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Review Article

The Regulatory Role of the Serotonergic System in The Kidneys

Alla Edward Lychkova[1], Fentisov VV[2], Puzikov AM[1]

[1]Department of Moscow's Clinical Research Practical Center, Moscow, Russia

[2]Department of Human Anatomy Assistant Medical Institute, Belgorod State University, Russia

[*]**Corresponding author:** Alla Edward Lychkova, Department Head of the Moscow's Clinical Research Practical Center, Shosse Enthusiasts 86, Moscow, Russia, Pin code-111123, Tel: (+7) 962-965-4923; E-mail: lychkova@mail.ru.

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Abstract

The role of the serotonin system in the kidney function is reviewed. The 5-Hlychkova@mail.ruT_{IA}-, 5-HT_{1B}-,5-HT_{1D}-, 5-HT_2- receptors expressed by nephron cells were characterized.The interaction of serotonin and parathyroid hormone and their impact on phosphorus and calcium metabolism in the tubules of the nephron were revealed. The chrono-rhythmological features of serotonin regulation on the diuresis particularly were addressed. In conclusion, the serotonin is considered as a paracrine / autocrine regulator of phosphate and calcium transportation, and the reduction of the glomerular filtration rate and calcium oxalate crystals precipitation in the renal tubules at hyper serotoninemia were indicated on.

Keywords: kidneys; serotonin receptors; parathyroid hormone; phosphorus and calcium metabolism

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is an ancient hormonal regulator of kidneys function. Regulatory influence is exercised directly by endogenous serotonin, and it can also be mediated by its receptors and SERT transporter. In their works Pishak V.P. and Kokoschuk G.I.in 1987, have established a permanent antidiuretic effect of serotonin, but the mechanism of this effect has not been studied. Over time, the deepening of morphological knowledge creates the basis forstudying the function of ultrastructure, and nowadays the works have appeared whichattempted to determine the role of serotonin receptors in the structure of the nephron [1], as well as to evaluate the role of agonists and antagonists of serotonin [2-4]. However, the role of serotonin and its receptors in the kidneys function is poorly studied.

The Receptor Mechanisms of Renal Function Regulation

According to the current classification of serotonin receptors, suggested in 1993 "Serotonin Club", 7 receptor populations are distinguished: 5-HT_1 – 5-HT_7. Their main amount is localized in the central nervous system, these same receptors are found in peripheral tissues, including kidneys [1-4]. 5-HT_{1A}-receptors.5-HT_{1A}-receptorsare detected in newborn kidney [5]. Mouse kidney medullary layer and opossum kidney cells express 5-HT_{1B}-receptors; 5-HT_{1D}-like receptorsare present in renal epithelial cells (MDOK) ofdog kidney; 5-HT_{1A}-receptors are expressed on the basolateral surface of the ascendingthintubular cells,distal convoluted tubulesand collecting tubules of nephrons of human and rat kidney [4, 6, 7]. In the human and rat kidneys the highest density of 5-HT_{1A}-receptors was observed in the thin ascending tubules, the lowest - in the cells of the collecting tubules [7].

At birth, rat renal papillae express 5-HT_{1A} -receptors; ascending thin tubules are absent. At 1-14 days of age, in many 5-HT_{1A}-receptors containing epithelial cells, apoptosis was observed, starting from the tip of the papilla. Electron microscopy confirmed the presence of apoptotic cells and phagocytosis apoptotic bodies in the thin ascending tubule of kidney nephron. The transformation of epithelium from cubic to squamous was accompanied by the disappearance of 5-HT_{1A}-receptors in transforming cells. According to the authors, the ascending thin tubule is formed from 5-HT_{1A}-receptors containing thin ascending tubule, through apoptotic removal of thin ascending tubule cells and transformation of the remaining cells in 5 HT_{1A}-receptor-negative thin ascending tubule cells [8].

The specific location of these cells suggests a certain role of 5-HT_{1A}-receptors not only in the formation of a thin ascend-

ing tubule epithelium, but also in the regulation of salt and water transportation in the kidney of mammals.The presence of 5-HT_{1A}-receptors in ascending thin tubules, where there is a very high level of Na + -K + -ATPase and activity of Na + / K + / Cl-, correlates with the fact of stable expression of these receptors in the HeLa cell line [4, 9]. In the latter, recombinant 5-HT_{1A}-receptors stimulates sodium-dependent phosphate capture with activated protein kinase C. In addition, these receptorsincrease the activity of Na + -K + -ATPase by increasing of intracellular Ca^{2+} level. That means that, the 5-HT_{1A}-receptors may play an important role in the regulation ofNa-associated transportation in the kidney cells of mammals.

