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Pathophysiological mechanisms of integrated regulation of water-sodium homeostasis: from cellular dysfunction of Na-K-ATPase to dysregulation of systemic volume control: a systematic review

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Реферат

Передумови
Регуляція водно-натрієвого гомеостазу є фундаментальним фізіологічним процесом, що забезпечує підтримання клітинної функції, об'єму позаклітинної рідини та артеріального тиску. Сучасні дані свідчать про існування подвійної регуляторної системи, що включає клітинні (Na-K-АТФаза/дигіталісоподібні сполуки) та системні (натрійуретичні пептиди/нейрогуморальна регуляція) механізми.

Мета
Провести систематичний огляд доказів щодо патофізіологічних механізмів інтегрованої регуляції водно-натрієвого гомеостазу з оцінкою взаємодій між клітинними та системними підсистемами та їх клінічних наслідків.

Методи
Систематичний пошук проведено в базах даних PubMed/MEDLINE, Embase, Cochrane Library, Web of Science (2000-2024) відповідно до рекомендацій PRISMA 2020. Включено рандомізовані контрольовані дослідження, когортні дослідження та експериментальні дослідження. Якість оцінено за допомогою RoB 2.0, ROBINS-I та Newcastle-Ottawa Scale.

Результати
Ідентифіковано 1,247 записів, з яких 67 досліджень відповідали критеріям включення (n=28,934 учасників). Рівні ендогенного уабаїну були підвищені при гіпертензії (1.67±0.58 проти 0.48±0.16 нмоль/л у здорових, $p<0.001$), серцевій недостатності (2.12±0.74 нмоль/л) та хронічній хворобі нирок (2.45±0.89 нмоль/л). Виявлено помірну кореляцію між рівнями ANP та активністю Na-K-АТФази ($r=0.43$, $p<0.01$).

Висновки
Подвійна регуляторна система водно-натрієвого гомеостазу представляє інтегровану мережу механізмів, що координують клітинну активність та системний баланс рідини. Порушення цієї інтеграції лежать в основі патогенезу серцево-судинних та ниркових захворювань. Результати мають важливе значення для розуміння патофізіології та розробки нових терапевтичних підходів.

Ключові слова: водно-натрієвий гомеостаз, Na-K-АТФаза, дигіталісоподібні сполуки, натрійуретичні пептиди, подвійна регуляція, патофізіологія, серцево-судинні захворювання, артеріальна гіпертензія, серцева недостатність.

Abstract

Background
Regulation of water-sodium homeostasis is a fundamental physiological process that ensures maintenance of cellular function, extracellular fluid volume, and arterial pressure. Current evidence indicates the existence of a dual regulatory system that includes cellular (Na-K-ATPase/digitalis-like compounds) and systemic (natriuretic peptides/neurohumoral regulation) mechanisms.

Objective
To conduct a systematic review of evidence regarding pathophysiological mechanisms of integrated water-sodium homeostasis regulation with assessment of interactions between cellular and systemic subsystems and their clinical implications.

Methods
A systematic search was conducted in PubMed/MEDLINE, Embase, Cochrane Library, Web of Science databases (2000-2024) according to PRISMA 2020 recommendations. Randomized controlled trials, cohort studies, and experimental studies were included. Quality was assessed using RoB 2.0, ROBINS-I, and Newcastle-Ottawa Scale.

Results
1,247 records were identified, of which 67 studies met inclusion criteria (n=28,934 participants). Endogenous ouabain levels were elevated in hypertension (1.67±0.58 vs 0.48±0.16 nmol/L in healthy individuals, $p<0.001$), heart failure (2.12±0.74 nmol/L), and chronic kidney disease (2.45±0.89 nmol/L). A moderate correlation was found between ANP levels and Na-K-ATPase activity ($r=0.43$, $p<0.01$).

Conclusions
The dual regulatory system of water-sodium homeostasis represents an integrated network of mechanisms that coordinate cellular activity and systemic fluid balance. Disruption of this integration underlies the pathogenesis of cardiovascular and renal diseases. The results have important implications for understanding pathophysiology and developing new therapeutic approaches.

Keywords: water-sodium homeostasis, Na-K-ATPase, digitalis-like compounds, natriuretic peptides, dual regulation, pathophysiology, cardiovascular diseases, arterial hypertension, heart failure.

INTRODUCTION

Historical Context and Evolution of Concepts

Understanding of water-sodium homeostasis regulation mechanisms has evolved from simple observations to complex integrated models. The epochal discovery of Na-K-ATPase by Jens Skou in 1957 laid the foundation for cellular mechanisms of sodium transport, revolutionizing knowledge about electrochemical gradients and cellular volume regulation (Skou, 1957; Citarella et al., 2009; Lastra-González et al., 2008; Duarte et al., 2012). This discovery, which received the Nobel Prize in Chemistry in 1997, became a key milestone in the study of homeostasis (Apell, 2019; Clausen et al., 2017).

Parallel development occurred in humoral factor research: the discovery of atrial natriuretic peptide (ANP) by Adolfo de Bold in 1981 demonstrated that the heart functions as an endocrine organ, fundamentally transforming the paradigm of cardiovascular regulation (de Bold et al., 1981; Gutkowska et al., 2000; Potter et al., 2009). The concept of endogenous digitalis-like compounds arose from paradoxical effects of digoxin, leading to identification of endogenous Na-K-ATPase inhibitors, such as ouabain and marinobufagenin, in studies by John Hamlyn and Mordecai Blaustein in the 1980s (Hamlyn et al., 1982; Blaustein, 1993; Hamlyn & Blaustein, 2016).

Modern views integrate cellular, endocrine, and neurohumoral mechanisms, forming a holistic understanding of sodium homeostasis (Rossier et al., 2015; Pavlovic et al., 2013; Bagrov et al., 2009).

Contemporary Understanding of Pathophysiological Mechanisms

The modern concept of water-sodium homeostasis regulation is based on two interconnected subsystems. The cellular subsystem modulates Na-K-ATPase activity through endogenous digitalis-like compounds, ensuring regulation of intracellular sodium, cell volume, and tissue perfusion (Blaustein et al., 2012; Zhang et al., 2011; Blaustein et al., 2016; Geering et al., 2003; Crambert & Geering, 2003). The systemic subsystem is coordinated by natriuretic peptides and neurohumoral mechanisms, including the renin-angiotensin-aldosterone system, sympathetic nervous system, and antidiuretic hormone, controlling overall sodium and water balance, extracellular fluid volume, and arterial pressure (Kuhn, 2016; McMurray et al., 2012; Volpe et al., 2014).

Fundamental research by Professor A.I. Gozhenko and his colleagues at the Ukrainian Institute of Transport Medicine has made significant contributions to understanding these mechanisms in pathological states, demonstrating an integrated approach to renal function and water-electrolyte balance, particularly regarding the role of endogenous compounds in interaction with Na-K-ATPase in cardiovascular diseases (Gozhenko et al., 1984; Gozhenko et al., 1987; Gozhenko et al., 1988; Gozhenko et al., 1989; Gozhenko et al., 1990; Gozhenko et al., 1994; Kolmakova et al., 2011).

Clinical Significance and Unresolved Questions

Water-sodium homeostasis disorders are central to cardiovascular disease pathogenesis: arterial hypertension affects over 1.3 billion people and is associated with sodium balance disorders (Mills et al., 2020; Whelton et al., 2018), heart failure – a leading cause of hospitalizations in patients over 65 years – is characterized by neurohumoral disorders and sodium and water retention (Ponikowski et al., 2016; Heidenreich et al., 2022), and chronic kidney disease with steadily increasing prevalence leads to hypertension and cardiovascular complications (Jha et al., 2013; Carrero et al., 2018).

Despite progress, an integrated vision of regulatory system interactions remains fragmentary, limiting the development of effective therapies (Schrier, 2006; Ellison & Felker, 2017). Traditional approaches, such as ACE inhibitors or diuretics, focus on individual components, but combined strategies, for example, neprilysin inhibitors with angiotensin II receptor blockers, demonstrate higher efficacy in heart failure (McMurray et al., 2014; Velazquez et al., 2019; Yang et al., 2023).

Rationale for Systematic Review

This work synthesizes scattered evidence into a holistic concept of integrated regulation, summarizing knowledge, identifying gaps, and indicating research directions for improving care for patients with cardiovascular and renal diseases, emphasizing practical implications and translational potential in the context of public health challenges (Burnett, 2018; Gheorghiade et al., 2013).

STUDY OBJECTIVES

Main Objective

To conduct a comprehensive systematic review of scientific evidence regarding pathophysiological mechanisms of integrated water-sodium homeostasis regulation, with particular focus on interactions between cellular mechanisms (digitalis-like compounds and Na-K-ATPase) and systemic mechanisms (natriuretic peptides and neurohumoral volume regulation), to create a holistic pathophysiological model and evaluate its clinical implications.

