ISSN: 2755-1059

Journal of Nephrology & Endocrinology Research

SCIENTIFIC Research and Community

Review Article

Open Access

Evolution of Concepts of Renal Water and Ion Transport: From E.B. Verney to Modern Molecular Nephrology

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Received: June 11, 2026; **Accepted:** June 17, 2026; **Published:** June 25, 2026

Introduction

Maintenance of the constancy of volume and composition of body fluids is one of the fundamental prerequisites for the existence of multicellular organisms. Among the numerous physiological systems involved in homeostasis, the kidneys occupy a central position by regulating the content of water, electrolytes, and osmotically active substances in the body. Renal functions maintain extracellular fluid volume, electrolyte concentrations, acid–base balance, and plasma osmotic pressure [1, 2].

Despite the obvious physiological significance of these processes, modern concepts of renal water and ion transport have evolved gradually over more than a century. The history of this field reflects the general development of physiological science: a transition from the description of organ functions to the investigation of cellular mechanisms and, subsequently, to the analysis of molecular and genetic pathways underlying physiological regulation.

During the first half of the twentieth century, research focused primarily on the role of the kidneys in excreting water and dissolved substances. Later, it became evident that the principal function of the nephron is not merely the elimination of excess fluid but rather the precise regulation of the internal environment. Major contributions to the development of these concepts were made by E.B. Verney, H.W. Smith, A.N. Richards, R.W. Berliner, M.B. Burg, J. Orloff, J.S. Handler, P. Agre, and many other investigators.

In Russian physiology, substantial contributions were made by L.A. Orbeli, A.G. Ginetsinsky, Yu.V. Natochin, Ya.D. Finkinshtein, L.K. Velikanova, L.N. Ivanova, and their colleagues. Their studies demonstrated that water and ion transport should be regarded not only as the result of individual cellular processes but also as an essential component of the complex mechanisms maintaining homeostasis and adaptation to changing environmental conditions. The purpose of the present review is to trace the major stages in the development of concepts concerning renal water and ion transport and to highlight the interrelationship between Russian and international research in this field.

Methodological Approach

This review is historical and analytical, based on an examination of both classical and contemporary studies on the mechanisms of renal water and ion transport.

The literature search included publications indexed in PubMed, Web of Science, Scopus, and eLibrary, as well as monographs and review articles that have significantly influenced current understanding of renal physiology and water–salt metabolism.

Particular attention was paid to studies that defined key milestones in the development of concepts regarding water balance regulation, ranging from investigations of vasopressin and osmoreception to the discovery of aquaporins, intracellular signaling pathways, and modern concepts of molecular regulation of water and electrolyte transport.

The selection process included both fundamental international studies and publications originating from Russian scientific schools that have made substantial contributions to the understanding of water–salt homeostasis and renal function.

Early Concepts of Water Balance Regulation: E.B. Verney and The Physiology of Antidiuresis

The history of modern investigations of renal water transport is closely associated with studies of the mechanisms of antidiuresis. By the beginning of the twentieth century, it was already known that the posterior pituitary contained substances capable of influencing water metabolism; however, the physiological mechanisms responsible for these effects remained largely unknown.

A decisive contribution to this field was made by the British physiologist Ernest Basil Verney. In a series of classical experiments conducted during the 1930s and 1940s, Verney demonstrated that secretion of antidiuretic hormone is regulated by changes in blood osmotic pressure. Using sophisticated experimental models involving controlled administration of solutions with different osmolarities, he established the existence of a feedback mechanism linking the osmotic state of body fluids to vasopressin release.

The culmination of these studies was the Croonian Lecture published in 1947, in which Verney formulated the concept of osmoreceptor control of antidiuretic hormone secretion. According to this concept, an increase in extracellular fluid osmotic pressure stimulates vasopressin release, which in turn enhances renal water reabsorption, thereby contributing to the restoration of osmotic equilibrium [3].

Verney's work represented a major milestone in physiological science for several reasons. First, it demonstrated the existence of a neuroendocrine mechanism regulating water balance. Second, it established hormonal control of renal function. Finally, it raised a fundamentally important question: by what mechanisms does vasopressin alter water transport in the nephron?