Exogenous serotonin, activating 5-HT_1-receptors of kidney, releases endogenous NO, which weakens the vasoconstriction, caused by stimulation of 5-HT_2-receptor in rats injected with cyclosporin-A [10].

5-HT_{1B}–receptors.Serotonin receptors are present on the membranes of the epithelial cells of proximal and distal tubules of nephrons [11]; epithelial tubulescells of opossumkidney express5-HT_{1B}-receptor.In particular, the presence of functioning serotonin receptors in the proximal tubules is confirmed by the increase of phosphate excretion after administration of a serotonin inhibitor [12].

Methiothepin weakens mediated by 5-HT_{1B}-receptor cAMP synthesisinhibit in the epithelial cells of the proximal tubules of opossum kidney (OK-cells) and rat kidney mesangial cells [13]; methiothepin blocks sserotonin-induced capture of phosphates by HeLa-cells, transfected with human 5-HT_{1A}-receptors [4, 7]. The effect of administeringthe methiothepin on phosphate excretion is caused byits blocking effect on the kidneys serotonin receptors [12].

5-HT_2–receptors. Epithelial cells of tubules of normal rat kidney express 5-HT_2-like receptors [14]. Moreover, 5-HT_{2A}-receptors are expressed by glomerular mesangial cells [15] and are also found in platelets, smooth muscle cells [16], renal arteries and urothelium.The inhibitors of 5-HT_{2A}-receptors are ketanserin and sarpogrelate hydrochloride; latterinhibitsserotonin-induced platelet aggregation and contractionof vascular smooth muscle cells [17]. These inhibitors, but not a 5-HT_3-receptor antagonist ondansetron, were suppressingcompletely serotonin-inducedcollagen secretion oftype IV increase, by mesangial human kidney cells [18]. This indicates that activation of collagen secretion of type IV byserotonin is mediated by 5-HT_{2A}-receptors, those present on human mesangial cells.

Serotonin and Nephron Cells

The cellular structure of kidney glomeruli is represented by endothelial, epithelial and mesangial cells. Glomerular mesangial cells largely provide structural integrity and renal filtration function. Their morphological position itselfin close proximity toward vascular structures makes cells susceptible to the influence of biologically active substances, causing contractile and relaxing effect: serotonin, angiotensin II, arginine-vasopressin, glucose, thromboxane [19, 20] are distinguished among contractile substances; inducing relaxation substances are PGE2 prostaglandins. Furthermore, a number of biologically active substances besides the contractile effect on mesangial cells contribute to their proliferation. Among these vasoactive substances it is important to note serotonin, angiotensin II, arginine vasopressin, thromboxane and glucose in high doses [21, 22].

Endogenous Serotonin

Serotonin is synthesized in the kidneys. Depotsof serotonin in kidneys are relatively small and situated in the kidney medullary layer. However, the activity of serotonin synthesizing enzymes in the kidney and central nervous system are comparable. Full serotonin synthesis cascade is localized in the proximal tubules of the renal cortex [23, 24].

Activation of intraglomerular platelet releases serotonin, acting on local hemodynamics, mesangial cell proliferation and contributing subsequent glomerular sclerosis. In the culture of rat mesangial cells, serotonin was increasing dose-dependently incorporation of (3H) thymidine into DNA, and enhancingthe proliferation of mesangial cells; both bioamine effects were excluded by administration of selective 5-HT_2-receptorinhibitorketanserin. Nexopamil (a derivative of verapamil), Ca-channel and 5-HT_2-receptors inhibitor also excluded dose-dependently the effects of serotonin, as well as the bioamine-induced contraction of mesangial cells [25, 26].

Synthesis of serotonin and dopaminefrom theirprecursors, respectively, 5-hydroxytryptophan (5-HTP) and 3, 4-dihydroxyphenylalanine (L-DOPA) occurs in the proximal tubule of the nephron. Capture of L-DOPA and 5-hydroxytryptophan by proximal tubule cells is carried out by the same transporter [27, 28] and both amines precursor are decarboxylated by L- aromamindecarboxylaseenzyme (L-AADC) with the formation of dopamine and serotonin. Due to common path capture and regulatory amines synthesis, stimulation of dopamine synthesis can lead to a decrease in the production of serotonin. This view is supported by the results of Soares-da-Silva et al [29]. At the kidney preparation.

