НИРКИ KIDNEYS

UDC 612.82+612.46].062:577.112.382.067 DOI: https://doi.org/10.22141/2307-1257.14.3.2025.531

N.D. Filipets[1], D.D. Ivanov[2], O.V. Gerush[1], O.O. Filipets[1], O.H. Kmet[1], N.M. Fundiur[1], K.V. Slobodian[1]
[1]Bukovinian State Medical University, Chernivtsi, Ukraine
[2]Bogomolets National Medical University, Kyiv, Ukraine

Gamma-aminobutyric acid as an element of the mechanisms of cerebro-renal interactions

For citation: Kidneys. 2025;14(3):260-265. doi: 10.22141/2307-1257.14.3.2025.531

Abstract. *The presence of many common aspects in autoregulatory mechanisms and processes of ensuring the constancy of the internal environment determines the uniqueness of the cerebro-renal system. Gamma-aminobutyric acid (GABA), in addition to the key coordinating role in brain activity and its metabolism, has inherent regulatory effects in non-neuronal tissues. Given the fact that there is a relationship between GABA levels and the functional and metabolic state of other organs and systems, the aim of the work is to focus on scientific information regarding local GABAergic systems, the location of their components in the nephron and the renal effects of GABA under different conditions. In addition to the fact that GABA has therapeutic potential against acute kidney injury and chronic kidney disease, pharmacological modulators of GABA can provoke nephrotoxicity. The reasons for the diversity of renal responses under the influence of GABA and agents with agonist activity are multifactorial in nature, which should be taken into account, and within the framework of GABAergic strategies, effective and safe therapeutic approaches should be sought and applied.*

Keywords: *gamma-aminobutyric acid; cerebro-renal system; mechanisms of interrelationship*

The nervous system and the kidneys interact to maintain normal body homeostasis. In pathological processes, disruption of these relationships can lead to impaired renal function and sodium ion processing, resulting in fluid and electrolyte imbalance. Increasing evidence suggests the importance of interactions between the nervous system and the kidneys, given the high prevalence of acute kidney injury (AKI) and chronic kidney disease (CKD) in patients with cerebrovascular diseases [1]. The presence of many common anatomical and physiological aspects determines the uniqueness of the cerebro-renal system. In addition to the need for a stable and constantly high blood volume and local autoregulation of blood flow, there is a close connection between the brain and the kidneys both in normal and pathological conditions. Nerve impulses from the central nervous system (CNS) regulate renal blood flow, glomerular and tubular processes. The kidneys interact with the CNS through thinly myelinated and unmyelinated nerve fibers to regulate sodium ion processing [2].

Among neurohumoral regulators of homeostasis, one of the most common neurotransmitters in mammals is gamma-aminobutyric acid (GABA), which is distributed in most brain regions and in 40 % of inhibitory synapses in adult vertebrates [3]. Components of the GABAergic system have structural, molecular, and functional differences and are present in neuronal and non-neuronal tissues, modulate physiological processes, and participate in the pathogenesis of a number of diseases [4].

The aim of the work is to focus on scientific information regarding local GABAergic systems, in particular the location of its components in the nephron, and the renal effects of GABA under different conditions of renal function.

GABA is a natural amino acid that acts as the primary inhibitory neurotransmitter in the CNS. Performing its biological function at the interneuronal synapse, GABA binds to postsynaptic receptors that modulate ion channels, hyperpolarize the cell, and inhibit action potential transmission [5]. GABA signaling in the CNS has been extensively

Для кореспонденції: Філіпець Наталія Дмитрівна, доктор медичних наук, професор, кафедра фармакології, Буковинський державний медичний університет, Театральна пл., 2, м. Чернівці, 58002, Україна; e-mail: natalya.dmi@gmail.com
For correspondence: Nataliia D. Filipets, MD, PhD, Professor, Department of Pharmacology, Bukovinian State Medical University, Theatre Sq., 2, Chernivtsi, 58002, Ukraine; e-mail: natalya.dmi@gmail.com
Full list of authors' information is available at the end of the article.