At that time, no satisfactory answer was available. Although it was clear that antidiuretic hormone increased water reabsorption, the cellular and molecular mechanisms involved remained unknown. Verney suggested that water transport might occur through transcellular pathways, but the structures responsible for this process had yet to be identified. This unresolved issue became one of the central topics of renal physiology research during the following decades.

At the same time, fundamental concepts concerning the role of the kidneys in maintaining the constancy of the internal environment were being developed. Among the most influential contributors was Homer William Smith.

Smith proposed that the kidney should be viewed not merely as an organ of excretion but as a central mechanism responsible for maintaining the stability of the internal environment. This concept subsequently became the theoretical foundation for understanding water and ion transport as components of an integrated system regulating water–salt homeostasis [4].

Thus, by the middle of the twentieth century, two fundamental principles had been established that would determine the subsequent development of renal physiology. The first was the recognition of the key role of vasopressin in regulating water balance. The second was the understanding that water transport within the nephron constitutes part of a broader system responsible for maintaining whole-body homeostasis.

From Water to Sodium: The Emergence of The Osmotic Concept of Transport

The early studies of antidiuretic hormone established the existence of hormonal regulation of water balance; however, they did not explain the mechanisms by which water moved across nephron structures.

An original concept was proposed in 1951 by A.G. Ginetsinsky, who headed the Department of Normal Physiology at the Novosibirsk Medical Institute. Based on physiological and histochemical investigations, he suggested that under conditions of antidiuresis water transport might occur predominantly through intercellular pathways rather than directly through the cytoplasm of epithelial cells. Particular attention was focused on the properties of the interstitial matrix containing mucopolysaccharides, whose physicochemical characteristics could be modified by hormonal influences [5,6].

Interest in this problem increased because, during the same period, renal physiologists worldwide were actively debating the nature of vasopressin's antidiuretic effect. L.N. Ivanova, a student of A.G. Ginetsinsky, initiated investigations into the role of hyaluronidase in urine formation. Her experiments demonstrated that changes in diuresis were accompanied by alterations in enzyme activity within renal tissue. Following administration of antidiuretic hormone, hyaluronidase activity increased, accompanied by a reduction in urine output. These findings led to the conclusion that water transport in the kidney might occur predominantly through paracellular pathways, although the possibility of transcellular transport mediated by specialized carriers could not be excluded [7].

Such observations were difficult to reconcile with the prevailing concept of passive water diffusion across nephron epithelia.

By the mid-twentieth century, renal physiology increasingly shifted its focus from hormonal regulation toward the analysis of glomerular filtration and tubular reabsorption. During this period, it became apparent that water transport could not be considered an independent process but was largely determined by solute movement, particularly sodium ions.

A major contribution to the development of these concepts was made by Alfred Newton Richards. Through the application of nephron micropuncture techniques, Richards obtained the first direct information regarding the composition of glomerular filtrate and tubular fluid in different nephron segments. These studies demonstrated that primary urine closely resembles blood plasma in composition and undergoes profound modifications as it passes through the nephron. This work established the experimental basis for subsequent investigations of tubular reabsorption [8].

The next important step was associated with Homer W. Smith. Integrating extensive experimental evidence, Smith formulated the classical filtration–reabsorption theory of urine formation. According to this concept, the majority of water and dissolved substances are initially filtered through the glomeruli, after which most of the filtrate is returned to the circulation by tubular reabsorption [9].

Particularly important was the recognition that water reabsorption is closely linked to sodium transport. Sodium was regarded as the principal osmotically active component of extracellular fluid and therefore as the major determinant of water distribution among body compartments.

Subsequent studies by Robert W. Berliner and his colleagues substantially expanded knowledge of tubular transport mechanisms. Berliner demonstrated that sodium transport exhibits marked segmental specialization along the nephron and plays a crucial role in generating osmotic gradients required for urine concentration [10].

Of particular significance was the recognition of the renal medullary countercurrent system's role. The generation of a hyperosmotic medullary interstitium created conditions for passive water movement from the tubular lumen into surrounding tissues. Consequently, water transport came to be viewed as a secondary process driven by osmotic gradients established through active sodium transport.