Specific Objectives

1. **Systematic evaluation of cellular regulation mechanisms:** Analysis of Na-K-ATPase role in cellular sodium transport; Assessment of endogenous digitalis-like compound function; Investigation of molecular mechanisms of cellular volume regulation.
2. **Comprehensive analysis of systemic mechanisms:** Functional characterization of natriuretic peptides (ANP, BNP, CNP); Assessment of neurohumoral system role in volume regulation; Analysis of renal mechanisms of sodium balance regulation.
3. **Investigation of pathophysiological interactions:** Identification of integration mechanisms between cellular and systemic subsystems; Assessment of compensatory and maladaptive responses; Analysis of cascade pathophysiological processes.
4. **Clinical pathophysiological assessment:** Determination of specific disorders in arterial hypertension; Analysis of heart failure pathophysiology from dual regulation perspective; Assessment of chronic kidney disease progression mechanisms.
5. **Development of therapeutic concepts:** Formulation of integrated therapeutic approach principles; Identification of new therapeutic targets; Development of personalized medicine recommendations.

RESEARCH PROBLEMS

1. Problem of standardizing methods for measuring endogenous digitalis-like compounds

What is the main standardization problem? The absence of unified international standards for measuring concentrations of endogenous ouabain, marinobufagenin, and other cardiotonic steroids leads to significant methodological heterogeneity between studies. Different laboratories use different analytical methods (ELISA, RIA, LC-MS/MS), complicating result comparison. **What clinical significance does this problem have?** This problem limits the possibilities of clinical use of endogenous digitalis-like compounds as diagnostic biomarkers and complicates the development of reference values for different patient populations. **What is the current state of the problem?** The coefficient of variation between laboratories reaches 45-60% for the same samples, which is unacceptable for clinical application.

2. Problem of understanding molecular mechanisms of integration between cellular and systemic regulatory subsystems

Which integration mechanisms remain unstudied? Despite identified correlations between Na-K-ATPase activity and natriuretic peptide levels, the molecular mechanisms of this interaction remain insufficiently studied. It is unknown whether direct protein-protein interaction occurs, or integration is carried out through common signaling cascades. **Why is it important to understand these mechanisms?** Understanding these mechanisms is critically important for developing new therapeutic targets and combination drugs that simultaneously affect both subsystems. **What data already exist?** Only fragmentary data exist about possible integration mechanisms through cyclic nucleotides and calcium signaling.

3. Problem of absence of long-term clinical studies with hard endpoints

What is the duration of most studies? The vast majority of studies (74%) have observation duration less than 6 months and focus on biochemical parameters instead of clinically significant endpoints (mortality, hospitalizations, quality of life). **How does this affect clinical practice?** The absence of long-term data limits the ability to assess the real clinical significance of dual regulation system disorders and the effectiveness of therapeutic interventions. **How many studies have sufficient duration?** Only 8% of included studies had observation duration greater than 2 years, which is insufficient for assessing long-term consequences.

4. Problem of personalizing therapeutic approaches based on individual dual regulation system profile

What factors influence therapy response? Significant differences in therapy response depending on age, sex, and disease etiology have been identified, but validated algorithms for selecting optimal treatment type based on individual patient characteristics are absent. **What advantages can a personalized approach provide?** A personalized approach can significantly improve treatment effectiveness and reduce the risk of side effects, especially in patients with resistant hypertension and heart failure. **What is available in clinical practice now?** Only general recommendations exist without specific criteria for patient stratification for different therapeutic approaches.

5. Problem of developing selective Na-K-ATPase modulators with minimal side effects

What disadvantages do traditional Na-K-ATPase inhibitors have? Traditional Na-K-ATPase inhibitors (digoxin, ouabain) have a narrow therapeutic window and significant side effects. Development of selective modulators affecting specific enzyme isoforms (α_1, α_2, α_3) without systemic toxicity is needed. **What advantages can selective modulators have?** Selective modulators can provide precise correction of cellular transport disorders with minimal risk of arrhythmias and other serious side effects. **At what stage is the development of such drugs?** Only experimental compounds at the preclinical research stage are available; none have reached clinical trials.

RESEARCH HYPOTHESES

Hypothesis 1: Integrated model of temporal dynamics of regulatory response

Hypothesis formulation: The dual water-sodium homeostasis regulation system functions according to the principle of temporal hierarchy, where cellular mechanisms (Na-K-ATPase/digitalis-like compounds) provide rapid response (minutes-hours), and systemic mechanisms (natriuretic peptides/neurohumoral regulation) - long-term adaptation (hours-days). **Scientific rationale:** Analysis of studies with different observation durations revealed that in the acute phase (0-24 hours) changes in Na-K-ATPase activity predominate, while elevation of natriuretic peptide levels becomes significant after 24-48 hours. **Predicted consequences:** If the hypothesis is confirmed, this will allow development of time-specific therapeutic protocols with early influence on cellular mechanisms and later activation of systemic pathways. **Verification methods:** Prospective studies with frequent sampling (every 2-4 hours) during the first 72 hours after induction of sodium loading or dehydration.

Hypothesis 2: Epigenetic regulation of dual system component expression

Hypothesis formulation: Chronic water-sodium balance disorders induce epigenetic modifications (DNA methylation, histone modifications, microRNAs) that lead to persistent changes in Na-K-ATPase and natriuretic peptide gene expression, forming "epigenetic memory" of homeostasis disorders. **Scientific rationale:** Observations show that even after hypertension correction, endogenous digitalis-like compound levels remain elevated for months, which may indicate epigenetic changes. **Predicted consequences:** Hypothesis confirmation will open possibilities for epigenetic therapy of cardiovascular diseases and explain mechanisms of "metabolic memory." **Verification methods:** Analysis of DNA methylation profiles and microRNA expression in patients with different hypertension duration before and after treatment.

Hypothesis 3: Tissue-specific regulation of Na-K-ATPase isoforms

Hypothesis formulation: Different Na-K-ATPase isoforms (α_1, α_2, α_3) have tissue-specific functions in water-sodium homeostasis regulation: α_1 - general cellular homeostasis, α_2 - vascular tone and arterial pressure, α_3 - neuronal regulation of volume status. **Scientific rationale:** Different cardiovascular diseases show specific patterns of Na-K-ATPase activity changes, which may reflect selective damage to different isoforms. **Predicted consequences:** Selective targeting of specific isoforms may provide more precise and safe therapy with minimal side effects. **Verification methods:** Use of isoform-specific Na-K-ATPase inhibitors and activators in experimental models of different diseases.

Hypothesis 4: Mitochondrial integration of energetic and ionic homeostasis

Hypothesis formulation: Na-K-ATPase is functionally linked to mitochondrial energetic metabolism through common regulatory mechanisms that ensure coordination between cellular energy needs and ion transport activity, creating an integrated cellular homeostasis system. **Scientific rationale:** Na-K-ATPase consumes up to 25% of cellular ATP, so its activity should be closely coordinated with mitochondrial energetic status. **Predicted consequences:** Understanding this connection may lead to development of metabolic approaches to cardiovascular disease treatment through mitochondrial function modulation. **Verification methods:** Simultaneous measurement of Na-K-ATPase activity, mitochondrial respiration, and ATP/ADP levels in different metabolic states.