studied. GABA, $GABA_A$, and $GABA_B$ receptors, despite their differences in physiological, biochemical, functional, and pharmacological properties, are the main inhibitory receptors in the CNS and they regulate neuronal excitability when GABA is released into the postsynaptic nerve terminal [6]. GABA is functionally opposite to the major excitatory neurotransmitter glutamate (glutamic acid, Glu), which, like GABA, is the most abundant neurotransmitter in the CNS. GABA-mediated neuronal activity occurs due to the coordinated and dynamically regulated balance between inhibitory (mainly GABAergic) and excitatory (mainly glutamatergic) effects mediated by GABA receptors and Glu receptors (NMDA receptors). Proper GABA/Glu balance is essential for the normal functioning of most complex brain processes, and imbalance has been implicated in neurodevelopmental pathology, neurodegenerative/neurological, psychiatric diseases, and acute neurological disorders [7, 8].

The biological significance of GABA is not limited to maintaining excitatory/inhibitory balance. In addition to the fact that GABA is a key coordinator of brain activity and its metabolism, the GABA system has regulatory functions in other, non-neuronal tissues and organs. It is now known that GABA levels are interconnected with the physiological state of metabolic organs and the pathogenesis of metabolic diseases. GABA is synthesized in significant quantities in the islets of the pancreas [9]. GABA released from β-cells can have both autocrine and paracrine effects in human islets of Langerhans. The result of the action of GABA through $GABA_A$ receptors on α-cells of the pancreas is the production of glucagon, on β-cells — insulin secretion [10].

Disturbances in GABA signaling have significant consequences in several physiological processes in the liver, as well as liver diseases. Today, there is a sufficient number of scientific reports that GABAergic innervation of the liver not only exists, but may also play an important role in the regulation of liver development and function. Activation of GABAergic processes can protect the liver from toxic damage to hepatocytes, and GABA production by hepatocytes plays a key role in the regulation of blood glucose and feeding behavior in obesity; therefore, reducing GABA in the liver improves insulin sensitivity [11].

GABA has been reported to affect cardiovascular regulation through central and peripheral GABAergic mechanisms. A systematic review and meta-analyses show that oral GABA reduces blood pressure in patients with high normal blood pressure and stage 1 hypertension [12]. $GABA_A$ receptor activation/inhibition affects post-infarction ventricular remodeling by modulating monocyte/macrophage subsets [13]. Atrioventricular node pacemaker cells have been shown to have an intrinsic GABAergic system [14]. Along with GABAergic vesicles, GABA metabolic enzymes, receptors, and transporters have been identified in atrioventricular node pacemaker cells. In the same study, the authors suggest that the endogenous GABAergic system, by ensuring consistent atrioventricular contraction, plays a key role in the conduction of impulses from the atria to the ventricles.

AKI is known to modulate the CNS, and the end result is an increase in central sympathetic influences, which exacerbates kidney damage [15]. In CKD, renal denervation modulates sympathetic outflow also through GABAergic mechanisms [16]. Stimulation of $GABA_B$ receptors in the CNS mediates the preventive effect of GABA in AKI due to inhibition of increased renal sympathetic activity during renal ischemia/reperfusion [17]. Functional relationship between the kidneys and the CNS through GABA was confirmed by research [18], where it was established that afferent renal nerves are involved in GABAergic changes in the paraventricular nucleus of the hypothalamus. Renal afferents are known to play a crucial role in the regulation of renal function, being activated by changes in pressure, fluid composition and oxygen levels in the kidneys. It is suggested that an increase in GABAergic inputs to the paraventricular nucleus occurs to attenuate sympathetic excitation in renovascular hypertension in rats, carrying information from the kidneys to the CNS.

It is worth noting that sympathetic activation increases the expression of the renin-angiotensin system, the synthesis of its components and the release into the circulatory system [19, 20]. When the renin-angiotensin system, which controls blood pressure and sodium homeostasis, is overactivated, its sodium-retaining effect is mediated by intrarenal and extrarenal, including central, mechanisms [21]. Evidence for the involvement of GABA in the integrated effects of the renin-angiotensin system in the kidneys, cardiovascular system, and CNS comes from studies indicating the dependence of GABAergic synaptic inputs in the CNS on the activity of angiotensin II [22].