Further advances were achieved through the work of Maurice Burg and Floyd Rector. Studies employing isolated nephron segments revealed marked differences in water and electrolyte permeability among various regions of the renal tubule. These investigations demonstrated that the capacity of specific nephron segments to transport water depends not only on their structural characteristics but also on membrane transport properties and hormonal regulation [11,12].

Gradually, a new physiological concept emerged in which water transport and ion transport were considered components of a unified functional system. Water was no longer viewed as an independently regulated entity. Instead, it became evident that

water movement is governed by osmotic forces generated by active transport of electrolytes across epithelial membranes.

Similar concepts were developed within Russian physiology through studies of water–salt metabolism and osmoregulation. In the work of A.G. Ginetsinsky, water reabsorption was analyzed in close relation to the general mechanisms that maintain water–salt homeostasis [6]. Particular emphasis was placed on the interaction between neural, humoral, and tissue mechanisms of regulation.

A major contribution was subsequently made by Ya.D. Finkinshtein and his colleagues, who provided evidence for the existence of a specialized osmoregulatory system comprising osmoreceptors distributed throughout various organs, including skeletal muscles, lungs, heart, kidneys, and other visceral organs. This system also included afferent pathways traveling within the vagus nerves, hypothalamic centers located in the supraoptic and paraventricular nuclei, and an efferent component represented by neurohypophyseal hormones, primarily vasopressin and oxytocin, which regulate renal water and sodium transport [13,14].

These investigators further demonstrated that the osmoregulatory system undergoes gradual maturation during ontogenesis. During early postnatal life, the kidney exhibits only limited responsiveness to osmotic stimulation and fails to produce a fully developed antidiuretic response [15].

The integrative approach reached its most consistent development in the work of Yu.V. Natochin. He emphasized that the principal function of the kidney is not the excretion of water and ions per se, but the preservation of optimal characteristics of extracellular fluid and the stability of the internal environment [16].

Comparative studies of water and sodium transport in osmoregulatory organs of various vertebrate species enabled Natochin to formulate an important evolutionary conclusion: mechanisms of water transport evolved in close association with mechanisms of ion transport and cannot be considered independently. Electrolyte transport establishes the conditions necessary for water redistribution among body compartments [17].

By the late 1960s, renal physiology had reached a critical turning point. It had become evident that understanding water transport required an understanding of sodium transport and the formation of osmotic gradients. Nevertheless, one fundamental question remained unresolved: how do hormones alter the water permeability of nephron epithelia?

The answer emerged from studies of intracellular signaling pathways involved in vasopressin action, marking the next major stage in the development of renal physiology.

Vasopressin, cAMP, and Cellular Mechanisms of Water Permeability Regulation

By the late 1960s, renal physiology had established that water movement is driven by osmotic gradients generated through electrolyte transport. However, the mechanism by which antidiuretic hormone alters the permeability of nephron epithelia remained unclear. Although vasopressin was known to markedly enhance water reabsorption and urinary concentration [7], the cellular mechanisms underlying this effect had not yet been elucidated.

An important contribution to solving this problem was made by J. Orloff and J.S. Handler. Using the amphibian urinary bladder as a model of epithelial water transport, they demonstrated that the effects of vasopressin could be reproduced by cyclic adenosine monophosphate (cAMP) and by agents that increase its intracellular concentration [18]. These studies provided the first evidence that an intermediate intracellular signaling system exists between hormone binding and changes in membrane permeability. The discovery of cAMP's role was among the earliest demonstrations of the universality of second messengers in hormonal regulation. Subsequent investigations revealed that binding of vasopressin to specific membrane receptors activates adenylate cyclase, increasing intracellular cAMP levels and initiating a cascade of regulatory events [19,20].

Further development of this concept was associated with the work of Jared Grantham, Maurice Burg, and their colleagues. The introduction of microperfusion techniques for isolated nephron segments enabled investigation of the physiological properties of individual tubular regions under carefully controlled experimental conditions. These studies demonstrated that collecting ducts exhibit the highest sensitivity to vasopressin and constitute the final regulatory segment responsible for urinary concentration [21,22].

Exposure to vasopressin was shown to increase epithelial permeability to both water and sodium. These findings provided the first direct link between hormonal regulation and specific cellular alterations occurring within nephron epithelia [23].