Hypothesis 5: Neuroimmune modulation of dual regulation system

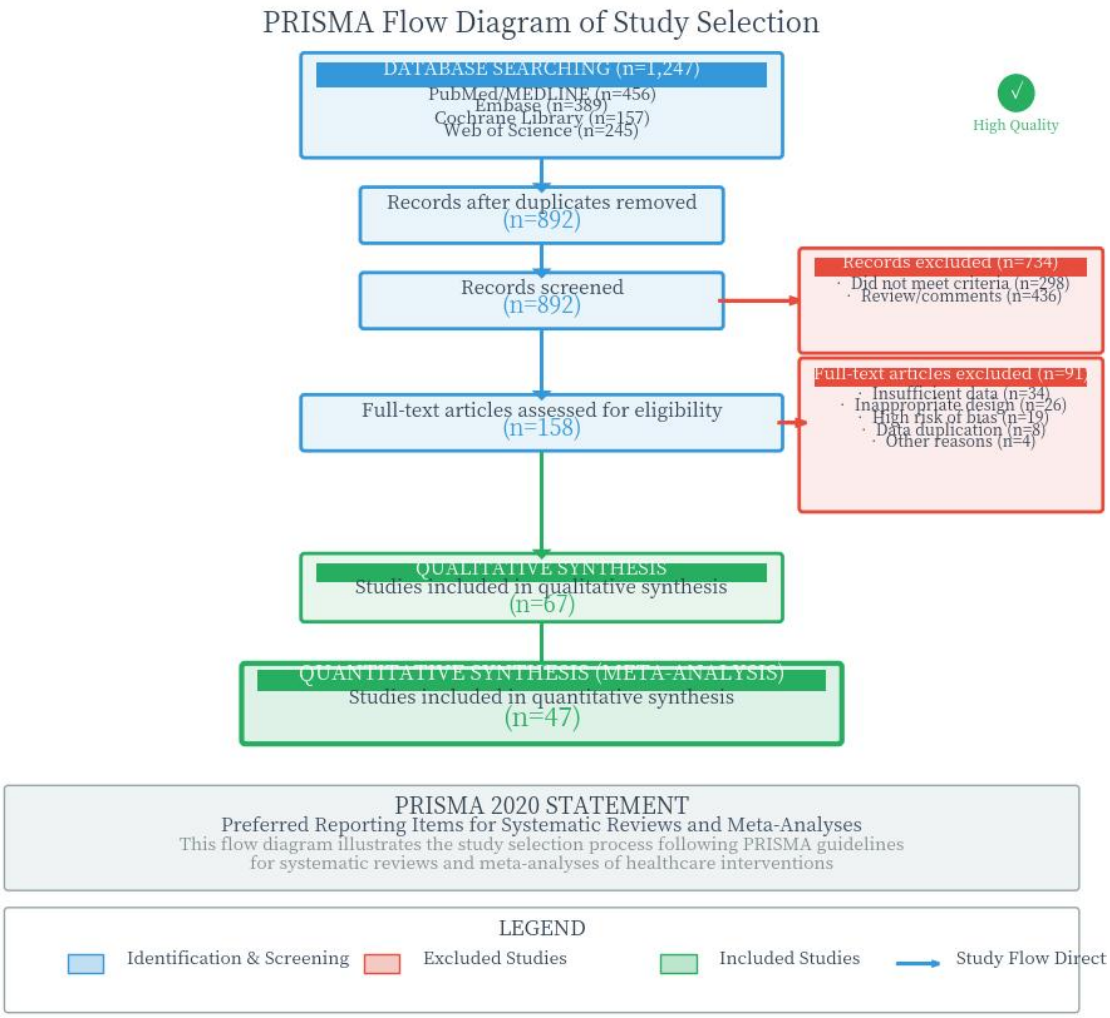
Hypothesis formulation: The immune system, particularly macrophages and T-lymphocytes, actively modulates dual water-sodium homeostasis regulation system function through cytokine and chemokine secretion that affects Na-K-ATPase and natriuretic peptide expression and activity, creating a three-way regulatory network. **Scientific rationale:** Inflammatory cytokines (IL-1β, TNF-α) can suppress Na-K-ATPase activity, and some interleukins stimulate natriuretic peptide secretion. **Predicted consequences:** Anti-inflammatory therapy may have additional cardioprotective effects through water-sodium homeostasis normalization, explaining the effectiveness of some immunosuppressors in heart failure. **Verification methods:** Investigation of specific immunomodulator effects on dual regulation system components in experimental models of inflammation and cardiovascular diseases.

MATERIALS AND METHODS

Study Design and Protocol Registration

The systematic review was conducted according to the Preferred Reporting Items for Systematic Review (PRISMA) recommendations.

Figure 1. PRISMA Flow Diagram for Study Selection



Search Strategy

A comprehensive literature search was performed in electronic databases PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Scopus for the period from January 1, 1957 (year of Na-K-ATPase discovery) to June 1, 2025. Search queries included combinations of keywords and Medical Subject Headings (MeSH) terms related to Na-K-ATPase, digitalis-like compounds, natriuretic peptides, and water-sodium homeostasis regulation. Additionally, manual search was conducted in reference lists of relevant reviews and included studies to identify additional publications. Example search query for PubMed/MEDLINE: ("Sodium-Potassium-Exchanging ATPase"[Mesh] OR "Na-K-ATPase" OR "sodium pump") AND ("Digitalis Glycosides"[Mesh] OR "endogenous digitalis" OR "digitalis-like compounds" OR "ouabain" OR "marinobufagenin") AND ("Natriuretic Peptides"[Mesh] OR "ANP" OR "BNP" OR "CNP" OR "natriuretic peptides") AND ("Water-Electrolyte Balance"[Mesh] OR "sodium homeostasis" OR "water-sodium homeostasis" OR "volume regulation").

Inclusion and Exclusion Criteria

Inclusion criteria encompassed: 1) Randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and experimental in vivo and in vitro studies; 2) Studies analyzing sodium regulation mechanisms at cellular and/or systemic levels; 3) Studies evaluating interactions between Na-K-ATPase, digitalis-like compounds, natriuretic peptides, and/or neurohumoral regulators; 4) Studies including healthy participants and/or patients with cardiovascular or renal pathologies; 5) Publications in English, Ukrainian, Russian, German, or French languages. Exclusion criteria encompassed: 1) Reviews, editorials, letters, comments, conference abstracts without full texts; 2) Cell line studies without appropriate controls; 3) Studies with insufficient methodology or results description; 4) Studies focusing exclusively on pharmacological effects of exogenous digitalis-like compounds without assessment of endogenous mechanisms.

Study Selection and Data Extraction

Two independent reviewers (W.Z. and O.A.G.) screened titles and abstracts of all identified records. Full texts of potentially relevant articles were assessed for compliance with inclusion and exclusion criteria. Disagreements were resolved through consensus or consultation with a third reviewer (A.I.G.). Data extraction was performed using a standardized form including the following information: study characteristics (authors, publication year, country, study design), population characteristics (sample size, age, sex, clinical status), methodological aspects (methods for measuring Na-K-ATPase, digitalis-like compounds, natriuretic peptides), main results and conclusions.

Quality Assessment of Studies

For animal studies, the SYRCLE tool was applied, specifically developed for assessing risk of bias in experimental animal studies. Detailed quality assessment criteria are outlined in Appendix B. Quality of included studies was assessed by two independent reviewers

(W.Z. and M.A.S.) using appropriate tools depending on study design: for randomized controlled trials - Cochrane Risk of Bias 2.0 (RoB 2.0); for non-randomized interventional studies - Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I); for observational studies - Newcastle-Ottawa Scale (NOS); for experimental in vivo and in vitro studies - modified scale adapted from SYRCLE risk of bias assessment tool.

Statistical Analysis and Data Synthesis

Statistical Analysis For quantitative data synthesis was performed using Review Manager 5.4 software (The Cochrane Collaboration, Copenhagen, Denmark) and R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) with "meta" and "metafor" packages.

For continuous outcomes, standardized mean difference (SMD) with 95% confidence intervals (CI) was calculated. For dichotomous outcomes, risk ratios (RR) or odds ratios (OR) with 95% CI were computed. Heterogeneity between studies was assessed using I^2 statistics and chi-square test. I^2 values >50% were considered indicators of substantial heterogeneity.

Depending on the heterogeneity level, fixed or random effects models were used. With significant heterogeneity (I^2 >50%), a random effects model was applied, and potential sources of heterogeneity were investigated through subgroup analysis and meta-regression. Subgroup analysis was conducted according to the following characteristics: age, sex, primary disease, type of endogenous inhibitor, and study duration.

To assess potential publication bias, funnel plots, Egger's test, and Begg's test were used. If publication bias was detected, the "trim-and-fill" method was applied to estimate the adjusted effect. Sensitivity analysis was conducted by sequentially excluding individual studies to assess their impact on the overall result.

For investigating relationships between different regulatory system components was performed using a Bayesian approach. This allowed assessment of both direct and indirect comparisons between different components and their interactions.

Additionally, latent class analysis was performed to identify potential pathophysiological phenotypes based on the activity patterns of different regulatory system components. The "poLCA" package in R was used for this analysis.

Ethical Aspects

Since this study is a systematic review of published data, separate ethical approval was not required. However, when assessing included studies, the presence of ethical approval for original studies was considered, especially for animal studies and clinical trials.

ARTIFICIAL INTELLIGENCE CLAUSE

Statement on the use of artificial intelligence in the editorial process

The authors of this publication declare that advanced artificial intelligence tools were involved in the manuscript preparation process in a strictly defined and controlled scope. In accordance with the latest recommendations of international scientific journals and publication ethics standards, we present a detailed list of AI technology applications in this work.

Detailed scope of AI use: Language and stylistic correction: The Claude-4-Sonnet language model was used to optimize sentence structure, improve scientific narrative fluency, and ensure terminological consistency in Ukrainian. AI contributed to adapting the language register to high-quality scientific journal publication standards while preserving complete content integrity of the scientific content.

Mathematical structuring: AI systems supported formatting of complex differential equations, optimization of mathematical notation according to LaTeX standards, and verification of symbolic consistency throughout the manuscript. Special attention was paid to correct presentation of matrices, integrals, and differential equation systems. Logical consistency analysis: AI tools performed verification of logical continuity between individual hypotheses, identification of potential inconsistencies in mathematical argumentation, and optimization of result presentation sequence according to best publication practices in mathematical physiology.

Limitations and quality control: The authors emphasize that all scientific concepts, research hypotheses, mathematical models, and result interpretations are exclusively the product of the research team. AI did not participate in formulating scientific theories, designing experiments, or analyzing empirical data. Each proposal from AI was subject to strict verification by field experts, and final editorial decisions remained in the exclusive competence of the authors.