Thus, the role of the GABAergic system in renal function has been practically established. The hypothesis of the existence of a renal GABAergic system has received evidence from the study on the effects of GABA on the prevention of renal pathology and the identification of GABA components in the kidneys. Studies in rats with hypertension and CKD showed that $GABA_B$ receptor expression in the CNS was increased, central GABA levels were reduced in the cerebrospinal fluid, and peripheral GABA levels were increased in serum. Renal denervation in CKD restored glutamate decarboxylase (GAD) activity, similar to the effect observed with baclofen (a $GABA_B$ receptor agonist), and systemic administration of gabapentin (a GABA analog) reduced blood pressure. It has been shown that improving GABA system dysfunction prevents the development and reduces the severity of cardiorenal syndrome in rats with CKD [23].

Of particular note is the information about the specificity of the distribution of GABA components in the nephron. An understanding of the peculiarities of the localization of the renal components of the GABAergic system provides an understanding of the functional significance of this amino acid in renal processes, the mechanisms of interaction between the nervous system and the kidneys through the GABA system, which is of great importance for the progress of knowledge in the field of the theory of diseases based on the patterns of pathology development [24].

Studies on the expression of the GABAergic system in non-neuronal tissues have shown that each of its components is present in the kidneys. Analysis of the presence of

GABA-like immunoreactivity (GABA-LI) in the rat kidney using light and electron microscopy revealed GABA-positive structures in vibratome sections of the medulla and cortex [25]. The specific distribution of GABA in the tubular epithelium demonstrated the functional significance of this amino acid in the transport processes in the tubules. Thus, the distribution of GABA-LI was heterogeneous: the inner strip of the outer medulla was most strongly and almost uniformly labeled, while GABA-LI in the cortical substance was mostly limited to only a few tubules. GABA-positive structures included epithelial cells of the thin and thick ascending parts of the loop of Henle, connecting tubules and collecting tubules. In GABA-positive connecting tubules and collecting tubules, immunoreactivity was present in the cytoplasm of approximately half of the epithelial cells. As shown by electron microscopy in this study, the labeled cells in the collecting tubules were light (principal) cells.

Analysis of GABA-related RNA template molecules by RT-PCR revealed a unique set of GABA receptor subunits and subtypes in the kidneys of Wistar-Kyoto rats [26]. Thus, in the renal cortex, as in the cerebral cortex of Wistar-Kyoto rats, the expression of $GABA_A$ receptor subunits, α1, β3, δ, ε, π, was detected, mainly in the apical region of the cortical tubules. Immunofluorescence study of protein localization showed that the α1 subunit is widely distributed in the proximal tubules; β3 subunits were observed in the proximal tubules, in particular in tall cells and cells with a structure similar to a brush border, as well as in the distal tubules. The staining of the π subunit was mainly in the distal tubules and to a lesser extent in the proximal tubules. At the same time, immunoblotting showed that the kidneys can express similar or higher amounts of β3, ρ1 subunits than the brain. Both subtypes of $GABA_B$ receptors, R1 and R2, and the ρ1 and ρ2 subunits of the $GABA_C$ receptor were also found in the rat kidney cortex. At the same time, GAD enzymes involved in the synthesis of GABA, GAD67 and GAD65, the GABA transporter, GAT2, and the GABA-transaminase enzyme that metabolizes GABA were expressed in the rat kidney, which, according to these scientists, suggests the existence of a local renal GABAergic system with an autocrine/paracrine mechanism.

It is worth noting that 90 % of the renal cortex is made up of renal tubules, which play an important role in homeostasis and are the structures with the greatest energy needs of the kidneys. Tubular segments (proximal and distal segments, nephron loop, collecting tubules) have unique reabsorption properties, most pronounced in the cells of the proximal convoluted tubules. Under normal conditions, all glucose, amino acids, 65 % of sodium ions and water are reabsorbed in the proximal segment; sodium, potassium and chloride ions are reabsorbed together through a symporter in the thick ascending limb of the loop of Henle; in the distal segment, as in the collecting tubules, primary active transport of sodium ions occurs on the basolateral membrane and secondary — on the apical membrane [27]. The energy supply of tubular reabsorption is carried out by Na+/K+-ATPase, which is able to modulate the sensitivity and expression of neurotransmitter receptors, in particular GABA and NMDA; therefore, it participates in the control of the functions of membrane neurotransmitter receptors [28]. In turn, modulation of Na+/K+-ATPase activity by endo- and exogenous ligands alters transtubular transport in the kidneys, suggesting a relationship between this pump and the renal GABA system.

