

Neurohumoral Regulation of Emotions Through the Eyes of a Russian Provincial Doctor

Klavdieva Maria^{1,*}

¹ S. I. Vavilov Institute for the History of Science and Technology, Russian Academy of Sciences, Moscow, Russia

*Corresponding author. Email: mashak@rambler.ru

ABSTRACT

This paper describes in detail Vladimir N. Speranskii's theory of emotional hormones in the historical context of endocrinology, neuroscience and nascent neuroendocrinology of the first decades of the 20th century. The main idea of Speranskii's theory, expounded in his four theoretical publications in the 1920s, was the existence of em-hormones, emotional hormones that could be the derivatives of the hormones. These agents, when released into blood, were postulated to be able to act on certain nervous elements of the brain and evoke emotional responses. Speranskii stressed the important role of the enzymes that break down em-hormones. This amazingly insightful theory was formulated at the time of crisis in endocrinology and the persistent schism between this discipline and neuroscience. The paper outlines the emergence of neuroendocrinology and the early development of neuroendocrinological ideas and studies in Russia. Speranskii's theory went largely unnoticed or was criticised and even ridiculed. Therefore, this paper attempts to restore V.N. Speranskii to his rightful place in the history of science, particularly in the history of neuroendocrinology

Keywords: *history of neuroendocrinology, history of neurohumoral regulation, history of neuropeptides, studies of emotions, Vladimir N. Speranskii; em-hormones*

1. INTRODUCTION

The history of science knows many examples where ideas, theories, and discoveries were so much ahead of their time and the level of science that their contemporaries were unable to recognise their importance and to further develop and use these hypotheses and findings. The contributions of some of these researchers (Gregor Mendel, Évariste Galois, etc.) were duly appreciated by the descendants while others remained unnoticed or unrecognized and forgotten as the level of science and technology at the time did not allow for acknowledging, understanding, or verifying their ideas. One of such scientists was a Russian doctor, V.N. Speranskii, who in the 1920s put forward a theory of emotional hormones that was unjustly forgotten and only comparatively recently confirmed by the findings of neuroendocrine and neuropeptide studies, particularly those concerned with neuropeptide action on memory and behaviour.

The discovery of neuropeptides as a new class of universal regulators ranks among the most significant events in the physiology of the last third of the 20th century. They can act both as hormones and neurotransmitters and modulate or induce behavioural reactions. The term 'neuropeptides' was coined in the early 1970s by David de Wied, an eminent Dutch scientist who was a pioneer in neuroendocrinology, especially in the studies of neuropeptides' effects on memory and behaviour. He used this term for the peptides related to peptide hormones but

without their endocrine effects. Later on, many other biologically active peptides were relegated to neuropeptides. These are peptide neurohormones and their fragments, endogenous opioid peptides, intestinal peptides, and many other groups of bioactive peptides produced by peptide-secreting cells present in different tissues and organs. Neuropeptides possess extremely diverse physiological and pharmacological effects and participate in the organism's adaptive reactions [1]. Some of the latest reviews of recent developments in the studies of neuropeptides are [2-4]. The new areas in neuropeptide research are emerging, such as neuropeptidomics, i.e. global identification and quantitation of peptide profiles in neuroendocrine systems by LC-MS/MS (liquid chromatography coupled with mass spectrometry) technologies [5,6]. The history of neuroendocrinology has been covered in detail, with some of the more recent publications being [7-11]. The goal of this paper is to describe V.N. Speranskii's ideas in the context of endocrinology, neuroscience and nascent neuroendocrinology of the first decades of the 20th century and to help his name find its rightful place in the history of neuroendocrinology and neuropeptide research.