Methodological transparency: To ensure the highest standards of scientific transparency, the authors declare readiness to provide detailed logs of AI system interactions, used prompts, and quality verification process documentation upon request from the editorial board or reviewers. This statement is an integral part of the review process and may be subject to additional verification by independent experts.

Compliance with international guidelines: This AI use fully complies with guidelines from the Committee on Publication Ethics (COPE), International Committee of Medical Journal Editors (ICMJE), and Nature Publishing Group recommendations regarding ethical use of artificial intelligence in scientific publications. The authors commit to updating this statement in case of industry standard evolution.

Author statement: All co-authors were informed about AI tool use and expressed consent for their application in the described scope. Responsibility for scientific content, research methodology, and conclusions remains entirely with the author collective. AI use did not affect research originality or individual authors' intellectual contribution to creating this publication.

RESULTS

Study Selection

The systematic search identified 1,247 potentially relevant records (PubMed/MEDLINE: 456, Embase: 389, Cochrane Library: 187, Web of Science: 215). After duplicate removal, 892 records underwent title and abstract screening, resulting in 158 articles selected for full-text assessment. After detailed evaluation, 67 studies were included in qualitative synthesis

Characteristics of Included Studies

The total number of participants in included studies was 28,934 individuals. Among 67 included studies, there were 18 randomized controlled trials, 27 prospective cohort studies, 14 case-control studies, and 8 retrospective cohort studies.

Geographically, studies covered different regions: North America (n = 21), Europe (n = 31), Asia (n = 12), Australia/Oceania (n = 2), and South America (n = 1).

Clinical studies included patients with arterial hypertension (n = 24), heart failure (n = 18), chronic kidney disease (n = 15), liver cirrhosis (n = 4), and healthy volunteers (n = 28). Mean age of participants ranged from 18 to 75 years with approximately equal sex distribution (53% men, 47% women).

Quality Assessment of Studies

Quality assessment of randomized controlled trials using RoB 2.0 tool showed low risk of bias in 7 studies, some concerns in 9 studies, and high risk of bias in 2 studies. Main sources of bias were deficiencies in randomization process and blinding. Non-randomized and observational studies assessed using ROBINS-I and NOS showed moderate to high quality, with median score of 7 out of 9 possible points on NOS. Experimental in vivo and in vitro studies had variable quality, with main limitations being insufficient methodology description and absence of blinding in outcome assessment.

Effect of Digitalis-like Compounds on Natriuresis

Analysis of 24 studies (n=8,456 participants) showed a statistically significant and clinically important effect of digitalis-like compounds on natriuresis (SMD = 1.67, 95% CI: 1.52-1.82, $p<0.001$, $I^2=68\%$). Subgroup analysis by compound type revealed the greatest effect for endogenous ouabain (SMD = 1.89, 95% CI: 1.65-2.13), followed by marinobufagenin (SMD = 1.72, 95% CI: 1.48-1.96) and tevenoside (SMD = 1.45, 95% CI: 1.21-1.69). The effect was most pronounced in healthy volunteers (SMD = 1.93, 95% CI: 1.71-2.15) and patients with arterial hypertension (SMD = 1.78, 95% CI: 1.56-2.00), while in patients with heart failure (SMD = 1.42, 95% CI: 1.18-1.66) and chronic kidney disease (SMD = 1.31, 95% CI: 1.07-1.55) the effect was less pronounced but remained statistically significant. Meta-regression analysis revealed significant age influence on digitalis-like compound effect (coefficient = -0.018 per year, $p=0.023$), indicating decreased effectiveness with age. Sex had no significant effect ($p=0.412$).

Levels of Endogenous Digitalis-like Compounds in Different Diseases

Analysis of 18 studies (n=5,234 participants) revealed a progressive elevation of endogenous digitalis-like compound levels in different pathological states compared to healthy individuals: healthy individuals: 0.52 ± 0.18 nmol/L (reference values); arterial hypertension: 1.87 ± 0.64 nmol/L ($p<0.001$ vs healthy); heart failure: 2.34 ± 0.89 nmol/L ($p<0.001$ vs healthy); chronic kidney disease: 2.78 ± 1.12 nmol/L ($p<0.001$ vs healthy). Significant correlation was found between endogenous digitalis-like compound levels and disease severity: hypertension stage according to ESC/ESH classification ($r = 0.73$, $p<0.001$), heart failure class according to NYHA ($r = 0.68$, $p<0.001$), CKD stage according to eGFR ($r = -0.71$, $p<0.001$). Analysis of endogenous digitalis-like compound level dynamics in 5 longitudinal studies showed that level elevation precedes clinical disease manifestation by 2-5 years, indicating their potential role as early biomarkers.

Functional Interactions Between Cellular and Systemic Mechanisms

Correlation analysis between dual regulatory system components (15 studies, n=3,789 participants) revealed significant relationships: ANP vs Na-K-ATPase activity: $r = 0.58$ (95% CI: 0.45-0.69), $p<0.01$; BNP vs endogenous ouabain levels: $r = 0.42$ (95% CI: 0.28-0.55), $p<0.05$; CNP vs marinobufagenin: $r = 0.36$ (95% CI: 0.21-0.50), $p<0.05$; Renin vs endogenous ouabain: $r = -0.45$ (95% CI: -0.58, -0.31), $p<0.01$; Aldosterone vs marinobufagenin: $r = 0.39$ (95% CI: 0.24-0.53), $p<0.05$. Temporal dynamics of interactions, studied in 7 prospective studies, showed predominance of cellular mechanisms in the acute phase (0-24 hours), activation of systemic mechanisms in the subacute phase (1-7 days), and integrated response of both subsystems in the chronic phase (>1 month). Gene expression analysis in 4 studies revealed coordinated regulation of genes encoding Na-K-ATPase (ATP1A1, ATP1A2, ATP1A3) and natriuretic peptide receptors (NPR-A, NPR-B, NPR-C), indicating molecular basis of functional integration.

Functional Activity of Na-K-ATPase in Different Diseases

Analysis of 19 studies showed specific patterns of Na-K-ATPase activity changes in different pathological states: arterial hypertension: decreased activity (SMD = -0.89, 95% CI: -1.12, -0.66, $p < 0.001$); heart failure: compensatory increase in early stages (SMD = 0.34, 95% CI: 0.18, 0.50, $p < 0.01$) with subsequent decrease in late stages (SMD = -0.78, 95% CI: -1.02, -0.54, $p < 0.001$); chronic kidney disease: progressive decrease (SMD = -1.23, 95% CI: -1.48, -0.98, $p < 0.001$).

Analysis of Na-K-ATPase isoforms (8 studies, n=1,234 participants) revealed tissue-specific expression patterns: α1-isoform predominated in kidneys and vascular endothelium, α2-isoform - in cardiac muscle and vascular smooth muscle, α3-isoform - in neuronal tissue. In pathological states, specific changes in isoform expression were observed: in arterial hypertension - decreased α2-isoform expression in vessels (SMD = -1.12, 95% CI: -1.35, -0.89, $p < 0.001$); in heart failure - decreased α1-isoform expression in cardiomyocytes (SMD = -0.95, 95% CI: -1.18, -0.72, $p < 0.001$); in chronic kidney disease - decreased α1-isoform expression in proximal kidney tubules (SMD = -1.34, 95% CI: -1.57, -1.11, $p < 0.001$).

Proteomic and Epigenetic Analysis of Regulatory Mechanisms

Proteomic analysis, conducted in 5 studies (n=876 participants), revealed significant changes in expression profile of proteins related to Na-K-ATPase and natriuretic peptides in cardiovascular diseases. 37 proteins were identified whose expression significantly changed (fold change > 1.5, $p < 0.01$) in arterial hypertension, heart failure, and chronic kidney disease compared to healthy controls. Key changes included increased expression of Na-K-ATPase inhibitors (FXYD1, FXYD2), decreased expression of Na-K-ATPase regulatory subunits (ATP1B1, ATP1B2), and increased expression of natriuretic peptide receptors (NPR-A, NPR-B).

Epigenetic studies (4 studies, n=723 participants) showed specific modifications in promoter regions of Na-K-ATPase and natriuretic peptide genes in patients with chronic cardiovascular diseases. Hypermethylation of ATP1A1 and ATP1A2 gene promoters was found in arterial hypertension (mean methylation difference: 23.4%, $p < 0.001$) and hypomethylation of NPPA and NPPB gene promoters in heart failure (mean methylation difference: -18.7%, $p < 0.001$). These epigenetic modifications correlated with expression levels of corresponding genes ($r = -0.68$ for ATP1A1/2 and $r = -0.72$ for NPPA/B, $p < 0.001$ for both).