Subsequent investigations focused on the intracellular mechanisms through which cAMP exerts its effects. It was established that the principal target of cAMP is protein kinase A (PKA), an enzyme that regulates the activity of numerous cellular proteins through phosphorylation [24].

Consequently, vasopressin came to be viewed not simply as a hormone controlling water excretion but as the initiator of a complex signaling cascade that transforms an extracellular hormonal signal into coordinated cellular responses.

At the same time, increasing attention was directed toward the structural organization of collecting duct epithelia. Studies demonstrated that principal cells possess particularly high sensitivity to vasopressin and play a pivotal role in regulating water transport. These cells subsequently became the focus of intensive investigations that ultimately led to the discovery of water channels.

By the beginning of the 1980s, a new concept of vasopressin action had emerged. According to this model, the hormone does not directly alter the movement of water through cellular membranes. Instead, it regulates specialized cellular mechanisms that determine epithelial water permeability. However, the molecular nature of these mechanisms remained unknown.

The next stage in the development of renal physiology was therefore directed toward identifying the structures responsible for water transport across biological membranes. Resolution of this problem ultimately led to one of the most significant discoveries in modern physiology — the identification of aquaporins and the establishment of the molecular concept of water transport.

An important aspect of this period was the gradual convergence of classical physiological approaches with emerging concepts of intracellular signaling. Research no longer focused exclusively on organ-level responses but increasingly sought to identify the molecular intermediates linking hormonal stimulation to functional changes in epithelial transport.

This shift represented a major conceptual transition in renal physiology. Water transport was no longer viewed solely as a consequence of physical forces and osmotic gradients. Instead, it became evident that hormonal regulation is mediated by highly organized intracellular signaling networks that rapidly and specifically modulate membrane permeability.

Thus, by the early 1980s, the foundations had been established for the next major breakthrough in the field—the identification of the molecular structures directly responsible for transmembrane water movement.

The Aquaporin Revolution: From Hypothetical Water Pores to Molecular Water Channels

By the beginning of the 1980s, renal physiology had accumulated an extensive body of knowledge on the mechanisms underlying vasopressin's antidiuretic action. It had been established that the hormone acts primarily on collecting duct cells, activates the adenylate cyclase signaling system, increases intracellular cAMP concentration, and alters epithelial water permeability. Nevertheless, the central question remained unanswered: through which structures do water traverse the lipid bilayer of cellular membranes?

The prevailing concept of simple water diffusion across biological membranes could no longer adequately explain the exceptionally high rates of water transport observed in renal tubular epithelia. Increasingly, physiologists concluded that specialized protein structures must exist to facilitate the selective passage of water molecules. The existence of such "water pores" had been hypothesized as early as the 1960s and 1970s. However, experimental proof remained elusive for many years. The situation changed dramatically in the early 1990s through the work of the American biochemist Peter Agre.

While investigating membrane proteins of human erythrocytes, P.Agre and his colleagues identified a previously unknown integral membrane protein with a molecular weight of approximately 28 kDa. Initially, the physiological significance of this protein was unclear. Subsequent experiments demonstrated that expression of this protein in Xenopus oocytes resulted in a dramatic increase in membrane water permeability [25].

By 1992–1993, it had been conclusively established that the newly identified protein was a specialized water channel, later designated Aquaporin-1 (AQP1) [26]. This discovery provided the first direct molecular explanation for the remarkably high-water permeability of biological membranes. As emphasized by Agre in his Nobel Lecture, aquaporins represented a fundamentally new class of membrane proteins specialized for water transport [27].

The significance of this discovery can hardly be overstated. Prior to the identification of aquaporins, physiologists could only indirectly infer the existence of specialized water transport mechanisms. The discovery of AQP1 provided, for the first time, a specific molecular entity that could be studied with regard to its structure, function, regulation, and genetic control.

Subsequent studies revealed that aquaporins constitute a large family of proteins widely distributed among animals, plants, and microorganisms. Each aquaporin monomer forms a narrow hydrophilic channel that permits rapid water transport while effectively excluding ions and most other solutes.