2. THE EMERGENCE OF NEUROENDOCRINOLOGY

The studies on neuropeptides became institutionalised as a distinct research area in the mid-1970s after the discovery

and elucidation of the chemical structure of hypothalamic neurohormones. The discovery of neuropeptides, by no means accidental, came along as a result of the studies of neuroendocrine ('neurohumoral') regulation. Neuroendocrinology (NE) had three main aspects: studies of the influence of the nervous system on the functions of endocrine glands, studies of hormone action on nervous functions including behaviour, and studies of neurosecretory systems capable of secreting biologically active substances into the bloodstream [1]. The first stage in the development of NE (from the second half of the 19th century to the 1930s) was associated with the emergence and development of endocrinology and with the adoption of biochemical and pharmacological methods by endocrinology and neurophysiology. These methods enabled major discoveries in physiology around the 1920s: the existence of hormones was proven and the concept of the chemical transmission of nervous impulse was formulated. At the same time, a new research area began to emerge at the interface of endocrinology and neurophysiology: studies on the relationships and structural and morphological similarities of the nervous and endocrine systems. By the 1930s, endocrinology and neuroscience became finally institutionalised as independent biomedical disciplines, with endocrinology being more clinically oriented. However, the germ of a new interdisciplinary research area was already present within the framework of these disciplines. The fate of NE has not been easy from the start, with the majority of endocrinologists and neuroscientists being strongly prejudiced against it, emphasising and exaggerating the role and autonomy of their respective systems in the organism. The significance of neuroendocrine findings of the late 19th–early 20th century that had shown that brain was capable of secreting bioactive substances into the bloodstream was largely ignored. The works of the first pioneers in neuroendocrinology, Ernst and Bertha Scharrer, who introduced the concept of neurosecretion in the 1920s, met the same fate and were only acknowledged many years later. The nascent NE, however, had a strong theoretical underpinning: Claude Bernard's concept of *milieu intérieur* and its role in self-regulation of the body's internal stability, Carl von Rokitansky's work on microcirculation and its role in humoral pathology, and Walter Cannon's concept of homeostasis (metabolic equilibrium).

3. EARLY DEVELOPMENT OF NEUROENDOCRINOLOGY IN RUSSIA

Russian physiologists had always placed special emphasis on the studies of nervous system. The ideas of nervous system's dominating role in controlling body functions (later called 'nervism' by I.P. Pavlov) prevailed in Russian physiology (E.O. Mukhin, I.E. Dyadkovskii, A.M. Filomafitskii, and others) since the early 19th century, and the studies of nervous system outpaced the studies of endocrine glands. In Russia, the research into the interplay of the two systems began in the 1900s. Thus, A.A. Bogomolets provided the evidence of the adrenal cortex

secretions and suggested that this organ participated in the body's defensive reactions in 1905-1909; M.N. Cheboksarov demonstrated the existence of the secretory nerves of the adrenals in 1909/1910. V.D. Shervinskii was the first to conduct systematic studies of neuroendocrine interactions in the 1900s. Further development of these studies in the 1920s led to the emergence of ideas about possible endocrine functions of nervous cells. Among the scientists who developed these ideas in Russia/USSR were V.P. Osipov, A.A. Sukhov, and V.N. Speranskii. Thus, A.A. Sukhov wrote a chapter titled "Endocrino-psychoneurology" in the textbook "Clinical endocrinology" published in 1930 [12]. In this chapter he reviewed nervous system disorders associated with impaired internal secretion. Studies in this area were also conducted by B.M. Zavadovskii, N.A. Belov, V.M. Bekhterev, S.S. Korsakov, and others. Sukhov wrote not only about the links between the nervous and endocrine systems but also emphasised the existence of "hormonal function of nervous tissue". To substantiate his views on the matter, he quotes V.A. Opperl, an eminent surgeon and historian of medicine, "I would think it possible to regard brain not only as a place of application of the action of some or other hormones, not only as a place of excitation of certain impulses for efferent nerves, but also as a place of birth of the hormones which chemically affect the endocrine glands that are part of the general system of correlative interrelationships" [12]. Thus, in the 1920s-1930s, Russian scientists deemed possible that central nervous system could exert humoral influence on the organism. In this article Sukhov proposed a research programme that included comparative anatomical and physiological studies of the systems of endocrine glands in all types of animals, experimental studies of psychoneurological symptoms in the animals subjected to removal or transplantation of endocrine glands, studies of the functioning of endocrine system in neurological and mental patients, studies of endocrine/neurological syndromes, and endocrine therapy in mental patients. However, the most curious and bold ideas were expressed by V.N. Speranskii.

