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CONTRIBUTION OF NOVOSIBIRSK RESEARCH SCHOOLS TO THE DEVELOPMENT OF RENAL PHYSIOLOGY

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Abstract. The article presents a brief history of the formation of scientific ideas about kidney physiology and the mechanisms of water-salt metabolism regulation in Novosibirsk, as well as the role of some physiologists in the development of these views. The beginning of the development of renal physiology in Novosibirsk was the idea by A.G. Ginetsinsky about the reflex osmoregulatory system of the organism, that was developed by his students (L.K. Velikanova, Ya.D. Finkinstein, L.N. Ivanova, Yu.V. Natochin, L.I. Kurduban). Later on, the veiws about the ion-regulating mechanisms and age-specific features of their formation in the ontogenesis of humans and animals have been formed (A.Ya. Terner, R.I. Aizman, I.V. Pantyukhin). The role of interconnections in this direction between the researchers from Novosibirsk and scientists from the USA (L. Rabinowitz), Sweden (A. Aperia, G. Celsi), Israel (H. Garty, S. Karlish) and others were shown. Knowledge of the history of the development of renal physiology in different countries and the results of cooperation between researchers play an important role in understanding the development prospects of this scientific area.

Keywords: history of physiology, scientists, kidneys, water-salt metabolism, Novosibirsk, research school.

The history of renal physiology in Siberia began with the arrival in Novosibirsk the corresponding member of the Academy of Medical Sciences of the USSR Alexander G. Ginetsinsky (1895–1962), who headed the department of normal physiology of the Novosibirsk Medical Institute from 1951 to 1955. A.G. Ginetsinsky began to develop a new problem, while insufficiently studied in Russia – the renal physiology. By that time, the concept expressed by the Canadian physiologist E. Verney (Verney, 1946), about the existence of an osmoregulatory system in the organism consisting of central hypothalamic osmoreceptors that produce an antidiuretic hormone (ADH) following an increase of the osmolality of the carotid artery blood, that increased reabsorption of fluid in the kidneys and, accordingly, a decrease in urination. A.G. Ginetsinsky suggested that central osmoreceptors are not able to regulate osmotic homeostasis throughout the organism; therefore, there must be peripheral osmoreceptors that perceive osmotic changes in any part of the circulatory system (Ginetsinsky, 1963). Testing of this hypothesis was carried out by the assistant of the Department of Normal Physiology of the Novosibirsk Medical Institute, Larissa K. Velikanova (1921–2010), later by Professor (1971), the Head of the Department of Anatomy, Physiology and Hygiene of the Novosibirsk Pedagogical Institute (1972–1987). She has demonstrated that in dogs, a decrease of blood osmolality in the systemic circulation after drinking of the water-milk mixture, the hypertonic solution injected into the region of central osmoreceptors by the Verney's method did not cause antidiuresis. The authors attributed this effect to competition between signals originating from supposed peripheral osmoreceptors and the opposite effect from central osmoreceptors. Only after separation of the nerve connections between the periphery and the center – the transection of the spinal cord – the activation of central osmoreceptors by hypertonic solutions caused antidiuresis at any level of organism hydration (Velikanova, 1958). Thus, the short period of work of A.G. Ginetsinsky in Novosibirsk was culminated by the creation of a theory about the reflex osmoregulatory system of the organism, that represented by peripheral osmoreceptors, afferent pathways of the spinal cord, a center consisting of supraoptical and paraventricular hypothalamic nuclei (central osmoreceptors according to E. Verney) and antidiuretic hormone that affected the level of urination.

This theory has put a number of new questions for solution, in particular, the localization of peripheral osmoreceptors and their structure, the mechanism of their activation by osmotic shifts, the transmission pathways of afferent information, the structure of the osmoregulatory reflex center, the efferent pathways, and mechanisms of the renal response. The attempts to solve these questions formed the basis of numerous studies by Ginetsinsky's students who remained in Novosibirsk.

The next stage in the development of renal physiology in Novosibirsk was the period from 1955 to 1970, which actively developed under the leadership of the head of the Department of Normal Physiology of the Novosibirsk Medical Institute Yakov D. Finkinshtein (1922–2009). Under his leadership, a team of employees undertook the experimental studies of all links of the osmoregulatory reflex (Finkinshtein, 1968). In particular, it was shown the existence of peripheral osmoreceptors in various organs and tissues (Velikanova *et al.*, 1967): in the liver (Velikanova & Finkinshtein, 1959), kidneys (Borisova, 1964; Saksonova, 1970), heart (Luchkin, 1968; Mitrakova, 1972), lungs (Kuzmin, 1964; Kuznetsova, 1968), spleen, skeletal muscles (Velikanova, 1966), the gastrointestinal tract (Terner, 1971). Injection in the circulatory system of these organs hypertonic solutions of sodium chloride, glucose, mannitol caused an antidiuretic, and in some cases, natriuretic response. Transection of the sympathetic nerves excluded the renal antidiuretic reaction, despite the osmotic shifts in the vasculature of the organs. Although numerous studies of osmoregulation by scientists from other countries (Ito *et al.*, 1961; Haberich *et al.*, 1965) have been provided from that time, there is still no evidence and understanding of the structure of these receptors and the mechanism of the osmotic stimulus perception.