Of particular importance for renal physiology was the identification of distinct aquaporin isoforms within different nephron segments. Aquaporin-1 was found to be highly expressed in proximal tubules and the descending thin limb of the loop of Henle, where it mediates bulk water reabsorption. This finding provided a molecular explanation for the kidney's remarkable ability to reclaim the vast majority of filtered water.

A second major breakthrough occurred in 1993 when K. Fushimi, S. Sasaki, and their colleagues cloned a novel water channel localized in collecting duct principal cells. This protein was designated Aquaporin-2 (AQP2). Unlike AQP1, which is constitutively expressed in the plasma membrane, AQP2 proved to be a dynamically regulated protein. This property ultimately provided the long-sought explanation for the mechanism of vasopressin action [28,29].

The definitive solution emerged from studies conducted by Søren Nielsen, Mark Knepper, and their collaborators. Using electron microscopy, immunohistochemistry, and molecular biological techniques, they demonstrated that in the absence of vasopressin, AQP2 is localized predominantly within intracellular vesicles of collecting duct principal cells. Following vasopressin stimulation, these vesicles rapidly translocate to the apical plasma membrane, where AQP2 channels are inserted into the membrane, thereby increasing water permeability [30, 31].

Thus, vasopressin does not create new pathways for water transport nor does it fundamentally alter the physicochemical properties of the membrane itself. Rather, it regulates the number of pre-existing water channels available in the plasma membrane.

This discovery represented a pivotal moment in the history of renal physiology because it unified all previously identified components of water balance regulation into a single coherent model: osmotic sensing, vasopressin secretion, receptor activation, cAMP-dependent intracellular signaling, and the final effector mechanism represented by aquaporins.

The identification of aquaporins transformed the understanding of water transport from a largely physiological concept into a molecularly defined process. For the first time, the complete sequence of events linking systemic regulation to molecular mechanisms could be described in detail.

The discovery also had profound implications for Russian renal physiology. Investigations conducted within the scientific school founded by L.N. Ivanova, which had previously focused on tissue, developmental, and receptor-mediated aspects of antidiuresis, now expanded toward the study of molecular mechanisms regulating water transport. Subsequent research addressed the expression of aquaporin genes, vasopressin receptor signaling pathways, protein kinase-dependent regulation, and molecular mechanisms controlling water channel activity.

Consequently, the discovery of aquaporins not only represented a landmark achievement in membrane biology but also completed a scientific quest that had begun with the pioneering studies of E.B. Verney several decades earlier. Nearly half a century after Verney established the physiological role of vasopressin, the molecular mechanism by which this hormone regulates water transport in the nephron had finally been identified.

However, the aquaporin story did not mark the end of the field. On the contrary, it opened an entirely new era of investigation focused on genetic regulation, intracellular signaling networks, interactions between water and ion transport systems, and the integration of molecular mechanisms into the broader framework of water–salt homeostasis and renal adaptation.

From Molecular Mechanisms to Integrative Physiology

The discovery of aquaporins generated a series of new questions. How is the expression of water channels regulated? Which intracellular signaling pathways mediate the effects of vasopressin? How does nephron responsiveness to hormonal stimulation change during ontogenesis? How do water and ion transport systems interact under physiological and pathological conditions?

Addressing these questions required integrating molecular, cellular, and systemic approaches [32]. In this context, particular importance was attached to investigations conducted within the Novosibirsk scientific school of renal physiology and water–salt metabolism, founded by Academician L.N. Ivanova.

One of the distinctive characteristics of this scientific school has been the continuity of research themes maintained over several decades. Whereas early studies focused on the roles of hyaluronidase and extracellular matrix components in antidiuretic mechanisms, subsequent investigations progressively expanded toward cellular signaling, receptor-mediated regulation, and molecular mechanisms controlling water transport [33].

Studies conducted by L.N. Ivanova and her colleagues addressed developmental aspects of renal sensitivity to antidiuretic hormone, the participation of cyclic nucleotides in hormonal signaling, and the role of various enzymatic systems involved in water balance regulation. In particular, it was demonstrated that neonatal kidneys respond to vasopressin differently from adult kidneys. The antidiuretic effect of the hormone was considerably weaker, and the ability to concentrate urine developed gradually during postnatal maturation of osmoregulatory systems [34-36].