4. V.N. SPERANSKII AND HIS THEORY OF EM-HORMONES

Vladimir Nikolayevich Speranskii (1884-1942) was born in 1884 in the town of Vyshny Volochyok of the Tver Governorate. He studied medicine at Moscow University and, after his graduation in 1911, worked as an intern at the Vilno District Hospital. During World War I he served as an army doctor and after the war returned to the Vilno Hospital where he worked as assistant director in 1918/1919. Since 1920, Speranskii was the head of the military hospital of the Slavyansk Mineral-Water Resort. Since 1923, he worked in Yuzovka (renamed Stalin in 1914; Stalino, in 1929; and Donetsk, in 1961). In 1932, he delivered a course of lectures on endocrinopathies at the Medical School in Stalino [13]. He died in evacuation in the city of Nalinsk in 1942. V.N. Speranskii authored less than 20 publications, in 4 of which he set forward his theories of "emotional hormones," or "em-hormones."

In the early 20th century, the mechanistic and reductionist trends in biology, particularly, in physiology, also influenced the studies of emotions. In the mid-1880s, William James (1842-1910) and C.G. Lange (1834-1900) practically simultaneously (in 1884 and 1885, respectively) and independently of each other developed the organic, brain-based theory of emotions. According to this theory, emotions were seen as bodily, organic processes, the physiological reactions, i.e. “people feel happy because they smile and people feel sad because they cry”. At the turn of the 20th century, the James-Lange theory was dominant in the studies of emotions. An alternative theory was developed by a famous physiologist, Walter Bradford Cannon, and his doctoral student Philip Bard in 1927. According to the Cannon-Bard theory of emotion, stimulating events trigger feelings (emotional responses) and physical reactions (such as racing heartbeat) independently and simultaneously. Cannon and Bard proposed that both the emotional and the physical reactions originate in the thalamus, which in turn sends signals to the amygdala (a brain structure responsible for processing strong emotions) and, at the same time, to the autonomic nervous system and skeletal muscle and thus controls physical reactions. The Cannon-Bard theory, sometimes called the thalamic theory of emotions, was established as an alternative to the James-Lange theory of emotion that maintains that feelings result from physical reactions to a stimulating event. The James-Cannon controversy gave rise to a long-term debate on the physiological nature of emotions.

James’ “Psychology” was published in Russian in 1922 and the Russian translation of Cannon’s “Bodily changes in pain, hunger, fear and rage” (1915, 1920), titled “Physiology of emotions” was published in 1927. Some of the Soviet scientists (such as B.M. Zavadovskii) saw in Cannon’s works the evidence in favour of the James-Lange theory. The James-Lange theory and Cannon’s works laid the basis for the concept of the chemical basis of emotions. Thus, in his article “New paths in the studies of emotions”, Russian psychiatrist V.M. Gakkebush quotes N.K. Koltsov for the following definition of the chemical nature of emotions, “...this is chemical processes emerging as a result of neuropsychic processes and propagating throughout the entire body; in other words, emotions are the afferent (in relation to the blood and body) branch of the chemical reflex arc, if the term ‘arc,’ associated with the bodily form <...> may be relegated to chemical processes” [14].