The central and efferent parts of this reflex have been studied in sufficient detail. By electrophysiological method it was proven that the hyperosmotic irritation of liver osmoreceptors caused an increase in the electrical activity of the supraoptical and paraventricular nuclei of the hypothalamus (Matveeva & Osipovich, 1970), which led to an increase in the antidiuretic activity of blood plasma and an increase of oxytocin secretion (Perekhvalskaya, 1969). This caused a decrease in urine output and increased excretion of the osmotically active cation – sodium. Hypophysectomy led to the disappearance of the osmoregulatory response of the kidneys to the osmotic irritation of any osmoreceptive zone (Perekhvalskaya, 1969). Thus, Ya.D. Finkinshtein formulated the idea of a two-component osmoregulatory renal reaction – antidiuretic and natriuretic (Finkinshtein, 1972; 1983), which occured following an increase of blood osmolality in any of the studied organs.

The mechanism of action of antidiuretic hormone on the kidneys remained little studied. Student A.G. Ginetsinsky and Y.D. Finkinshtein, later an academician of the Russian Academy of Sciences, the Head of the laboratory of physiological genetics of the Institute of Citology and Genetics of Russian Academy of Sciences Lyudmila N. Ivanova (born 1929), has proved that ADH activates the enzyme hyaluronidase, that promotes the depolymerization of hyaluronic acid, which is a part of the intercellular matrix. It increases the permeability of intercellular contacts in collecting tubes, resulting in increased reabsorption of fluid in the distal nephron and urination decrease (Ivanova, 1958; 1972).

The formation of osmoregulatory mechanisms in ontogenesis have studied by the staff of the Department of Normal Physiology of the Novosibirsk Medical Institute L.I. Kurduban, E.D. Dinnits (Kurduban & Dinnits, 1971) and N.M. Subbotina (Subbotina, 1971). They showed that osmoregulatory reflexes in newborns were absent and appeared only with the appearance of sensitivity of the kidneys to pituitrin, which affected not only the glomerular, but also the tubular apparatus of the kidney. In newborns, there were no separate regulation of water and cations, and was appearing only at later stages of ontogenesis. The mechanism of diuresis regulation matures much earlier than the mechanism of sodium excretion regulation.

To the beginning of the 70s of the XX century, data began to appear that, in addition to osmoregulatory mechanisms, the kidneys play an important role in ion regulation. One of the students of Y.D. Finkinshtein – A.Ya. Terner – who studied renal function during the injection of osmotically active substances into the gastrointestinal tract, showed that the natriuretic component of the osmoregulatory reaction developed mainly only on sodium stimuli and depended on the base level of cation excretion (Terner, 1971).

Similar data obtained in parallel and almost simultaneously in the laboratory of Yu.V. Natochin (born 1932), a graduate of the Novosibirsk Medical Institute, Ginetsinsky's student and successor at the Sechenov Institute of Evolutionary Physiology and Biochemistry in St. Petersburg. He found that a solution with an increased concentration of sodium caused a more pronounced renal response than sodium-free solutions with a similar osmotic concentration (Natochin *et al.,* 1972). These works formed the basis for studying the mechanisms of ion regulation.

Under the leadership of Ya.D. Finkinshtein in Novosibirsk and in the St. Petersburg's laboratory of Yu.V. Natochin studying the mechanisms of potassium regulation (Finkinshtein *et al.,* 1973; Sokolova, 1975), and later magnesium regulation (Gusev & Natochin, 1970; Pantyukhin & Finkinshtein, 1977) have begun. In the mid-80s of the XX century, based on the works of these researchers, a clear idea about the presence in the organism of reflex systems for regulating sodium, potassium and magnesium homeostasis has formed (Finkinshtein *et al.,* 1973; Pantyukhin & Finkinshtein, 1977). Experimentally it was proved that the sensor part of these reflex mechanisms was localized in the liver and had ion-selective properties. The injection of different ionic solutions caused specific afferentation in various afferent fibers of the hepatic nerves (Tyryshkina & Finkinshtein, 1977), information from which was transmitted via the parasympathetic nerves to the central nervous system, most likely, to the hypothalamic centers of regulation of water-salt metabolism – supraoptic and paraventricular nuclei. Evidence of this were the results of experiments in which there was no renal ionuretic response to potassium or magnesium stimuli after bilateral transection of the vagus nerves (Finkinshtein *et al.,* 1973; Pantyukhin & Finkinshtein, 1977), while the preservation of the antidiuretic reaction. L.I. Kurduban and I.N. Zabello (Kurduban & Zabello, 1974) investigated the formation of a potassium-regulating reflex in ontogenesis and showed that its formation took place in three stages: the first one was characterized by the absence of reflex potassium excretion; the second stage was submitted by undifferentiated renal ion excretion; the third one was the final formation of selective specific potassium excretion.