In vivo studies determined that the acute administration of L-DOPA does not affect serotonin excretion in the kidney. Similarly, administration of equimolar doses of specific for kidneys dopamine and serotonin precursors γ-L-glutamyl-L-DOPA or γ-L-glutamyl 5-HTP has not led to competitive decrease of human kidneys synthesis each of the two amines. However, according to García N.H. et al. [30], chronic oral administration of L-

DOPA, increasing dopamine excretion, at the same time reduces the excretion of serotonin by kidneys ofthe ratswith normal and reduced organweight. In addition, the kidneys of rats with reduced organ weight have synthesized more dopamine and serotonin perone nephron, than in intact animals, which, in our opinion, reflects a compensatory role of serotonin at the organ damage. A similar result was obtained in our research in condition of bilateral kidney vagotomy and bilateral vagotomy under a prior administration of serotonin; morphological study showed greater structural and functional kidney preservation with the prior administration of serotonin [31, 32-33].

Reduced by kidneys serotonin synthesis has a natriuretic and phosphateuretic character due to the fact that the sharp increase in the serotonin level enhances the sodium and phosphatereabsorption, which was shown in the culture of epithelial cells of the proximal tubules [6]. Perhaps there was also a decrease in excitability of serotonin receptors. In the culture of epithelial cells of proximal tubule of opossum kidney was shown that a three-hour incubation with serotonin led to a decrease in functional response, with following loss of receptor excitability [7, 9].

The results of *in vitro* studies on epithelial cells of proximal tubules of opossum kidney demonstrate that the serotonin, synthesized by proximal tubule cells, acts as a paracrine / autocrine modulator of phosphate transportation, stimulating the sodium-dependent phosphate transportation [34]. Incubation of the culture of these cells expressing 5-HT_{1B}-receptors with the 5-tryptophan hydroxide, leads to chrono and substrate-dependent serotonin accumulation and stimulates sodium-dependent phosphate transportation [35]. That means that proximal tubular cells can synthesize serotonin, which enhances calcium transportation, promoting phosphate transportation.

Serotonin in culture of epithelial tubule cells of kidney weakens blocking effect of parathyroid hormone on Na-dependent phosphate capture [34]. Endogenous kidney serotonin enhances reabsorption of phosphate in vivo; parathyroid hormone blocks phosphate reabsorption in the proximal tubules and increases their excretion, indicating the competitive interaction of serotonin and parathyroid hormone in the regulation of phosphate reabsorption.

The pulsatile daily secretion of parathyroid hormone was detected, which is more intense at night. After 3-4 hours from the beginning of the night sleep, its blood content is 2. 5-3 times more than the average daily rate. Circadian rhythms of parathyroid hormone are correlated with the diurnal rhythm of the total serotonin content. Serotonin level rises during the day and significantly decreases in the dark time.Perhaps reduction of serotonin at nighttime is caused byits partial O-methylation with the formation ofmelatonin and competitive interaction of serotonin and parathyroid hormone in the regulation of Ca-metabolism. Parathyroid hormone, as a functional serotonin antagonist, blocks theenhancing of calcium and phosphorus level in the proximal tubules. Moreover, regulated by parathyroid hormone, reabsorption processes occur mostly at night time, while the increase by serotonin of calcium and phosphorusreabsorption in the nephron tubulesoccurs atthe day time, which increases the calcium oxalate content in the epithelium of the nephron tubules withfollowing development of calcifications [34-35]. Serotonin, increasing calcium and phosphorus reabsorption and oxalate formation, contributes to calcium oxalate crystals precipitation in the renal tubules, progressing with the age and enhancingat hyper serotoninemia.

Conclusion

Serotonin system is an ancient system of hormonal regulation of kidneys function. Serotonin synthesized by the proximal tubules cells is a paracrine / autocrine regulator of phosphate transportation and stimulator of calcium transportation, weakens the excretion of water, reduces the glomerular filtration rate and increases tubular reabsorption.The constancy of homeostasis is supported by mechanisms of competitive interaction between serotonin and parathyroid hormone. Latter inhibits increase in the phosphor and calcium level in the proximal renal tubules at night time. Increased nighttime activity is typical formetabolite of serotonin - melatonin, anindependent hormone, which performs regulatory functions in relation to the cardiovascular system, gastrointestinal tract, reproductive function, sleep and behavior, ageing processand tumor growth.Thus, the synchronous night increase of the parathyroid hormone synthesis and serotonin metabolites, can indicate the presence of the interaction between the regulatory effects of serotonin on the main cells of the parathyroid glands, the synthesis of parathyroid hormone by them, bone tissue condition and calcium-phosphorus metabolism.