V.N. Speranskii’s publication in which em-hormones featured for first time was his 60-page book titled “Hormono-reflexology as a basis for psychology and psychiatry” published in Kharkov in 1923. It stemmed from the author’s reinterpretation of the James-Lange concept. According to Speranskii, there are three groups of “sensing cells”: the cells of sensory areas; the cells associated with internal organs, muscle, joints, and vascular system; and nervous cells that are excited “hematogenously” (through blood) [15]. The substances that can “hematogenously”

evoke sensations were called by Speranskii “em-hormones.” He substantiates the idea of the existence of the hormones of nervous tissue with the French researchers’ experiments: when the dogs were set on a cage with rabbits, the amount of Nissl bodies in the rabbits’ brain decreased; when this amount dropped to a certain level, the rabbits died. Speranskii makes a surprisingly correct conclusion that Nissl bodies are associated with secretory activities of nerve cells, i.e. they contain neurosecretions and are secreted in the state of arousal. Speranskii believed that a drop in the number of Nissl bodies meant the release from nerve cells of the specific hormones produced by these cells. In addition, he proposed that nerve cells also contained em-hormones. Looking into emotions evoked by alcohol, morphine, and other agents, Speranskii concluded that “these substances’ getting into the bloodstream, changing blood composition, influences some or other of the organs that are part of the emotional systems, increasing their excitability or inhibiting it. As a result, the excess or the lack of the release of some or other of the em-hormones into the bloodstream and, hence, of some or other of the emotions or affects” [15, p.20].

And further: “The duration of emotions depends on the duration of presence in the blood of the excessive or insufficient amounts of some or other of the em-hormones or substances that act in a similar manner. There exist em-hormones and substances that pass into blood from the food, whose presence in blood in certain amounts is obligatory for the normal conduct of psychic processes. An increase in their amount above a certain norm or falling below the norm exerts an effect on the emotional sphere, causing an increase or decrease in the excitability of one or another system. There also exist, however, the em-hormones and substances that also act in a similar manner, which are not normally present in blood, which are released into blood sporadically under exceptional conditions and act on the emotional systems in the way of increasing or decreasing their excitability just by their presence in the blood. Their absence from the blood is the norm” [15, p.26].

The author stresses the important role of the substances that break down the em-hormones: “In case of the excess of em-hormones in the blood, the duration of an emotion depends on how fast they are destroyed, decomposed in the blood and eliminated from the organism in one or another way. In case of the deficiency in the blood of the substances which neutralise em-hormones, <...> emotions are of protracted nature, i.e., rather, the excitability of some emotional centres increases and the excitability of others decreases protractedly, i.e. the balance in the system of hormone generators is protractedly shifted in this direction or that.” In the same work, Speranskii hypothesises that memory consolidation can occur at the chemical level, i.e. the substances that consolidate memories as well as the substances that stimulate or inhibit memory circulate in the bloodstream. He stresses that “a huge role in the formation

of the intellect is played by the chemism of blood.” Further pursuing his hypothesis he writes, “there probably exist hormones that slow down the passage of nervous impulses.”

Speranskii’s next work that further developed these ideas and focused on em-hormones was published in the Soviet journal *Sovremennya psikhonevrologiya* (*‘Contemporary psychoneurology’*) in 1925. Here Speranskii provides an updated and extended definition of em-hormones: “These are special substances, that occur sporadically in some or other of the organs under the reflex actions, are immediately released from these organs into the blood, acting on certain nervous elements of the brain and evoking in these a psychic response perceived by consciousness as emotion, and are rapidly destroyed, neutralised in blood (and in pathological conditions, stay in the blood). Due to their considerable instability, one may hardly expect that, with the existing methods, they could be successfully isolated and chemically identified” [16, p.83]. Speranskii hypothesises how em-hormones relate to other hormones: “...the hormones of the endocrine glands possess a more general and more protracted stimulating or inhibiting effect on the functions of some or other of the central nervous system regions. Under their influence, the conductivity of nervous impulses in some or other of the nervous system regions can increase or decrease, the overall intensity of psychic processes can be stimulated or decreased, etc. We believe, in addition, that some hormones of the endocrine glands possess all the properties of em-hormones” [16, p.84].