Thus, the reflex mechanisms of the regulation of renal ion excretion began to be considered as urgent reactions to short-term loadings, and the ion-deposion function of organs and tissues (primarily, the liver, sceletal muscles, and connective tissue) as a reserve additional mechanism for maintaining ion homeostasis under intake or depletion of large amount of ion (Aizman & Velikanova, 1978).

The mechanisms of potassium homeostasis regulation were most studied. This was due to the cooperation of the Novosibirsk scientist prof. Roman I. Aizman, the head of the Department of anatomy and physiology of the Novosibirsk State Pedagogical University with Western researchers. So, in 1993-1994 together with prof. L. Rabinowitz from University of California (Davis), who for the first time in the West expressed the idea of reflex regulation of potassium excretion (Rabinowitz *et al.,* 1984), they studied the role of neural and humoral factors in the regulation of potassium excretion (Rabinowitz & Aizman, 1993), the diurnal rhythms of renal potassium output in norm, after opposite change in biorhythms and following unilateral nephrectomy (Aizman *et al.,* 1994; 1996).

These works attracted prof. A. Aperia to cooperate on the study of potassium homeostasis regulation in ontogenesis. In particular, together with Swedish colleagues, R.I. Aizman found that in early ontogenesis, potassium transport in the digestive tract was more efficient than in adult rats. This was due to the different contribution of potassium transport systems: in early ontogenesis, apically located potassium transporters (H^+-K^+-; K^+-ATPases), which contributed to potassium retention, were highly active, that played an important role in the development of the body. At later stages of ontogenesis, potassium secretion predominated due to the greater expression and activity of basal transporters (Na^+-K^+-ATPase; Na^+,K^+, 2Cl⁻-cotransporter), that protected cells from hyperkalemia (Aizman *et al.,* 1996; Aizman *et al.,* 1998). Hormones and biologically active substances (nitric oxide) (Aizman *et al.,* 1999), β-sympathomimetics (Aizman *et.al.,* 1999), corticosteroids (Wang *et al.,* 1995) were involved in the regulation of potassium transport in the gut depending on age. However, their contribution to the selective response of the kidneys to the ion stimulus has not yet been studied. Subsequently, in collaboration with Israeli scientists, it was found that the regulation of potassium transport in the colon and kidneys was regulated by the CHIF protein, which controlling the activity of one of the main potassium transporter – sodium-potassium ATPase (Garty *et al.,* 2002).

To the beginning of the 2000s, a fairly clear picture of the regulation of potassium homeostasis in ontogenesis was presented both at the level of the whole organism and its organs and systems (absorption/secretion in the gastrointestinal tract, distribution in depot organs and kidney excretion) (L.I. Kurduban, I.N. Zabello; R.I. Aizman, G. Celsi, L. Grahnquist, Z.M. Wang at al.), as well the role of some hormons in its regulation (L. Rabinowitz; R.I. Aizman, O. Aizman, H. Brismar, G. Celsi).

Thus, the collaboration of Novosibirsk researchers with scientists from other countries made it possible to reveal the systemic and molecular mechanisms of regulation of potassium homeostasis, which indicated the promise of such creative approach.

Particular attention was paid in Novosibirsk in the 1960–1990s to the consideration of hormonal mechanisms in regulation of sodium homeostasis. The role of the renin-angiotensin-aldosterone system (Kolpakov *et al.,* 1974) and corticosteroids (Kolpakov *et al.,* 1969) in the regulation of water-salt metabolism in norm and pathology was studied under the guidance of the founder of the Siberian school of endocrinologists prof. M.G. Kolpakov (1922–1974), as well the hormonal regulation of sodium transport and excretion by the kidneys (Terner, 1971), that was performed in parallel with studies of Western researchers (Gauer & Henry, 1963).