Given the presence of the GABAergic system in the kidneys, a study was conducted on the influence of the GABA/glutamate system on the vasoactive response from renal microvessels [29]. The results demonstrate for the first time that activation of endogenous GABA and NMDA receptors in the kidneys significantly alters microvascular diameter with important consequences for renal blood flow. The GABA- and Glu-mediated effects on renal capillaries revealed in this study were surprisingly similar to their central regulatory effects on the CNS capillaries. It was noted that since dysregulation of renal blood flow is associated with CKD, alterations in the GABA system may have a significant impact on long-term renal function.

The important role of GABA in renal physiology and pathology is evidenced by the results of studies on its renoprotective effects. GABA-enriched salt has a protective effect against the negative impact of high salt intake in patients with cisplatin-induced nephrotoxicity, which is characterized by suppression of hematological and biochemical toxicity, renal cell apoptosis, and renal inflammation [30]. GABA administration significantly improved the markedly elevated blood urea nitrogen and creatinine levels and decreased creatinine clearance in the progression of glycerol-induced renal failure, and fractional excretion of sodium ions was also reduced [31].

The first study to investigate the immunomodulatory mechanisms of GABA in renal failure demonstrated the effects of GABA on renal inflammation both *in vivo* and *in vitro*. GABA regulates renal inflammation by significantly reducing serum inflammatory markers, induction of monocyte migration, and the number and infiltration of macrophages, which are crucial for the initiation of renal inflammation. The results suggested that GABA has a protective effect against renal injury [32]. The use of a combination of amikacin and GABA without/with loading on chitosan nanoparticles confirmed the protective effects of GABA against amikacin nephrotoxicity, as it improves renal function, oxidative stress and demonstrates a significant homeostatic role mediated by the suppression of inflammatory cytokines of the Th1, Th2 and Th17 types [33].

Recent studies have revealed a novel role for GABA in combating oxidative stress under high glucose conditions. In Mongolian sheep kidney cells, GABA markedly increased cell viability and effectively mitigated oxidative damage induced by high glucose stress through upregulation of antioxidant genes and regulation of metabolic pathways, suggesting a potential mechanism for adaptation to extreme conditions [34]. The antioxidant effects of GABA are linked to its impact on mitochondria [35, 36]. The kidneys, especially the cells of the proximal tubules, are rich in mitochondria, so nephrotoxicity of drugs is manifested, in particular, by mitochondrial damage [37]. GABA type A receptor-associated protein is a protein that plays a role in stabilizing $GABA_A$ receptors and is involved in mitophagy.

By removing dysfunctional mitochondria from renal tubular epithelial cells, reducing local inflammation and oxidative damage, activation of mitophagy is protective in AKI [38].

Of particular note are reports of nephrotropic effects of pharmacological neuromodulators that act through the GABAergic system. Piracetam, a nootropic drug, a cyclic derivative of GABA, improves markers of renal function such as urea and creatinine, reduces histological damage, the presence of inflammatory cells in the renal tubules, and inhibits apoptosis in cisplatin-induced nephrotoxicity [39]. At the same time, the use of GABA analogues for adequate control of postoperative pain was associated with a risk (higher for gabapentin compared to pregabalin) of decreased kidney function and the development of CKD [40]. Use of the tranquilizer diazepam, which increases GABA receptor sensitivity, is associated with an increased risk of AKI in children [41]. Valproic acid, whose anticonvulsant activity is provided by inhibition of the enzyme GABA-transaminase and GABA reuptake in brain tissues, can cause obvious damage to the renal tubules, which is associated with proximal tubular mitochondrial toxicity [42]. The renal effects of new-generation anticonvulsants with anxiolytic activity, neurosteroids (ganaxolone), which, like their endogenous analogues, activate extrasynaptic $GABA_A$ receptors, have not yet been studied. However, their need for complex molecules to enhance biopharmaceutical properties such as β-cyclodextrin raises the risk of nephrotoxicity, especially in renal disease [43].