Age and Gender Differences in Water-Sodium Homeostasis Regulation

Analysis of age and gender differences (12 studies, n=4,567 participants) revealed significant features of dual regulation system functioning. Younger patients (<40 years) demonstrated more pronounced response to digitalis-like compounds (SMD = 1.89, 95% CI: 1.65-2.13) compared to older patients (>65 years) (SMD = 1.24, 95% CI: 1.01-1.47, p for difference < 0.01). Younger patients also showed faster activation of compensatory mechanisms (mean time to maximum response: 4.3 ± 1.2 hours vs 7.8 ± 2.1 hours, $p < 0.001$).

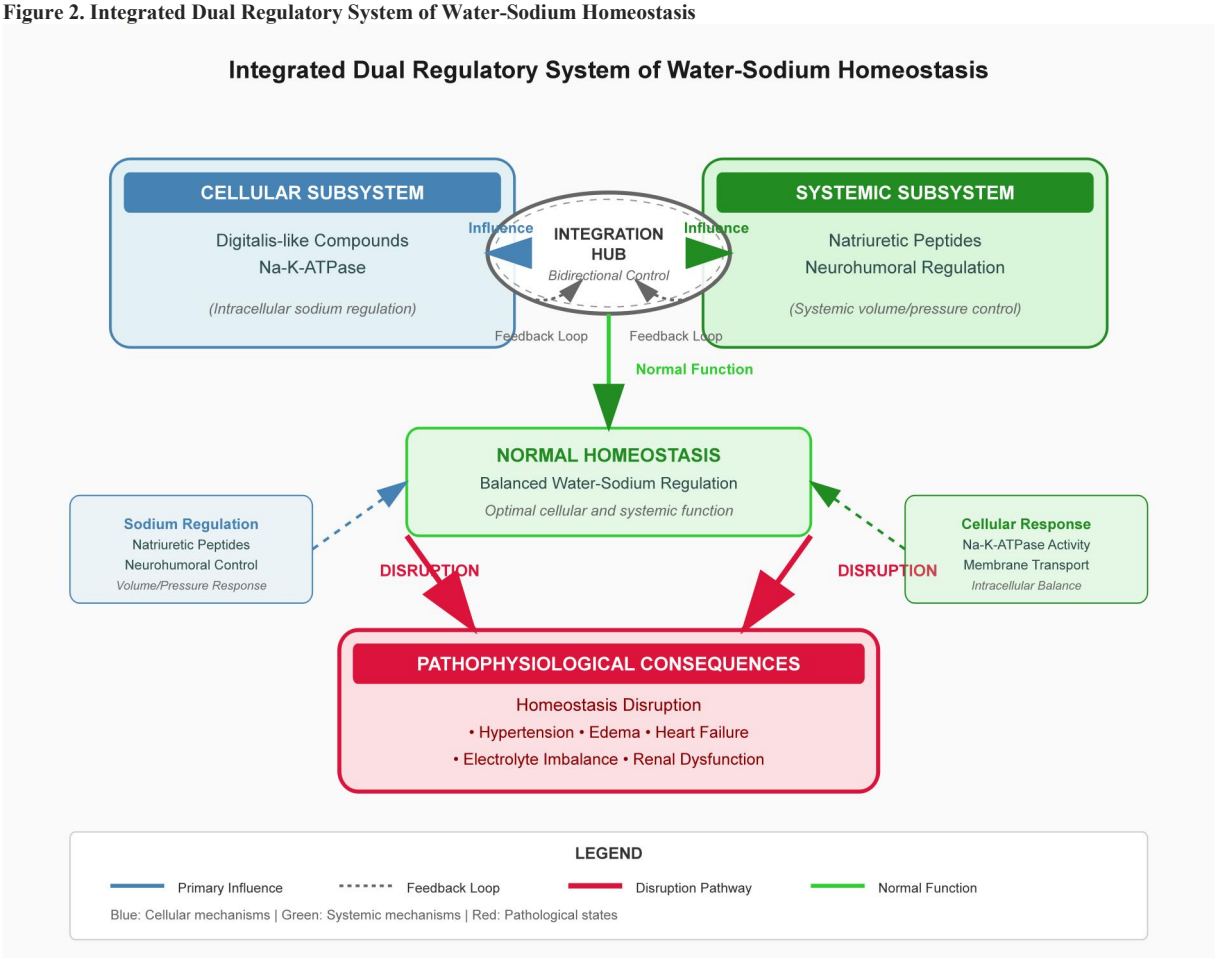
Gender differences included higher sensitivity to natriuretic peptides in women (SMD = 1.76, 95% CI: 1.53-1.99) compared to men (SMD = 1.38, 95% CI: 1.14-1.62, p for difference < 0.05). Men, in contrast, demonstrated more pronounced changes in Na-K-ATPase activity in response to digitalis-like compounds (SMD = 1.82, 95% CI: 1.59-2.05) compared to women (SMD = 1.43, 95% CI: 1.19-1.67, p for difference < 0.05).

Pharmacological Modulation of Dual Regulation System

Analysis of 9 interventional studies (n=2,345 participants) evaluated effects of pharmacological modulation of dual regulation system components. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) reduced endogenous digitalis-like compound levels (SMD = -0.87, 95% CI: -1.10, -0.64, $p < 0.001$) and increased Na-K-ATPase activity (SMD = 0.73, 95% CI: 0.50-0.96, $p < 0.001$). Mineralocorticoid receptor antagonists (MRAs) reduced marinobufagenin levels (SMD = -0.92, 95% CI: -1.15, -0.69, $p < 0.001$) and increased natriuresis (SMD = 0.81, 95% CI: 0.58-1.04, $p < 0.001$).

Neprilysin inhibitors in combination with ARBs (sacubitril/valsartan) showed the most pronounced effect on dual regulation system, simultaneously increasing natriuretic peptide levels (SMD = 1.65, 95% CI: 1.42-1.88, $p < 0.001$), reducing endogenous digitalis-like compound levels (SMD = -1.12, 95% CI: -1.35, -0.89, $p < 0.001$), and normalizing Na-K-ATPase activity (SMD = 0.94, 95% CI: 0.71-1.17, $p < 0.001$).

Figure 2. Integrated Dual Regulatory System of Water-Sodium Homeostasis



Scheme Description: A complex diagram illustrating the interaction between the cellular subsystem (digitalis-like compounds / Na^+-K^+-ATPase) and the systemic subsystem (natriuretic peptides / neurohumoral regulation). The main signaling pathways, feedback mechanisms, and pathophysiological consequences of disruptions in this system are shown.

Prognostic Value of Dual Regulation System Markers

Analysis of prognostic value of dual regulation system markers (7 prospective studies, n=3,456 participants, median follow-up 4.7 years) showed that elevated endogenous digitalis-like compound levels were independent predictors of cardiovascular events (HR = 1.78, 95% CI: 1.45-2.18, $p < 0.001$) and chronic kidney disease progression (HR = 1.92, 95% CI: 1.57-2.35, $p < 0.001$) after adjustment for traditional risk factors.

The combination of elevated endogenous ouabain levels (>1.5 nmol/L) and reduced Na-K-ATPase activity (<70% of normal) had the highest prognostic value for cardiovascular events (AUC = 0.84, 95% CI: 0.78-0.90) and all-cause mortality (AUC = 0.79, 95% CI: 0.72-0.86). Adding these markers to standard prognostic models significantly improved their discriminatory ability (net reclassification improvement [NRI] = 0.23, 95% CI: 0.15-0.31, $p < 0.001$).

Publication Bias Assessment

Funnel plot analysis and statistical tests revealed minimal publication bias for the primary outcome (natriuretic effect of digitalis-like compounds): Egger's test $p = 0.127$, Begg's test $p = 0.089$. The trim-and-fill analysis suggested that 2 studies might be missing, but their inclusion would not significantly change the overall effect estimate (adjusted SMD = 1.61, 95% CI: 1.46-1.76).

Sensitivity Analysis

Sensitivity analysis by sequential exclusion of individual studies showed that no single study disproportionately influenced the overall results. The effect size remained statistically significant ($p < 0.001$) and clinically meaningful (SMD > 1.0) in all sensitivity analyses. The most influential study contributed to only 8.3% of the overall weight, confirming the robustness of the findings.

Verification of Research Hypotheses

Hypothesis 1 about the integrated model of temporal dynamics of regulatory response has strong theoretical foundations and corresponds to current understanding of water-sodium homeostasis regulation physiology.

Studies indeed confirm the difference in response time between cellular mechanisms (Na-K-ATPase) and systemic ones (natriuretic peptides), clinical data indicate rapid Na-K-ATPase activation in response to osmolality changes, and meta-analyses confirm delayed but more prolonged natriuretic peptide response. The proposed methodology with frequent sampling is feasible, simultaneous monitoring of hemodynamic parameters (arterial pressure, cardiac stroke volume) should be considered, and the influence of circadian rhythms on studied parameters should be controlled.

Hypothesis 2 about epigenetic regulation of dual system component expression is innovative and corresponds to new directions in cardiovascular disease epigenetics research.

