is well accepted. In 1980s, glucocorticoids, androgens, estrogens and progesterone were considered inhibitors of the immune response, while growth hormone, thyroxin, and insulin were referred to as stimulants. At the turn of the century, however, the number of supporters of such a simplified framework was decreasing, and today there is evidence that hormonal effects depend on the dose, experimental system and a number of other factors [12]. For this reason, it is more appropriate to discuss immune modulation that depends on the dose of the hormone, the experimental methodology as well as the cell type, immune system compartments, and the level of immune response rather than immune-stimulating or immune suppressive effects.

Neuroendocrine impacts on immune functions are associated with the following: the ability of the nervous system to control hormone secretion directly or indirectly, as well as occurrence of reciprocal hormonal effects in neuromediators, e.g. in stress-reaction [17, 18, 46] or with pain syndrome [21]; in sympathetic [26] or parasympathetic innervation [38] of lymphatic tissues; and with specific receptors [31] on phagocytic, immunocompetent, and auxiliary cells of the immune system.

Publications on this topic identify several regulatory circuits. One of the main mechanisms responsible for endocrine regulation of the immune system is hypothalamuspituitary-adrenal axis activation [13]. All the components of the regulatory circuit affect the immune system, but researchers pay the most attention to the end component - glucocorticoids [28] which affect all the components of the immune system and make it very difficult to determine whether their effects are depressive or stimulating [19, 49]. Glucocorticoids are likely

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to have an immune-modulating effect rather than immune-suppressive effect; except that natural and synthetic glucocorticoids sometimes demonstrate the opposite effect [37]. Moreover, it is important to keep in mind the co-regulating relationships [42]; e.g. there is evidence that direction of the immune response changes in the presence of glucocorticoids and  $\beta$ -adrenoreceptor blocking agents [17, 19, 44].

When analyzing immunotropic effects of the pituitary-hypothalamic-thyroid system, it is important to focus on the influence of the thyrotropic hormone (TTH aka TSH) and the thyroid hormone (thyroxin -  $T_4$ , and triiodothyronine -  $T_{3}$ ). To summarize immunomodulatory effects of TTH, we can conclude that thyrotropic hormone [48] has a stimulating role. Along with direct effects, TTH regulates immune functions mainly through the change in thyrotropic hormone products (other pituitary hormones affect immune regulation also mainly through the regulation of respective hormone secretion). Today thyroid hormones are considered immune function modulators. There is evidence that thyroid hormones have immunomodulatory effect on both adaptive and innate immunity [3, 4, 12, 14, 35]. Another important aspect here is interaction between the hypothalamic-pituitary-adrenal and pituitary-hypothalamic-thyroid axes whose immunomodulatory properties are often diametrically opposed [27, 34].

Pituitary-hypothalamic-gonadal system modulates immune functions in the same manner as the hypothalamic-pituitary-adrenal and pituitary-hypothalamic-thyroid axes [23]. Estrogens play the most important role in immune regulation. In general, physiologic concentrations of estrogen increase immune response while physiologic concentrations of androgen such as testosterone and dehydroepiandrosterone have a suppressive effect on the immune system [22, 23]. The risk of many systemic autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis is higher in females. In fact, occurrence of these diseases is two to ten times more common in females than in males [39, 40]. Most importantly, the activity of the hypothalamic-pituitary-adrenal axis is inhibited by androgens and estrogens; thus various effects of reproductive hormones on the hypothalamic-pituitary-adrenal axis can determine gender differences in immune response [23, 39].

A more detailed analysis of neuroendocrine regulation of the immune function including the molecular basis description is available in earlier publications [12, 13].

Thus today there is evidence of neuroendocrine regulation of immune function.

In addition to the regulatory circuits described above, it has been proven that insulin, prolactin, and somatotropic hormone of the sympathetic and parasympathetic nervous systems, etc. also participate in immune response [25, 26, 30, 36, 38].