As noted above, GABA receptor subunits are widely represented in the renal tubules, which probably causes a similar damaging effect of other drugs with nephrotoxicity (antimicrobials, cytostatics, nonsteroidal anti-inflammatory drugs), mainly in the proximal segment of the nephron. The presence of GABA receptors in vascular smooth muscle receptors determines the vascular mechanisms of renal effects. The following should be noted here: not only components of the GABAergic system can be targets; the pharmacological action of GABA analogues, like any drugs, has a multifactorial dependence; the function of GABA receptors in the kidneys has not been definitively determined; the activity of GABA receptor subunits is specific and depends on their structure and function; the direct and indirect mechanisms of GABA in the norm and pathophysiology of the kidneys remain completely unknown. At the same time, taking into account the broad relationships of GABA in the functional and metabolic continuum of the body, its diverse reactions in non-neuronal tissues, and the spectrum of protective effects, research on the renal GABA system, the search and application of effective and safe approaches to pathogenetic therapy of kidney pathology remain relevant for GABAergic strategies.

References

1. *Tanaka S, Okusa MD. Crosstalk between the nervous system and the kidney. Kidney Int. 2020 Mar;97(3):466-476. doi: 10.1016/j.kint.2019.10.032.*
2. *Rajamani K. The Cerebro-Renal System - Anatomical and Physiological Considerations. J Stroke Cerebrovasc Dis. 2021 Sep;30(9):105541. doi: 10.1016/j.jstrokecerebrovasdis.2020.105541.*
3. *Ochoa-de la Paz LD, Gulias-Cañizo R, Ruíz-Leyja ED, Sánchez-Castillo H, Parodí J. The role of GABA neurotransmitter in the human central nervous system, physiology, and pathophysiology. Revista Mexicana de Neurociencia. 2021;22(2):67-76. doi: 10.24875/rmn.20000050.*
4. *Ngo DH, Vo TS. An Updated Review on Pharmaceutical Properties of Gamma-Aminobutyric Acid. Molecules. 2019 Jul 24;24(15):2678. doi: 10.3390/molecules24152678.*
5. *Jewett BE, Sharma S. Physiology, GABA. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2025 Jan.*
6. *Ghit A, Assal D, Al-Shami AS, Hussein DEE. GABAA receptors: structure, function, pharmacology, and related disorders. J Genet Eng Biotechnol. 2021 Aug 21;19(1):123. doi: 10.1186/s43141-021-00224-0.*
7. *Kmet OG, Filipets ND, Kmet TI, Hrachova TI, Vepriuk YM, Vlasova KV. Pharmacological correction of cognitive disorders in experimental neurodegeneration caused by 2 type diabetes mellitus. Problems of Endocrine Pathology. 2019;70(4):52-59. doi: 10.21856/j-PEP.2019.4.07.*
8. *Sears SM, Hewett SJ. Influence of glutamate and GABA transport on brain excitatory/inhibitory balance. Exp Biol Med (Maywood). 2021 May;246(9):1069-1083. doi: 10.1177/1535370221989263.*
9. *Wan Y, Wang Q, Prud'homme GJ. GABAergic system in the endocrine pancreas: a new target for diabetes treatment. Diabetes Metab Syndr Obes. 2015 Feb 3;8:79-87. doi: 10.2147/DMSO.S50642.*
10. *Hagan DW, Ferreira SM, Santos GJ, Phelps EA. The role of GABA in islet function. Front Endocrinol (Lausanne). 2022 Sep 29;13:972115. doi: 10.3389/fendo.2022.972115.*
11. *Geisler CE, Ghimire S, Bruggink SM, et al. A critical role of hepatic GABA in the metabolic dysfunction and hyperphagia of obesity. Cell Rep. 2021 Jun 29;35(13):109301. doi: 10.1016/j.celrep.2021.109301.*
12. *Yoshida K, Sunao S, Shingo T. Blood pressure-lowering effect of oral intake of gamma-aminobutyric acid (GABA) - An updated systematic review with meta-analysis. Jpn Pharmacol Ther. 2024;52(8):901-926.*
13. *Bu J, Huang S, Wang J, et al. The GABA A Receptor Influences Pressure Overload-Induced Heart Failure by Modulating Macrophages in Mice. Front Immunol. 2021 May 31;12:670153. doi: 10.3389/fimmu.2021.670153.*
14. *Liang D, Zhou L, Zhou H, et al. A GABAergic system in atrioventricular node pacemaker cells controls electrical conduction between the atria and ventricles. Cell Res. 2024 Aug;34(8):556-571. doi: 10.1038/s41422-024-00980-x.*
15. *Wang Y, Liu S, Liu Q, Lv Y. The Interaction of Central Nervous System and Acute Kidney Injury: Pathophysiology and Clinical Perspectives. Front Physiol. 2022 Mar 4;13:826686. doi: 10.3389/fphys.2022.826686.*
16. *Nishihara M, Takesue K, Hirooka Y. Renal denervation enhances GABA-ergic input into the PVN leading to blood pressure lowering in chronic kidney disease. Auton Neurosci. 2017 May;204:88-97. doi: 10.1016/j.autneu.2016.09.018.*
17. *Kobuchi S, Tanaka R, Shintani T, et al. Mechanisms underlying the renoprotective effect of GABA against ischaemia/reperfusion-induced renal injury in rats. Clin Exp Pharmacol Physiol. 2015 Mar;42(3):278-286. doi: 10.1111/1440-1681.12350.*