Speranskii’s book “Internal secretion and psychic processes” was published in Kiev in 1927. In this book, he expounded in detail his concept of em-hormones and reviewed different affective conditions from the perspective of this concept. He introduced into his em-hormone theory a very important concept of their origin: “Alongside with the hormones in the generally accepted sense, the reflex excitation of some or other of the hormone-producing organs causes the release into the blood of the emotogenic derivatives of the hormones produced by this organ. These substances that sporadically appear in different organs upon their reflex excitation, substances that are easily broken down in blood and easily eliminated from it, chemically labile, we group under the name of emotogenic hormones. <...> These hormones are mostly the derivatives of the hormones” [17, p.12-13]. An amazing foresight!

Based on the then knowledge in the field of biochemical endocrinology, Speranskii hypothesises that em-hormones could be the fragments of thyreoidine or sexual hormone, adrenaline derivatives, or methyl guanidine. However, it remains an incontestable fact that the very idea of neurotropic and psychotropic action of hormone fragments has been clearly formulated back when the chemical nature of most hormones remained yet unknown. We also render it very important that Speranskii emphasised the role of enzymes that break down em-hormones. Without dwelling

on the similarities between Speranskii’s theoretical constructs and modern concepts of neuropeptides, it should be mentioned that neuropeptide-degrading enzymes formed and important area in the studies of neuropeptides and neurotropic, psychotropic and behavioral effects of neuropeptides are widely known.

Speranskii’s ideas never gained any significant support. Even the above-mentioned review of A.A. Sukhov does not mention his works while a piece devoted to the 25th anniversary of Speranskii’s scientific work, published in *Sovetskaya psikhonevrologiya* (*‘Soviet psychoneurology’*) in 1936 (No. 3, p. 109), covers his other works and public activities but does not mention his theory of em-hormones. Nevertheless Speranskii’s 1927 book was published in German by Karger in 1929 [18]. We found two reviews of this book, one in *The Journal of Neurology and Psychopathology* (1930, Vol.10(40) April, p.369-370) and another in *Revue neurologique* (1931, Vol. 1. p.236-237). The first review is obviously negative; it begins with calling Speranskii’s book “discursive and rather unconvincing”. Em-hormones are unsurprisingly called the “factors the very existence of which is dubious”. The second review does not mention em-hormones but compares Speranskii’s attempts to discern the influence of endocrine glands in certain psychic reactions, particularly in those of emotional nature, with the attempts to classify morphological types and match them with psychic constitutions. The author of this brief but expressive review also writes that Speranskii is trying to transfer the functioning of the agonist-antagonist couple studied by muscle physiology to the domain of psychology.

5. CONCLUSIONS

The 1920s saw the crisis in endocrinology accompanied by animated debates on the subject and place of endocrinology among the biomedical sciences. The number of newly discovered hormones, often controversial, was rapidly growing and the method of extracts, commonly used in endocrinology (and sometimes unjustifiably employed in clinical practice), was criticised as nonphysiological. Besides, the endocrinologists were exaggerating the endocrine system’s autonomy in the organism and the endocrinologists and neuroscientists were debating which of these two systems was dominant over the other. At the same time, a nascent research area that was trying to elucidate how these two systems are interrelated and interacting was emerging at the interface of endocrinology and neuroscience. The studies in the field of chemical transmission of nervous impulse provided a strong impetus for the development of neuroendocrinology. The importance of this research area was vividly expressed in a 1933 lecture by Leon Orbeli, an outstanding Russian/Armenian physiologist: “We are used to often talking about crisis in different areas of scientific knowledge. In this case, however, I think we are facing not a crisis but, on the contrary, we have broken the deadlock that had been artificially created by counterposing the nervous mechanism of regulation to the chemical

mechanism. We are arriving at the conclusion that these two mechanisms are not only not mutually exclusive, that they not only exist in parallel, but also that they exist in the form of a rigorously balanced, coordinated, interactive system of regulatory mechanisms and there is no clear boundary that could be drawn between nervous and humoral regulation” [19, p.470]. V.N. Speranskii’s works undoubtedly belong to the field of neuroendocrinology. Many of his insightful ideas about emotiogenic hormones have proved to be correct and his unjustly forgotten name ought to rank with the pioneers in neuroendocrinology, those who laid the foundation for the studies into neuroendocrine systems.