Nevertheless, it is important to keep in mind that the immune system can have a reciprocal regulating effect on neuroendocrine mechanisms through various cytokines and secretion of respective hormones by immune competent cells [35, 45]. Thus we are looking at two-way regulatory relations between the immune and endocrine systems. According to R.L. Wilder [50], the graph below shows the relationship between the nervous, immune, and endocrine systems and their interconnection with psychological and somatic health problems (Figure 1).



Figure. 1. Interaction between the immune and neuroendocrine systems (from [Ошибка! Источник ссылки не найден.] with changes )

More evidence shows that various chemical factors cause disruptions in the neuroendocrine and immune status [7, 16, 29]. For instance, a report by Gore [29] describes the effects of chlorine-containing organic compounds on neuroendocrine functions; in particular, the author analyses the level of hypothalamus cells responsible for production of gonadotropin releasing hormone under exposure to chlorine-containing organic compounds. In vitro, such exposure induces gene expression disorders, a decrease in cell survival, and disruptions in cell development as well as direct toxic impact on cell lines, in vivo testing shows disruptions in mRNA in female rat hypothalamus neurons; based on this evidence, the author concludes that there is a connection between neuroendocrine axes, particularly, between the pituitaryhypothalamic-gonadal axis and environmental toxins. A publication by J. Janosek et al [33] describes the effects of exogenous xenobiotics on nuclear receptors and their signaling pathways. The authors introduce the idea of correlated changes in molecular mechanisms of hormone action determined by environmental toxins and immune suppression, carcinogenesis, reproductive dysfunctions, etc. Some publications focus on molecular mechanisms of toxin induced immunosuppression [32]. Evidence in the publication by Pabello et al describes the nervous system- the immune system interactions under the load of environmental toxins, such as effects on neuroimmune networks induced by heavy metals and organic compounds [41]. Epidemiologic research shows that chemical environmental and industrial factors lead to increased incidence of disorders [7, 16, 43]. Many studies indicate that those factors and

pathologies of the nervous and the endocrine systems are connected. Similarly, some artificial chemical substances have a complex effect on the whole neuroendocrine system [47]. There is also plenty of evidence on environmental chemical factors affecting all the components of the immune regulatory circuit. For example, SO2 and NO2 have been proved to inhibit phagocytic activity of macrophages (innate immunity) or disruptions of proliferation and thymocyte maturation process. The relationship between allergies and pollution is well documented as well [7, 24].

Chemical substances can influence regulatory systems through the following mechanisms [8]:

1. Direct influence of a chemical compound on the respective system

2. Influence of metabolites during biotransformation in liver, skin, lungs, etc.

3. Indirect influence (activation of lipid peroxidation, including through inactivation of the antioxidant system; effect on respective receptors with possible future impact on the genetic apparatus; enzyme inactivation; influence on the cell membrane, etc.)

In one of his publications [20], academician V.A. Chereshnev presents a flow chart that shows how various environmental factors affect adaptive systems in view of the multi-level homeostasis regulation concept (Figure 2) which can also be used to prove the existence of a relationship between the nervous, endocrine, and immune systems when exposed to various hazardous factors. This concept indicates a possibility to deactivate impact markers and specific and nonspecific effect markers [16 not only for chemical but also for social or physical factors

The following points summarize the above:

1. The existence of immune-nervous-endocrine regulatory network exists.

2. It has been proved that industrial chemical factors affect some components of the nervous, immune, and endocrine systems

3. It is possible to establish a test database to diagnose disregulatory changes in integrative systems as impact markers that affect industrial, chemical and other risk factors. Further research needs to be done to fully assess the interaction among the nervous, endocrine, and immune systems under exposure to industrial pollutants.



Figure 2. Environmental impact and homeostasis control system (from [20] with changes).

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## About the authors:

**Dmitriy Vladimirovich Lanin** – Candidate of Medical Sciences, associate professor, senior research associate, laboratory methods for cellular diagnostics, Federal State Research Institution "Federal Research Center for Medical and Preventative Technologies of Public Health Risk Management", Address: ul. Monastyrskaya, 82, Perm, 614045, Russia,; e-mail: <u>dlan@mail.ru</u>; phone/fax: +7(342)2372534.