18. Milanez MIO, Veiga AC, Martins BS, et al. Renal Sensory Activity Regulates the γ-Aminobutyric Acidergic Inputs to the Paraventricular Nucleus of the Hypothalamus in Goldblatt Hypertension. Front Physiol. 2020 Dec 15;11:601237. doi: 10.3389/fphys.2020.601237.

19. Filipets ND, Gozhenko AI, Ivanov DD, Filipets OO, Gabunia L. Regulatory mechanisms for maintaining homeostasis of sodium ions. Kidneys. 2022;11(3):175-180. Ukrainian. doi: 10.22141/2307-1257.11.3.2022.378.

20. Filipets ND, Ivanov DD, Gozhenko AI. Renin-angiotensin-aldosterone system blockers as the main pathogenetic approach of drug nephroprotection. Kidneys. 2019;8(1):34-39. Ukrainian. doi: 10.22141/2307-1257.8.1.2019.157794.

21. Philipets ND. Local renin-angiotensin system in cerebro-renal continuum (review). Actual problems of transport medicine. 2019;1(55):42-48. Ukrainian. doi: 10.5281/zenodo.2612929.

22. Li DP, Pan HL. Angiotensin II attenuates synaptic GABA release and excites paraventricular-rostral ventrolateral medulla output neurons. J Pharmacol Exp Ther. 2005 Jun;313(3):1035-1045. doi: 10.1124/jpet.104.082495.

23. Chen HH, Cheng PW, Ho WY, et al. Renal Denervation Improves the Baroreflex and GABA System in Chronic Kidney Disease-induced Hypertension. Sci Rep. 2016 Dec 5;6:38447. doi: 10.1038/srep38447.

24. Gozhenko AI. Theory of disease: monograph. Odesa: Feniks; 2017. 236 p. Russian.

25. Párducz A, Dobó E, Wolff JR, Petrusz P, Erdö SL. GABA-immunoreactive structures in rat kidney. J Histochem Cytochem. 1992 May;40(5):675-680. doi: 10.1177/40.5.1573248.

26. Takano K, Yatabe MS, Abe A, et al. Characteristic expressions of GABA receptors and GABA producing/transporting molecules in rat kidney. PLoS One. 2014 Sep 4;9(9):e105835. doi: 10.1371/journal.pone.0105835.

27. Ogobuiro I, Tuma F. Physiology, Renal. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2025 Jan.

28. Pivovarov AS, Calahorro F, Walker RJ. Na+/K+-pump and neurotransmitter membrane receptors. Invert Neurosci. 2018 Nov 28;19(1):1. doi: 10.1007/s10158-018-0221-7.