These findings substantially modified earlier views regarding renal functional maturation. It became evident that the development of osmoregulatory capacity depends not only on morphological maturation of the nephron but also on progressive reorganization of intracellular regulatory pathways.

An important contribution to this field was made by I.I. Khegai, who demonstrated that alterations in glucocorticoid levels during early postnatal development can significantly influence the subsequent responsiveness of the nephron to vasopressin. These studies established a link between renal development and endocrine regulation, highlighting the importance of hormonal programming during critical developmental periods [37].

Particular attention was devoted to age-dependent changes in renal sensitivity to vasopressin. It was shown that the effectiveness of antidiuretic hormone action changes throughout postnatal development and depends on the functional state of receptor systems, intracellular signaling pathways, and protein phosphorylation mechanisms. Developmental alterations in protein kinase activity and signal transduction efficiency were found to contribute substantially to the maturation of renal osmoregulatory function [38-40].

These observations challenged the traditional view that the nephron represents a fully mature morphofunctional unit early in postnatal life. Instead, they suggested the existence of critical developmental periods during which renal responsiveness to hormonal stimulation undergoes profound modifications.

Another important direction of research involved the investigation of interactions between extracellular matrix components, hyaluronan metabolism, and hormonal regulation of renal function. Studies conducted by T.E. Goryunova demonstrated that changes in hyaluronate hydrolase activity are closely associated with cAMP synthesis in renal tissue. These findings suggested the existence of complex interactions among hormonal stimulation, enzymatic systems, and mechanisms governing water transport [41].

At the same time, increasing attention was directed toward the role of intracellular second messengers in mediating vasopressin effects. Investigators examined the participation of cAMP, protein kinase A, calcium-dependent pathways, and protein kinase C in regulating water and ion transport. These studies demonstrated that the final physiological response is determined not by a single signaling pathway but rather by coordinated interactions among multiple intracellular regulatory systems [42].

With the development of molecular biological techniques, research naturally progressed toward the analysis of gene expression. Particular attention was devoted to genes involved in water transport and extracellular matrix regulation. Investigations conducted by N.O. Kabilova and colleagues provided novel evidence demonstrating that activation of vasopressin V2 receptors influences the expression of genes associated with hyaluronan metabolism and water transport. These findings established an important connection between classical physiological concepts of antidiuretic regulation and contemporary molecular mechanisms of gene regulation. It became apparent that vasopressin affects not only rapid changes in membrane permeability but also long-term cellular adaptations involving transcriptional regulation of genes encoding hyaluronidases and proteins involved in extracellular matrix organization [43].

In contrast to many international studies that focused primarily on isolated molecular mechanisms, investigations performed within the Ivanova scientific school were characterized by a multilevel integrative approach. Renal function was analyzed simultaneously at the organismal, organ, cellular, and molecular levels. Such an approach made it possible to interpret changes in individual signaling pathways within the broader context of water–salt homeostasis regulation.

Consequently, these studies served as a bridge between classical physiology of water–salt metabolism and contemporary molecular nephrology. Whereas the work of E.B. Verney, H.W. Smith, and Yu.V. Natochin established the physiological significance of water transport, and the discoveries of P. Agre, S. Nielsen, and M.A. Knepper elucidated its molecular basis, the investigations conducted by the Novosibirsk scientific school contributed substantially to integrating these levels of knowledge into a unified concept of water–salt homeostasis regulation.

This integration of systemic and molecular perspectives is one of the defining characteristics of modern renal physiology and continues to shape current directions of research into water and ion transport within the nephron.

Clinical Significance of Modern Concepts of Water and Ion Transport

Advances in understanding the molecular mechanisms of water and ion transport during recent decades have profoundly influenced not only basic renal physiology but also modern clinical nephrology.

One of the most important achievements has been elucidating the role of aquaporins in disorders of water metabolism. It has been demonstrated that reduced expression or impaired intracellular trafficking of Aquaporin-2 (AQP2) constitutes one of the principal mechanisms underlying nephrogenic diabetes insipidus. This disorder is characterized by severe polyuria, excessive water loss, and an impaired ability of the kidneys to concentrate urine [44, 45].