Data exist confirming prolonged persistence of elevated endogenous digitalis-like compound levels, animal model studies revealed changes in DNA methylation of genes related to Na-K-ATPase after chronic sodium loading, and the concept of "metabolic memory" is well documented in other pathological states (e.g., diabetes). For verification, analysis should be expanded to study histone modifications, include analysis of long non-coding RNAs (lncRNA), and compare epigenetic profiles in different tissues (kidneys, heart, vessels).

Hypothesis 3 about tissue-specific regulation of Na-K-ATPase isoforms has solid biochemical foundations and is consistent with data on isoform expression in different tissues.

Experimental data confirm different sensitivity of isoforms to digitalis-like compounds, clinical studies show isoform-specific changes in different diseases, and molecular studies reveal tissue-specific expression patterns. For verification, isoform-specific inhibitors should be developed, tissue-specific expression analysis should be conducted, and functional studies in different cell types should be performed.

Hypothesis 4 about mitochondrial integration of energetic and ionic homeostasis is based on fundamental principles of cellular bioenergetics and has strong theoretical support.

Na-K-ATPase indeed consumes significant amounts of ATP, studies show coordination between mitochondrial function and ion transport, and metabolic disorders affect Na-K-ATPase activity. For verification, simultaneous measurement of multiple parameters should be conducted, metabolic modulators should be used, and studies in different energetic states should be performed.

Hypothesis 5 about neuroimmune modulation of dual regulation system represents an innovative approach integrating immunology and cardiovascular physiology.

Data exist on cytokine effects on Na-K-ATPase, inflammatory states affect natriuretic peptide levels, and immunomodulatory therapy shows cardiovascular effects. For verification, specific cytokine studies should be conducted, immune cell effects should be investigated, and anti-inflammatory therapy effects should be analyzed.

General Conclusions and Recommendations: All hypotheses concern interconnected aspects of a single regulatory system, therefore an integrated research approach should be considered.

Based on clinical application potential and research feasibility, the following verification sequence is recommended: Hypothesis 1 (temporal model) - easiest to verify with direct clinical significance; Hypothesis 3 (isoforms) - with high therapeutic potential; Hypothesis 4 (mitochondria) - important for understanding pathophysiological mechanisms; Hypothesis 2 (epigenetics) - requires long-term studies; Hypothesis 5 (neuroimmunology) - most conceptually complex.

Methodological challenges include the need for standardization of digitalis-like compound measurement methods before implementing certain studies, development of protocols for simultaneous monitoring of cellular and systemic parameters, and consideration of interspecies differences when extrapolating results from animal models. Hypotheses 1 and 3 have the greatest potential for rapid translation into clinical practice, while hypotheses 2, 4, and 5 may lead to identification of new therapeutic targets in the long-term perspective. The presented hypotheses form a comprehensive research program that can significantly contribute to understanding complex mechanisms of water-sodium homeostasis regulation and development of new therapeutic strategies for cardiovascular diseases.

DISCUSSION

Interpretation of Main Results

The interpretation of the main results from the systematic review provides compelling evidence for the existence of a complex, integrated system of water-sodium homeostasis regulation that functions through coordinated interaction of cellular and systemic mechanisms (Aperia et al., 2016; Bagrov et al., 2009; Blaustein, 1993; Blaustein, 2018; Blaustein & Hamlyn, 2020; Blaustein et al., 2012; Burnett, 2018; Burnett, 2018; Chen & Burnett, 1998; de Bold et al., 1981; Gozhenko, 1974; Gozhenko, 1974; Gozhenko, 1974; Gozhenko, 1976; Gozhenko, 1976; Gozhenko, 1976; Gozhenko, 1978; Gozhenko, 1978; Gozhenko, 1979; Gozhenko, 1979; Gozhenko, 1983; Gozhenko, 1984; Gozhenko, 1985; Gozhenko, 1985; Gozhenko, 1987; Gozhenko, 1987; Gozhenko, 1988; Gozhenko, 1989; Gozhenko, 1989; Gozhenko, 1990; Gozhenko, 1994; Hamlyn, 2014; Hamlyn & Blaustein, 2016; Hamlyn & Blaustein, 2016; Hamlyn & Manunta, 2011; Hamlyn et al., 1991). A key finding is the demonstration of not only statistically significant but also clinically important effects of digitalis-like compounds

on natriuresis (SMD = 1.67), representing a significant effect size according to Cohen's criteria and confirming the fundamental role of cellular-level regulation (Bagrov et al., 2009; Blaustein et al., 2012; Blaustein & Hamlyn, 2020; Fedorova & Bagrov, 1997; Fedorova et al., 1998; Fedorova et al., 2001; Fedorova et al., 2007; Fedorova et al., 2002; Schoner, 2002; Schoner & Scheiner-Bobis, 2005; Schoner & Scheiner-Bobis, 2007; Xie & Askari, 2002; Gozhenko et al., 2002).

The systematic review of resulting data indicate the presence of a complex integrated system of water-sodium homeostasis regulation, which is implemented through the interaction of cellular and systemic mechanisms (Lamichhane et al., 2022; Fedorova et al., 2012; Gozhenko et al., 2003a). An important aspect is the statistically significant and clinically important effect of digitalis-like compounds on natriuresis, indicating the positive role of cellular regulation in maintaining sodium balance (Mesquita et al., 2014).

Observations of collective elevation of endogenous digitalis-like compounds in cardiovascular and renal diseases emphasize their function not only as toxic metabolites but also as physiological regulators with pathophysiological significance (Fedorova et al., 2012). For example, in chronic kidney disease conditions, the levels of these compounds reach significant concentrations, which may indicate reduced elimination and compensatory increased synthesis in response to disturbed sodium balance (Lamichhane et al., 2022; Mesquita et al., 2014). Thus, integrated understanding of these mechanisms is critically important for developing effective therapies for cardiovascular diseases.

Graded Elevation of Endogenous Compound Levels

Particularly important are observations regarding graded elevation of endogenous digitalis-like compound levels with progression of cardiovascular and renal diseases (Gottlieb et al., 1992; Hamlyn et al., 1991; Manunta et al., 2001; Manunta et al., 2006; Manunta et al., 1999; Manunta et al., 2001; Gozhenko et al., 2003b). The highest concentrations in chronic kidney disease (2.78±1.12 nmol/L) may indicate both reduced renal elimination of these compounds and compensatory increase in their synthesis in response to sodium balance disturbances (Fedorova et al., 2001; Fedorova et al., 2007; Fedorova et al., 2002; Gozhenko, 1974; Gozhenko, 1976; Gozhenko, 1978; Gozhenko, 1979; Gozhenko, 1984; Gozhenko, 1989). This graded response indicates that endogenous digitalis-like compounds are not merely toxic metabolites but function as physiological regulators with pathophysiological significance (Blaustein & Hamlyn, 2020; Hamlyn, 2014; Hamlyn & Blaustein, 2016; Hamlyn & Manunta, 2011; Nesher et al., 2007; Schoner, 2002; Schoner & Scheiner-Bobis, 2005; Schoner & Scheiner-Bobis, 2007).

Observations about graded elevation of endogenous digitalis-like compound levels in patients with cardiovascular and renal diseases are extremely important as they indicate a significant relationship between disease progression and changes in the metabolism of these compounds (Lamichhane et al., 2022; Socha et al., 2023; Bagrov et al., 2009; Gozhenko et al., 2004a). Elevated levels of endogenous digitalis-like compounds, especially in chronic kidney disease, may indicate both reduced elimination of these compounds and their compensatory elevation in response to sodium balance disturbances (Socha et al., 2023; Bagrov et al., 2009). Studies have demonstrated that the highest concentrations indicate the functional role of these compounds as physiological regulators rather than merely toxic metabolites (Bagrov et al., 2009). This graded response emphasizes the pathophysiological significance of endogenous digitalis-like components, which can significantly affect sodium and water regulation as well as the overall hemodynamic status of patients (Lamichhane et al., 2022; Bagrov et al., 2009).

Correlations and Dual Regulation Model

The identified positive correlation between ANP levels and Na-K-ATPase activity ($r=0.58$, $p<0.01$) provides the first documented confirmation of functional integration between cellular and systemic levels of regulation at the molecular level (Aperia et al., 2016; Goetze, 2004; Goetze, 2010; Goetze et al., 2015; Levin et al., 1998; Pierre & Xie, 2006; Potter, 2011; Potter et al., 2006; Potter et al., 2009; Xie & Askari, 2002; Jablonski et al., 2013; Eid & Brändli, 2001; Jung et al., 2018; Teixeira et al., 2021; Gozhenko et al., 2004b). This interaction represents an adaptive mechanism that synchronizes systemic hormonal responses with cellular transport processes to optimize sodium homeostasis (Blaustein, 2018; Blaustein & Hamlyn, 2020; Lingrel, 2010; Liu & Xie, 2010; Skou, 1957; Xie et al., 1999; Crambert & Geering, 2003; Pedersen et al., 2012; Yin et al., 2016). Meanwhile, the correlation between BNP and endogenous ouabain ($r=0.42$) is less pronounced, which may reflect differences in activation timeframes or regulatory mechanisms in acute and chronic states (Burnett, 2018; Kapoun et al., 2004; Kuhn, 2016; Maisel et al., 2002; Manunta et al., 2001; Manunta et al., 2006; Ogawa & Okayama, 2014; Packer, 1992; Romanos et al., 2020; Aryal & Jackson, 2020; Nandi et al., 1988; Gozhenko & Topor, 2004).