29. Wildman SS, Dunn K, Van Beusecum JP, et al. A novel functional role for the classic CNS neurotransmitters, GABA, glycine, and glutamate, in the kidney: potent and opposing regulators of the renal vasculature. Am J Physiol Renal Physiol. 2023 Jul 1;325(1):F38-F49. doi: 10.1152/ajprenal.00425.2021.

30. Lee H, Ji SY, Hwangbo H, et al. Protective Effect of Gamma Aminobutyric Acid against Aggravation of Renal Injury Caused by High Salt Intake in Cisplatin-Induced Nephrotoxicity. Int J Mol Sci. 2022 Jan 3;23(1):502. doi: 10.3390/ijms23010502.

31. Kim HY, Yokozawa T, Nakagawa T, Sasaki S. Protective effect of gamma-aminobutyric acid against glycerol-induced acute renal failure in rats. Food Chem Toxicol. 2004 Dec;42(12):2009-2014. doi: 10.1016/j.fct.2004.06.021.

32. Huang HY, Hsu T, Lin BF. Gamma-aminobutyric acid decreases macrophages infiltration and suppresses inflammatory responses in renal injury. Journal of Functional Foods. 2019;60:103419. doi: 10.1016/j.jff.2019.103419.

33. Madbouly N, Ooda A, Nabil A, et al. The renoprotective activity of amikacin-gamma-amino butyric acid-chitosan nanoparticles: a comparative study. Inflammopharmacology. 2024 Aug;32(4):2629-2645. doi: 10.1007/s10787-024-01464-5.

34. Su R, Chang L, Zhou T, Meng F, Zhang D. Effects of GABA on Oxidative Stress and Metabolism in High-Glucose Cultured Mongolian Sheep Kidney Cells. Int J Mol Sci. 2024 Sep 18;25(18):10033. doi: 10.3390/ijms251810033.

35. Kmet OG, Filipets ND, Rohovyi YuYe, Hrachova TI, Vepriuk YM, Vlasova KV. Assessment of carbacetam effect with cerebral mitochondrial dysfunction of rats with type 2 diabetes mellitus. Problems of Endocrine Pathology. 2020;73(3):16-24. doi: 10.21856/j-PEP.2020.3.02.

36. Kmet OG, Filipets ND, Yaremii IM, Kmet TI, Vepriuk YM, Hrachova TI. Experimental assessment of carbacetam effect on the cerebral mitochondria under conditions of scopolamine-induced Alzheimer's disease. Arch Balk Med Union. 2020;55(1):14-21. doi: 10.31688/ABMU.2020.54.5.01.

37. Gai Z, Gui T, Kullak-Ublick GA, Li Y, Visentin M. The Role of Mitochondria in Drug-Induced Kidney Injury. Front Physiol. 2020 Sep 4;11:1079. doi: 10.3389/fphys.2020.01079.

38. Su L, Zhang J, Gomez H, Kellum JA, Peng Z. Mitochondria ROS and mitophagy in acute kidney injury. Autophagy. 2023 Feb;19(2):401-414. doi: 10.1080/15548627.2022.2084862.

39. El-Dessouki AM, Alzokaky AA, Raslan NA, Ibrahim S, Salama LA, Yousef EH. Piracetam mitigates nephrotoxicity induced by cisplatin via the AMPK-mediated PI3K/Akt and MAPK/JNK/ERK signaling pathways. Int Immunopharmacol. 2024 Aug 20;137:112511. doi: 10.1016/j.intimp.2024.112511.

40. He Y, Mo L, Li J, et al. Association of perioperative initiation of gabapentin versus pregabalin with kidney function: a target trial emulation study. Front Med (Lausanne). 2024 Dec 10;11:1488773. doi: 10.3389/fmed.2024.1488773.

41. Zhang M, Huang L, Zhu Y, et al. Diazepam exposure associated with an increased risk of acute kidney injury in children: an observational cohort study. BMC Pediatr. 2025 Mar 1;25(1):159. doi: 10.1186/s12887-025-05494-y.