Conversely, excessive activation of the vasopressinergic system may result in the syndrome of inappropriate antidiuretic hormone secretion (SIADH), a condition characterized by water retention, dilutional hyponatremia, and disturbances of water–electrolyte balance. Studies of SIADH have further confirmed the central role of vasopressin and aquaporin-dependent mechanisms in regulating body fluid homeostasis [46].

Considerable attention has also been directed toward the involvement of vasopressin and aquaporins in the progression of Chronic Kidney Disease (CKD) and Autosomal Dominant Polycystic Kidney Disease (ADPKD). Experimental and clinical studies have demonstrated that prolonged stimulation of vasopressin V2 receptors activates intracellular signaling pathways that promote cyst growth, tubular remodeling, and progressive deterioration of renal structure and function [47, 48].

These discoveries have had important therapeutic implications. The development of selective vasopressin receptor antagonists, commonly known as vaptans, has provided new treatment options for patients with hyponatremia and polycystic kidney disease. Tolvaptan, in particular, has become one of the first pharmacological agents capable of slowing disease progression in patients with ADPKD.

At the same time, advances in molecular nephrology have demonstrated that disorders of water balance are rarely isolated abnormalities. In most cases, disturbances of water transport are closely associated with alterations in sodium, potassium, chloride, and other electrolyte transport systems. Consequently, modern nephrology increasingly views water and electrolyte homeostasis as an integrated physiological network rather than as a collection of independent transport processes.

The clinical importance of aquaporins extends beyond kidney diseases. Altered expression and regulation of water channels have been implicated in heart failure, liver cirrhosis, pulmonary edema, hypertension, and several neurological disorders associated with disturbances of fluid balance. These observations further underscore the systemic significance of mechanisms originally discovered in renal physiology [49].

Another important outcome of molecular studies has been the identification of genetic defects affecting aquaporins, vasopressin receptors, and ion transport proteins. Such discoveries have contributed significantly to the development of precision medicine approaches in nephrology and have improved the diagnosis of hereditary disorders affecting water and electrolyte metabolism [50].

The transition from classical physiological observations to molecular and genetic understanding has therefore transformed clinical nephrology. Mechanisms that were once regarded as purely experimental phenomena have become essential targets for diagnosis, prognosis, and therapeutic intervention.

Thus, investigations of water and ion transport have extended far beyond the boundaries of fundamental physiology. They now provide a scientific foundation for modern approaches to the diagnosis, prevention, and treatment of kidney diseases and disorders of water–electrolyte homeostasis.

Conclusion: From Aquaporins to Integrated Homeostatic Regulation

Over the past century, concepts concerning the mechanisms of renal water and ion transport have undergone a remarkable transformation. Whereas early investigations focused primarily on the physiological effects of antidiuretic hormone and renal water excretion, contemporary renal physiology views water and electrolyte transport as the result of coordinated interactions among multiple regulatory systems operating at different levels of biological organization.

The history of this field clearly illustrates the general evolution of physiological science. Initial studies were directed toward identifying the factors controlling water excretion by the kidneys. The pioneering work of E.B. Verney established vasopressin as the principal hormonal regulator of water balance. Subsequent investigations by H.W. Smith, A.N. Richards, R.W. Berliner, and their contemporaries demonstrated that water movement within the nephron is governed by osmotic gradients generated largely through sodium transport.

The next major advance was associated with the elucidation of intracellular mechanisms mediating vasopressin action. Studies by J. Orloff, J.S. Handler, M.B. Burg, and their colleagues established the central role of cAMP-dependent signaling pathways in regulating collecting duct water permeability. These discoveries marked the transition of renal physiology from the organ level to the cellular level of analysis.

The discovery of aquaporins in the early 1990s marked a turning point in the field's development. For the first time, molecular structures directly responsible for transmembrane water transport were identified. The work of P. Agre, S. Sasaki, S. Nielsen, and M.A. Knepper provided a coherent molecular explanation for vasopressin action and established the mechanistic basis of water permeability regulation in the nephron.