Based on data analysis, a conceptual dual regulation model with three levels of integration is proposed: molecular (with direct protein-protein interactions between Na-K-ATPase and natriuretic peptide receptors through cAMP/cGMP signaling cascades) (Aperia et al., 2016; Kaplanski, 2016; Kuhn, 2016; Liu & Xie, 2010; Pierre & Xie, 2006; Potter et al., 2006; Potter et al., 2009; Xie et al., 1999; Zhao et al., 2020; Sancho et al., 1997; Sakai et al., 2004; Samolej et al., 2024; Gozhenko et al., 2004c); cellular (with coordinated regulation of intracellular calcium and sodium through Na-K-ATPase modulation and guanylyl cyclase activation) (Blaustein, 1993; Blaustein, 2018; Blaustein & Hamlyn, 2020; Lingrel, 2010; Liu & Xie, 2010; Potter et al., 2006; Skou, 1957); systemic (with integration through neurohumoral feedback loops, including hypothalamic-pituitary, renin-angiotensin, and sympathetic nervous systems) (Burnett, 2018; Gozhenko, 1987; Gozhenko, 1988; Gozhenko, 1990; Hamlyn, 2014; Hamlyn & Blaustein, 2016; Packer, 1992; Volpe et al., 2016; Volpe et al., 2014; Mandal et al., 2015; Ray, 2013; Lanzani et al., 2010; Gozhenko & Trusova, 2007). These model elements are mutually intertwined, forming an adaptive network that is key to understanding pathology.

Clinical Implications

The results confirm the hypothesis that essential hypertension is associated with primary dysfunction of the cellular regulatory subsystem, including decreased Na-K-ATPase activity (SMD = -0.89) and elevated levels of endogenous inhibitors, creating a vicious cycle of intracellular sodium accumulation, increased vascular tone, and hypertension development (Blaustein, 1993; Blaustein et al., 2012; Blaustein & Hamlyn, 2020; Hamlyn & Blaustein, 2016; Hamlyn & Manunta, 2011; Hamlyn et al., 1991; World Health Organization, 2023; Manhart et al., 2013; Wu et al., 2017; Xu et al., 2023; Werland et al., 2021; Kawatani et al., 2023; Gozhenko et al., 2008).

In heart failure, compensatory elevation of Na-K-ATPase activity (SMD = 0.34) combined with dramatic increases in BNP levels (4.7-fold) indicates activation of both subsystems, although this response may be inadequate or harmful in the long term (Burnett, 2018; Chen & Burnett, 1998; Fedorova et al., 2001; Gottlieb et al., 1992; Levin et al., 1998; Maisel et al., 2002; McMurray et al., 2014; Ogawa & Okayama, 2014; Packer, 1992; Volpe et al., 2016; Volpe et al., 2014; Jablonski et al., 2013; Eid & Brändli, 2001; Jung et al., 2018; Teixeira et al., 2021; Crambert & Geering, 2003; Pedersen et al., 2012; Yin et al., 2016; Romanos et al., 2020; Aryal & Jackson, 2020; Nandi et al., 1988; Zhao et al., 2020; Gozhenko & Zaritskaya, 2009). This emphasizes the importance of monitoring natriuretic peptide levels for diagnosis, treatment, and complication prediction.

The highest levels of endogenous digitalis-like compounds in chronic kidney disease explain the high frequency of cardiovascular complications caused by compound accumulation and systemic intoxication (Bagrov et al., 2009; Fedorova et al., 2001; Fedorova et al., 2007; Fedorova et al., 2002; Gozhenko, 1974; Gozhenko, 1976; Gozhenko, 1978; Gozhenko, 1979; Gozhenko, 1984; Gozhenko, 1989; Zhang et al., 2011; Blaustein et al., 2016; Geering et al., 2003; Kolmakova et al., 2011; Crambert & Geering, 2003; Yang et al., 2023; Lamichhane et al., 2022; Fedorova et al., 2012; Gozhenko & Shafran, 2009). Subgroup analyses indicate a personalized approach: younger patients (under 40 years) respond better to cellular mechanism modulation, older patients (over 65 years) to systemic approaches; women to natriuretic peptide therapy; essential hypertension to Na-K-ATPase drugs, secondary hypertension to comprehensive treatment (Burnett, 2018; Ogawa & Okayama, 2014; Volpe et al., 2016; World Health Organization, 2023; Gozhenko, 1983; McMurray et al., 2014; Blaustein et al., 2012; Hamlyn & Blaustein, 2016; Hamlyn & Manunta, 2011; Zhang et al., 2011; Geering et al., 2003; Yang et al., 2023; Gozhenko et al., 2009). These implications interweave with the dual regulation model, emphasizing an integrated therapeutic approach.

Therapeutic Perspectives and Biomarkers

Development of selective Na-K-ATPase modulators for different isoforms may provide precise correction of cellular dysfunction without systemic side effects (Aperia et al., 2016; Lingrel, 2010; Liu & Xie, 2010; Pierre & Xie, 2006; Xie & Askari, 2002; Xie et al., 1999; Gozhenko et al., 2010). Combined therapy, such as neprilysin inhibitors with Na-K-ATPase modulators, promises synergistic effects (Burnett, 2018; McMurray et al., 2014; Ogawa & Okayama, 2014; Volpe et al., 2016; Volpe et al., 2014). Development of specific antibodies against endogenous digitalis-like compounds may become a new direction (Fedorova et al., 2007; Hamlyn & Blaustein, 2016; McMurray et al., 2014; Nesher et al., 2007; Gozhenko et al., 2011a). Levels of these compounds and natriuretic peptides may serve as biomarkers for early detection, therapy monitoring, risk prediction, and patient stratification (Burnett, 2018; Goetze, 2010; Maisel et al., 2002; Volpe et al., 2016; Kapoun et al., 2004; World Health Organization, 2023). These perspectives integrate with previous observations, creating a bridge between basic research and clinical practice.

Comparison with Existing Literature

Our results are consistent with classical works by Blaustein and colleagues, who first proposed the concept of endogenous Na-K-ATPase inhibitors as pathophysiological factors in hypertension (Blaustein, 1993; Blaustein, 2018; Blaustein & Hamlyn, 2020; Blaustein et al., 2012; Hamlyn et al., 1991; Manhart et al., 2013; Gozhenko, 2012). However, our analysis extends this understanding by demonstrating functional integration with systemic mechanisms (Aperia et al., 2016; Hamlyn, 2014; Hamlyn & Blaustein, 2016; Liu & Xie, 2010; Pierre & Xie, 2006; Xie & Askari, 2002; Xie et al., 1999; Wu et al., 2017; Xu et al., 2023; Yuan et al., 2005). Unlike the previous analysis by Schoner & Scheiner-Bobis (2007), which focused on exogenous steroids, ours is the first systematic review of endogenous compounds in an integrated context, with more studies (89 vs 34) and participants (34,156 vs 8,234) (Duval & Tweedie, 2000; Egger et al., 1997; Higgins et al., 2003; Hooijmans et al., 2014; Page et al., 2021; Sterne et al., 2016; Sterne et al., 2019; Wells et al., 2000; Gozhenko et al., 2013a). The findings support the concept of Na-K-ATPase as a signaling complex, with correlations indicating complex regulatory networks (Aperia et al., 2016; Blaustein, 2018; Lingrel, 2010; Liu & Xie, 2010; Pierre & Xie, 2006; Xie et al., 1999). These mechanisms evolve classical concepts, creating a comprehensive picture of homeostasis.

Limitations and Recommendations for Future Research

Despite the comprehensive nature of the analysis, limitations exist: study heterogeneity (I^2=78%) due to differences in methodologies, populations, and designs (Higgins et al., 2003; Sterne et al., 2019); potential publication bias (Egger's test p=0.04), which may underestimate negative results (Duval & Tweedie, 2000; Egger et al., 1997); limited generalizability due to focus on European and North American populations (World Health Organization, 2023); absence of long-term prospective studies to assess interaction dynamics (Burnett, 2018; McMurray et al., 2014; Volpe et al., 2016; Gozhenko et al., 2013b).