42. Anguissola G, Leu D, Simonetti GD, et al. Kidney tubular injury induced by valproic acid: systematic literature review. Pediatr Nephrol. 2023 Jun;38(6):1725-1731. doi: 10.1007/s00467-022-05869-8.

43. Reddy DS. Neurosteroids as Novel Anticonvulsants for Refractory Status Epilepticus and Medical Countermeasures for Nerve Agents: A 15-Year Journey to Bring Ganaxolone from Bench to Clinic. J Pharmacol Exp Ther. 2024 Jan 17;388(2):273-300. doi: 10.1124/jpet.123.001816.

Received 10.05.2025
Revised 26.06.2025
Accepted 10.07.2025

Information about authors

N.D. Filipets, MD, PhD, Professor, Department of Pharmacology, Bukovinian State Medical University, Chernivtsi, Ukraine; https://orcid.org/0000-0001-8582-6685

D.D. Ivanov, MD, PhD, Professor, Head of the Department of Nephrology and Extracorporeal Technologies, Bogomolets National Medical University, Kyiv, Ukraine; https://orcid.org/0000-0003-2609-0051

O.V. Gerush, PhD, Associate Professor, Head of the Department of Pharmacy, Bukovinian State Medical University, Chernivtsi, Ukraine; https://orcid.org/0000-0001-9100-0070

O.O. Filipets, PhD, Associate Professor, Department of Neurology, Psychiatry and Medical Psychology named after S.M. Savenko, Bukovinian State Medical University, Chernivtsi, Ukraine; https://orcid.org/0000-0002-9566-4277
O.H. Kmet, MD, PhD, Professor, Department of Pharmacology, Bukovinian State Medical University, Chernivtsi, Ukraine; https://orcid.org/0000-0003-0336-1103
N.M. Fundiur, PhD, Associate Professor, Department of Hygiene and Ecology, Bukovinian State Medical University, Chernivtsi, Ukraine; https://orcid.org/0000-0002-5336-0355
K.V. Slobodian, PhD, Associate Professor, Department of Pathological Physiology, Bukovinian State Medical University, Chernivtsi, Ukraine; https://orcid.org/0000-0001-7872-6731

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.
Authors' contribution. Filipets N.D. — concept and design of the work, search and processing of the material, writing the text; Ivanov D.D., Gerush O.V., Filipets O.O. — search and processing of the material, writing the text; Kmet O.H. — writing the text; Fundiur N.M., Slobodian K.V. — literature analysis.

Філіпець Н.Д.[1], Іванов Д.Д.[2], Геруш О.В.[1], Філіпець О.О.[1], Кметь О.Г.[1], Фундюр Н.М.[1], Слободян К.В.[1]
[1]Буковинський державний медичний університет, м. Чернівці, Україна
[2]Національний медичний університет ім. О.О. Богомольця, м. Київ, Україна

Гамма-аміномасляна кислота як ланка механізмів цереброренальних взаємозв'язків

Резюме. Наявність багатьох спільних аспектів в авторегуляторних механізмах і процесах забезпечення сталості внутрішнього середовища зумовлює унікальність цереброренальної системи. Гамма-аміномасляній кислоті (ГАМК), окрім ключової координаторної ролі в активності мозку і його метаболізмі, притаманні регуляторні впливи в ненейрональних тканинах. Беручи до уваги те, що існує взаємозв'язок між рівнями ГАМК і функціональним та метаболічним станом інших органів і систем, метою роботи є зосередження уваги на наукових відомостях щодо локальних ГАМКергічних систем, розташування їхніх компонентів у нефроні та ренальних впливів ГАМК за різних умов. Поруч із тим, що ГАМК має терапевтичний потенціал проти гострого пошкодження і хронічної хвороби нирок, фармакологічні модулятори ГАМК можуть спровокувати нефротоксичність. Причини різноманітності ниркових реакцій під впливом ГАМК і агентів з агоністичною активністю мають багатофакторну природу, що слід брати до уваги, а в межах ГАМКергічних стратегій потрібно шукати та застосовувати ефективні й безпечні терапевтичні підходи.

Ключові слова: гамма-аміномасляна кислота; цереброренальна система; механізми взаємозв'язків