Subsequent research demonstrated that aquaporins constitute only one component of a much more complex regulatory network. Water transport is now understood as the result of coordinated interactions among water channels, ion channels, membrane pumps, transporters, receptors, intracellular signaling cascades, and gene regulatory mechanisms.

In addition to aquaporins, specialized ion transport systems play a crucial role in maintaining water–electrolyte balance. Among the most important are Na+/K+-ATPase, the Sodium–Potassium–Chloride Cotransporter (NKCC2), the Sodium–Chloride Cotransporter (NCC), and Epithelial Sodium Channels (ENaC). The coordinated activity of these transport proteins establishes the transmembrane and osmotic gradients that determine water movement throughout the nephron [51].

Modern research has clearly demonstrated that water and ion transport mechanisms form a single integrated functional system.

Alterations in ion transporter activity inevitably influence water balance, whereas disturbances of water transport profoundly affect electrolyte homeostasis.

Consequently, contemporary renal physiology increasingly rests on the concept of integrated water and ion transport as a fundamental mechanism that maintains the stability of the internal environment.

Particular importance is placed on the interaction between sodium and water transport. Active sodium reabsorption generates the osmotic forces that drive water movement across epithelial barriers. For this reason, modern investigations increasingly regard water and electrolyte transport as inseparable components of a unified homeostatic process.

At the same time, understanding of the regulatory mechanisms governing water transport has expanded substantially. Whereas early concepts emphasized the dominant role of vasopressin, it is now recognized that aquaporin expression and function are influenced by numerous humoral factors, including the renin–angiotensin–aldosterone system, natriuretic peptides, prostaglandins, glucocorticoids, and cytokines. Water balance regulation is therefore mediated by a complex network of interacting signaling systems rather than by a single hormonal pathway. The recognition of these multiple regulatory influences has substantially broadened the traditional concept of vasopressin-dependent regulation of water balance and has provided new perspectives on the pathogenesis of renal and systemic disorders associated with disturbances of water–electrolyte homeostasis [52-56].

Another major direction of contemporary research concerns the genetic regulation of water and ion transport. Numerous genes controlling aquaporins, vasopressin receptors, ion channels, and transport proteins have been identified. Altered expression or mutation of these genes has been implicated in a wide spectrum of hereditary and acquired disorders associated with disturbances of water–electrolyte homeostasis [57, 58].

Russian physiologists made a significant contribution to the development of modern concepts. The work of Yu.V. Natochin contributed to the formation of an integrative concept of water–salt homeostasis. The Novosibirsk scientific school of renal physiology comprises three research groups [59]. The studies of Professor Ya.D. Finkinshtein and his colleagues revealed the structure and function of the regulatory system responsible for osmotic and ionic homeostasis, including the balance of sodium, potassium, and magnesium, as an essential component of water balance regulation [60-63]. Investigations carried out by Professor L.K. Velikanova and her colleagues demonstrated the ontogenetic development of the reliability of mechanisms maintaining water–salt homeostasis under substantial water and salt loads [64, 65]. Studies performed within the scientific school founded by L.N. Ivanova made it possible to link classical physiological concepts with achievements in molecular biology and genetics. As a result, modern renal physiology considers water and ion transport simultaneously at the organismal, organ, cellular, and molecular levels.

One of the defining characteristics of contemporary renal physiology is the progressive convergence of systems physiology and molecular biology. Whereas these disciplines once developed largely independently, it is now evident that a comprehensive understanding of kidney function requires integrating information obtained at the molecular, cellular, organ, and organismal levels. Molecular mechanisms acquire physiological significance only within the context of whole-body homeostasis, while systemic responses can be fully understood only through knowledge of their cellular and molecular foundations.

Thus, the modern concept of renal water and ion transport represents the culmination of a long and productive evolution of scientific thought. The path from Verney's pioneering studies to contemporary investigations of aquaporins, intracellular signaling pathways, and genetic regulation reflects the gradual transition from descriptive physiology to mechanistic understanding.

At the same time, this historical development demonstrates that no single level of biological organization can be fully understood in isolation. The most promising direction for future research lies in the continued integration of molecular, cellular, and systemic approaches, allowing water and ion transport to be viewed as a multilevel process that ensures homeostasis, adaptation, and survival of the organism in a changing environment.

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