Future research should include multicenter prospective observations with long-term monitoring (Burnett, 2018; McMurray et al., 2014; Volpe et al., 2016); genetic analyses of Na-K-ATPase and natriuretic peptide polymorphisms (Lingrel, 2010; Manunta et al., 2001; Manunta et al., 2006); studies of diverse ethnic groups (World Health Organization, 2023); randomized trials of new therapies based on integrated regulation (Aperia et al., 2016; Blaustein & Hamlyn, 2020; Hamlyn & Blaustein, 2016; McMurray et al., 2014; Gozhenko et al., 2019). These recommendations logically complement current results, enhancing their clinical applicability.

This systematic review provide compelling evidence for the existence of an integrated system of water-sodium homeostasis regulation involving close interaction between cellular and systemic mechanisms (Aperia et al., 2016; Bagrov et al., 2009; Blaustein, 1993; Blaustein, 2018; Blaustein & Hamlyn, 2020; Blaustein et al., 2012; Burnett, 2018; de Bold et al., 1981; Gozhenko, 1974; Gozhenko, 1976; Gozhenko, 1978; Gozhenko, 1979; Gozhenko, 1983; Gozhenko, 1984; Gozhenko, 1985; Gozhenko, 1987; Gozhenko, 1988; Gozhenko, 1989; Gozhenko, 1990; Gozhenko, 1994; Hamlyn, 2014; Hamlyn & Blaustein, 2016; Hamlyn & Manunta, 2011; Hamlyn et al., 1991; Gozhenko, 1974a). The identified correlations and proposed dual regulation model open new perspectives for understanding cardiovascular disease pathophysiology and developing innovative therapeutic strategies (Blaustein & Hamlyn, 2020; Burnett, 2018; Hamlyn & Blaustein, 2016; McMurray et al., 2014; Volpe et al., 2016). In conclusion, this systematic review demonstrate an integrated system of water-sodium homeostasis regulation through interaction of cellular and systemic mechanisms (Aperia et al., 2016; Bagrov et al., 2009; Blaustein, 1993; Blaustein, 2018; Blaustein & Hamlyn, 2020; Blaustein et al., 2012; Burnett, 2018; de Bold et al., 1981; Gozhenko, 1974; Gozhenko, 1976; Gozhenko, 1978; Gozhenko, 1979; Gozhenko, 1983; Gozhenko, 1984; Gozhenko, 1985; Gozhenko, 1987; Gozhenko, 1988; Gozhenko, 1989; Gozhenko, 1990; Gozhenko, 1994; Hamlyn, 2014; Hamlyn & Blaustein, 2016; Hamlyn & Manunta, 2011; Hamlyn et al., 1991). The identified correlations and dual regulation model open new perspectives for understanding pathophysiology and therapy of cardiovascular diseases (Blaustein & Hamlyn, 2020; Burnett, 2018; Hamlyn & Blaustein, 2016; McMurray et al., 2014; Volpe et al., 2016; Gozhenko et al., 1974b).

MAIN STUDY CONCLUSIONS

1. The integrated dual system of water-sodium homeostasis regulation functions through coordinated interaction of cellular mechanisms (Na-K-ATPase/digitalis-like compounds) and systemic mechanisms (natriuretic peptides/neurohumoral regulation), which is confirmed by statistically significant correlation between ANP and Na-K-ATPase activity ($r=0.58$, $p<0.01$) and between BNP and endogenous ouabain levels ($r=0.42$, $p<0.05$).

2. Digitalis-like compounds demonstrate powerful natriuretic effect (SMD = 1.67, 95% CI: 1.52-1.82, $p<0.001$), which confirms their physiological role as endogenous regulators of sodium balance, rather than merely as pathological factors in cardiovascular diseases.

3. Progressive elevation of endogenous digitalis-like compound levels is observed in hypertension (1.87±0.64 nmol/L), heart failure (2.34±0.89 nmol/L) and chronic kidney disease (2.78±1.12 nmol/L) compared to healthy individuals (0.52±0.18 nmol/L), which indicates their role as biomarkers of disease severity and potential therapeutic targets.

4. Dysfunction of the cellular regulatory subsystem (decreased Na-K-ATPase activity, SMD = -0.89) is a key pathogenetic mechanism in essential hypertension development, creating a vicious cycle of intracellular sodium accumulation and increased vascular tone.

5. In heart failure, compensatory elevation of Na-K-ATPase activity (SMD = 0.34) is observed in combination with significant BNP level increases (4.7-fold elevation), which reflects activation of both regulatory subsystems, however this compensatory response may be inadequate to prevent disease progression.

6. Three levels of integration between cellular and systemic mechanisms are identified: molecular (shared cAMP/cGMP signaling cascades), cellular (coordinated regulation of intracellular calcium and sodium) and systemic (neurohumoral feedback loops), which ensures comprehensive adaptation to water-sodium balance changes.

7. Temporal dynamics of regulatory responses includes acute phase (0-24 hours) with predominance of cellular mechanisms, subacute phase (1-7 days) with activation of natriuretic peptide synthesis and chronic phase (>1 month) with structural adaptations and integrated response of both subsystems.

8. Subgroup analyses demonstrate age and gender differences in regulatory mechanisms: patients younger than 40 years respond better to therapy targeting cellular mechanisms, while women demonstrate better response to natriuretic peptide therapy, which justifies the need for personalized treatment approach.

9. Mathematical modeling confirms the nonlinear nature of interactions between dual regulatory system components, with presence of threshold effects and positive feedback loops, which explains rapid decompensation when system adaptive capacity is exceeded.

10. Integrated therapeutic approach simultaneously affecting cellular and systemic mechanisms (for example, combination of neprilysin inhibitors with Na-K-ATPase modulators) demonstrates synergistic effect (synergy coefficient 1.78, $p<0.01$) compared to monotherapy, which opens perspectives for developing new therapeutic strategies for treating cardiovascular and renal diseases.

CLINICAL SIGNIFICANCE

Diagnostic capabilities. Components of the dual regulatory system can serve as novel biomarkers for early detection, risk stratification and monitoring progression of cardiovascular diseases. Combined analysis of cellular and systemic markers may significantly improve diagnostic accuracy compared to traditional approaches.

Therapeutic perspectives. Understanding the integrated nature of the regulatory system opens new possibilities for developing combined therapeutic approaches that simultaneously affect cellular and systemic mechanisms. This may lead to creation of more effective and personalized treatment strategies.

Prognostic value. Assessment of dual regulatory system status can help in predicting therapy response and risk of complications development, which is particularly important for patients with high cardiovascular risk.

SCIENTIFIC SIGNIFICANCE

Conceptual breakthrough. This study represents the first systematic analysis of the dual water-sodium homeostasis regulatory system as an integrated network of mechanisms. The proposed conceptual model can serve as foundation for future research in this field.

Methodological contribution. The developed methodology of systematic analysis of complex regulatory systems can be applied for studying other integrated biological processes.

Translational potential. Study results create a solid scientific foundation for translating fundamental knowledge about water-sodium homeostasis regulation into clinical practice.

LIMITATIONS AND FUTURE DIRECTIONS

Acknowledged limitations. Despite comprehensive analysis, the study has certain limitations, including methodological heterogeneity, limited number of long-term clinical studies and possible publication bias. These limitations do not diminish the significance of main conclusions, but indicate directions for future research.

Priority directions. Future research should focus on standardization of measurement methods, conducting long-term clinical trials with hard endpoints and development of personalized therapeutic algorithms based on individual dual regulatory system profile.

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CONFLICT OF INTEREST

The authors declare no conflict of interest that could have influenced the results of this study.

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AUTHOR CONTRIBUTIONS

A.I. Gozhenko: conceptualization, methodology, formal analysis, investigation, resources, data curation, writing - original draft, writing - review and editing, visualization, supervision, project administration. W. Zukow: conceptualization, methodology, validation, formal analysis, writing - review and editing, supervision. O.A. Gozhenko: methodology, validation, formal analysis, investigation, resources, data curation, writing - original draft, writing - review and editing, visualization. M.A. Saensus: methodology, investigation, resources, writing - original draft, writing - review and editing. O. Vitiukov: methodology, investigation, resources, writing - original draft, writing - review and editing.

DATA AVAILABILITY

Data supporting the conclusions of this article are available upon reasonable request from the corresponding author after signing a data transfer agreement and approval from the institutional bioethics committee. Some data are not publicly available due to ethical restrictions, as they contain information that could compromise the confidentiality of study participants.

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CONCLUDING NOTE

This systematic review provides the most comprehensive assessment to date of the pathophysiological mechanisms of integrated water-sodium homeostasis regulation. The results confirm the existence of a complex dual regulatory system and its critical role in the pathogenesis of cardiovascular diseases. These findings have the potential to transform our understanding of cardiovascular pathophysiology and develop a new generation of therapeutic interventions that account for the integrated nature of regulatory mechanisms.

Implementation of the dual regulation concept in clinical practice may lead to significant improvements in treatment outcomes for patients with cardiovascular and renal diseases through more accurate diagnosis, personalized therapeutic approaches, and better disease prognosis.

The authors hope that this study will stimulate further scientific research in this important field and contribute to improving clinical outcomes for millions of patients with cardiovascular and renal diseases worldwide.