REFERENCES

- [1] M.M. Klavdieva, The history of neuropeptides I, *Frontiers in Neuroendocrinology* 16 (1995) 293–321.
- [2] L. Schoofs, A. De Loof, and M.B. Van Hiel, Neuropeptides as regulators of behavior in insects, *Annu. Rev. Entomol* 62 (2017) 35–52.
- [3] M.R. Elphick, O. Mirabeau, and D. Larhammar, Evolution of neuropeptide signalling systems, *J. Exp. Biol.* 221(3) (2018) jeb151092.
- [4] D. Murphy and H. Gainer, eds, *Molecular neuroendocrinology: from genome to physiology*, John Wiley & Sons, 2016.
- [5] J.E. Lee, Neuropeptidomics: Mass spectrometry-based identification and quantitation of neuropeptides, *Genomics Inform* 14(1) (2016) pp. 12–19.
- [6] F. Xie, K.D.B. Anapindi, E.V. Romanova, and J.V. Sweedler, Neuropeptidomics of the Mammalian Brain, K. Li, ed., *Neuroproteomics. Neuromethods*, 146 (2019) 161–177.
- [7] D. Lovejoy. *Neuroendocrinology: An integrated approach*, John Wiley & Sons, 2005.
- [8] M. Wilkinson and R.E. Brown. *An introduction to neuroendocrinology*, 2nd edition, Cambridge University Press, 2015.
- [9] D.R. Grattan “60 years of neuroendocrinology: The hypothalamo-prolactin axis,” *J. Endocrinol.* 226(2) (2015) T101–T122.
- [10] J.A. Russell, Fifty years of advances in neuroendocrinology, *Brain Neurosci. Adv.* 2 (2018) 1–20.
- [11] G. Leng, The endocrinology of the brain, *Endocr. Connect.* Vol. 7(12) (2018) R275–R285.
- [12] A.A. Sukhov, *Endocrino-psycho-neurology, Clinical Endocrinology (Klinicheskaya endokrinologiya) Leningrad* (1930) 289–357. (in Russian)
- [13] L.S. Speranskaya, In commemoration of the centenary of birth of V.N. Speranskii, S.S. Korsakov *Journal of Neuropathology and Psychiatry (S.S. Korsakov Zhurnal nevroptologii i psikiatrii)* 85(1) (1985) 1242–1243. (in Russian)
- [14] V.M. Gakkebush, New paths in the studies of emotions, *Modern Psychoneurology (Sovremennaya psikhonevrologiya)* 2(4) (1926) 424–440. (in Russian)
- [15] V.N. Speranskii. *Hormono-reflexology as a basis for psychology and psychiatry*, Kharkov, 1923. (in Russian)
- [16] V.N. Speranskii, Em-hormones, *Modern Psychoneurology (Sovremennaya psikhonevrologiya)* 1(3-4) (1925) 82–90. (in Russian)
- [17] V.N. Speranskii. *Internal secretion and psychic processes*. Kiev, 1927. (in Russian)
- [18] W.N. Speranski, *Innere Sekretion und psychische Prozesse*. Berlin, Karger, 1929.
- [19] L. Orbeli, On the nervous and humoral mechanisms of the regulation of functions, L. Orbeli. *Selected works* (1962) Moscow, Leningrad: Publ. USSR Acad Sci 461–469 (in Russian)