References

1. Bond RA, Craig DA, Charlton KG, Ornstein AG, Clarke DE (1989) Partial agonistic activity of GR43175 at the inhibitory prejunctional 5-HT1-like receptor in rat kidney. J Auton Pharmacol 9: 201-210.
2. Nebigil CG, Garnovskaya MN, Spurney RF, Raymond JR (1995) Identification of a rat glomerular mesangial cell mitogenic 5-HT2A receptor. Am J Physiol 268: 122-127.
3. Raymond JR, Mukhin YV, Gelasco A, Turner J, Collinsworth G, et al (2001) Multiplicity of mechanisms of serotonin receptor signal transduction. PharmacolTher 92: 179-212.
4. Pou C, Nénonéné EK, Reader TA, Fargin A (1997) The human 5-HT1A receptor: comparison of its binding properties in transfected cells and cortical tissue. Gen Pharmacol 29: 737-747.
5. Turner JH, Garnovskaya MN, Raymond JR (2007) Serotonin 5-HT1A receptor stimulates c-Jun N-terminal kinase and induces apoptosis in Chinese hamster ovary fibroblasts. Biochim Biophys Acta 1773: 391-399.

6. Raymond JR, Mukhin YV, Gettys TW, Garnovskaya MN (1999) The recombinant 5-HT1A receptor: G protein coupling and signalling pathways. Br J Pharmacol 127: 1751-1764.

7. Kim JM, Jeong SW, Yang J, Lee SH, Kim WM, et al. (2015) Spinal 5-HT1A, not the 5-HT1B or 5-HT3 receptors, mediates descending serotonergic inhibition for late-phase mechanical allodynia of carrageenan-induced peripheral inflammation. Neuro sci Lett 23: 91-97.

8. Turner JH, Garnovskaya MN, Coaxum SD, Vlasova TM, Yakutovich M et al (2007) Ca2+-calmodulin and janus kinase 2 are required for activation of sodium-proton exchange by the Gi-coupled 5-hydroxytryptamine 1a receptor. J Pharmacol Exp Ther 320: 314-322.

9. Verbeke M, Van de Voorde J, de Ridder L, Lameire N (1999) Beneficial effect of serotonin 5-HT2-receptor antagonism on renal blood flow autoregulation in cyclosporin-treated rats. J Am Soc Nephrol 10: 28-34.

10. Van Oekelen D, Megens A, Meert T, Luyten WH, Leysen JE (2003) Functional study of rat 5-HT2A receptors using antisense oligonucleotides. J Neurochem 85: 1087-1100.

11. Wang Y, Berndt TJ, Gross JM, Peterson MA, So MJ et al. (2001) Effect of inhibition of MAO and COMT on intrarenal dopamine and serotonin and on renal function. Am J Physiol RegulIntegr Comp Physiol 280: 248-254.

12. Pauwels PJ, Colpaert FC (2003) Ca^{2+} responses in Chinese hamster ovary-K1 cells demonstrate an atypical pattern of ligand-induced 5-HT1A receptor activation. J Pharmacol Exp Ther 307: 608-614.

13. Kitamura S, Kawano T, Kaminaga S, Yamanaka D, Tateiwa H et al. (2016) Effects of fentanyl on serotonin syndrome-like behaviors in rats. J Anesth 30: 178-182.

14. Nebigil CG, Etienne N, Schaerlinger B, Hickel P, Launay JM et al. (2001) Developmentally regulated serotonin 5-HT2B receptors. Int J Dev Neurosci 19: 365-372.

15. Hannon J and Hoyer D (2008) Molecular biology of 5-HT receptors. Behav Brain Res 195: 198-213.

16. Hira T, Yahagi A, Nishimura S, Sakaino M, Yamashita T et al. (2015) Diunsaturated Aldehyde, trans, trans-2,4-Decadienal in the Intestinal Lumen Suppresses Gastric Emptying through Serotonin Signaling in Rats. J Agric Food Chem 23: 8177-8181.