Further development of research in renal physiology in Novosibirsk was associated with the study of the integration of the regulation mechanisms of osmotic, ion and volume homeostasis in the ontogenesis of humans and animals and the development of their reliability. This research direction was mainly implemented at the Department of Anatomy, Physiology and Life Safety of the Novosibirsk State Pedagogical University (Head Prof. L.K. Velikanova (1972–1987) and Prof. R.I. Aizman (1987 – present) (Panova & Subotyalov, 2017). A significant impetus for the progress of knowledge in this area was the water-salt loading tests developed at the department, that made possible to study the renal reaction of men and animals of different ages to selective ion and water loadings, to evaluate the functional reserves of each homeostatic system. Approved by the USSR Ministry of Health in 1984, they began to be widely used in nephrology, space physiology, and experimental research (Orekhov *et al.,* 1984). For the first time in healthy humans, all stages of the formation of mechanisms of regulation of water-salt metabolism were studied. It was proved that in human ontogenesis, the mechanisms of volume regulation were formed first (by 4 years of life), then osmotic (7-8 years), and later (10-11 years) the ion regulation (Velikanova & Aizman, 1983; Aizman *et al.,* 1990; Aizman, 2000). The specificity of ion regulation is formed only by 10–11 years of a child's life. Integration between these mechanisms is formed to the 10-12 years old, which ensures restoration, first of all, the volume of body fluids (under hypovolemia) or osmolality (under hyperosmia). The functionality of the ion-osmotic balance regulating system decreases in adolescence (13-15 years old), which causes a decline of the selectivity of the renal response to ions intake, homeostatic shifts after water and ion loadings, an increase in the reactivity of the renal excretory function to NaCl intake (Aizman, 2000).

It was shown that the process of ontogenetic formation of the reserve capabilities of the water-salt metabolism regulation system was ensured by the formation of intra- and intersystem integration of various processes: the depot ability of tissue depots, the excretory function of the kidneys, the effectiveness of the hormonal response, and integration with other types of metabolism. The influences of various factors and disorders (learning, smoking, alcohol intake, diabetes mellitus, acute renal failure, constitutional features (Aizman & Terner, 1991; Khorina *et al.,* 2012) on renal homeostatic functions and mechanisms of their regulation in children of different ages and adults, as well as in model experiments on animals.waere investigated In recent years the possibility of using various medicinal plants has been evaluated to correct homeostatic shifts caused by the main pathology and functional disorders of the kidneys (Gilinsky *et al.,* 2010; Koroshchenko *et al.,* 2014; Koroshchenko *et al.,* 2014).

In the laboratory of L.N. Ivanova study continues of the molecular and genetic mechanisms of hormonal regulation of water-electrolyte balance, which made it possible to reveal the intracellular pathways of ADH in the nephron and the mechanisms of their regulation. It was found that the antidiuretic reaction after the intravenous injection of physiological doses of pituitrin was accompanied by an increase in urinary sodium excretion (Melidi, 1970). Then, a priority area of laboratory research was the study of the system of cAMP-dependent protein kinases involved in the implementation of the antidiuretic effect of vasopressin (Ivanova & Goryunova, 1981) under normal ontogenesis (Solenov *et al.,* 1986) and after neonatal injection of hydrocortisone, which causes a delay in the development of concentrating kidney function (Hegai, 1983). Later, her colleagues and students studied the water permeability of the epithelium membranes of the collecting tubes of the mammalian kidney under conditions of water deprivation and under the action of desmopressin (dDAVP) (Solenov *et al.,* 2003), as well as the role of protein kinase C (PKC) (Katkova *et al.,* 2009), intracellular calcium and aquaporin-2 (Solenov *et al.,* 2006) in its regulation. At the same time, studies were conducted on the effect of aldosterone on the kinetics of the distribution of intracellular sodium in the kidney of rats, including age-related features of the regulation of this process (Logvinenko *et al.,* 2007). The concentration function of the rat kidneys with different neurohypophysial status was studied against the suppression of the synthesis of prostaglandin E2, a modulator of the cellular effect of vasopressin in the epithelium of collecting tubes (Babina *et al.,* 2011). Together with foreign colleagues (Larissa, Greece), the influence of hypoosmic shock on the volume of epithelial cells in rat's collecting tubes with a hereditary defect in the synthesis of vasopressin was studied (Zarogiannis *et al.,* 2013).

Thus, to date, the Novosibirsk research school of renal physiology, founded by the outstanding scientist A.G. Ginetsinsky, unites 4 generations of researchers who continue to study the systemic, molecular, genetic and age-related mechanisms of regulation of renal functions in normal and pathological conditions. This work is most fruitfully carried out in collaboration with researchers from other countries, that allows to combine ideas, opportunities, and resources to achieve progress in renal physiology, the results of which are so important not only for basic science, but also for medical practice.

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