17. Kasho M, Sakai M, Sasahara T, Anami Y, Matsumura T et al. (1998) Serotonin enhances the production of type IV collagen by human mesangial cells. Kidney Int 54: 1083-1092.

18. Menè P and Stoppacciaro A (2009) Isolation and propagation of glomerular mesangial cells. Methods Mol Biol 466: 3-17.

19. Habib SL and Abboud HE (2016) Tuberin regulates reactive oxygen species in renal proximal cells, kidney from rodents, and kidney from patients with tuberous sclerosis complex. Cancer Sci 107: 1092-1100.

20. Xi PI, Xu YY, Chen XL, Fan YP, Wu JH (2016) Role of the prostaglandin E2 receptor agonists in TGF-β1-induced mesangial cell damage. Biosci Rep 36: 383.

21. Liu F and Zhuang S (2016) Role of Receptor Tyrosine Kinase Signaling in Renal Fibrosis. Int J Mol Sci 17: 972.

22. Stier CT Jr (2013) Serotonin and dopamine in essential hypertension. Am J Hypertens 26: 151.

23. Kushnir IH and Kokoshchuk HI (2009) Influence of citalopram selective serotonin reuptake inhibitor on circadian rhytms of excretory function of the kidneys. Fiziol Zh 55: 125-127.

24. Wolf K, Braun A, Haining EJ, Tseng YL, Kraft P et al. (2016) Partially Defective Store Operated Calcium Entry and Hem(ITAM) Signaling in Platelets of Serotonin Transporter Deficient Mice. PLoS One 22: 147664.

25. Kuo HH, Fan R, Dvorina N, Chiesa-Vottero A, Baldwin WM 3rd (2015) Platelets in early antibody-mediated rejection of renal transplants. J Am Soc Nephrol 26: 855-863.

26. JantschakF, Brosda J, Franke RT, Fink H, Möller D et al. (2013) Pharmacological profile of 2-bromoterguride at human dopamine D2, porcine serotonin 5-hydroxytryptamine 2A, and α2C-adrenergic receptors, and its antipsychotic-like effects in rats. J Pharmacol ExpTher 347: 57-68.

27. Lukasiewicz S, Polit A, Kędracka-Krok S, Wędzony K, Maćkowiak M et al. (2010) Hetero-dimerization of serotonin5-HT(2A) and dopamineD(2) receptors. Biochim Biophys Acta 1803:1347-1358.

28. Vieira-Coelho MA, Gomes P, Serrão MP, Soares-da-Silva P (1997) Renal and intestinal autocrinemonoaminergic systems: dopamine versus 5-hydroxytryptamine. Clin Exp Hypertens 19: 43-58.

29. García NH, Berndt TJ, Tyce GM, Knox FG (1999) Chronic oral L-DOPA increases dopamine and decreases serotonin excretions. Am J Physiol 277: 1476-1480.

30. Lychkova AE, Hoschenko Yuri Osipov PG Fentisov VV (2016) Effect of serotonin on the structural and functional condition of the kidneys (literature review and own data) Scientific statements Belgorod State University. Series: Medicine. Farmatsiya 34: 22-26.

31. Lychkova AE (2006) Mechanisms of synergies divisions of the autonomic nervous system Advances of Physiological Sciences 37: 50-67.

32. Juncos LI, Martín FL, Baigorria ST, Pasqualini ME, Fiore MC et al. (2012) Atorvastatin improves sodium handling and decreases blood pressure in salt-loaded rats with chronic renal insufficiency. Nutrition 28: 23-28.

33. Chiba T, Matsuo H, Kawamura Y, Nagamori S, Nishiyama T et al. (2015) NPT1/SLC17A1 is a renal urate exporter in humans and its common gain-of-function variant decreases the risk of renal under excretion gout. Arthritis Rheumatol 67: 281-287.

34. Valdés-Fuentes M, Vera-Rivera G, De Ita-Pérez D, Méndez I, Miranda MI et al. (2015) Effect of daytime-restricted feeding in the daily variations of liver metabolism and blood transport of serotonin in rat. Physiol Rep 3: 12389.

35. Peng FF, Xiao ZL, Chen HM, Chen Y, Zhou J et al. (2016) Parathyroid hormone inhibits TGF-β/Smad signaling and extracellular matrix proteins upregulation in rat mesangial cells. Biochem Biophys Res Commun 478: 1093-1098.