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Review Article

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Serotonin Effect on Glomerulosclerosis Development Mechanism

Alla Edward Lychkova[1*], Vytaly Fentisov[2], Alexander Puzikov[1]

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

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

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

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Abstract

This article deals with the development of glomerulosclerosis and tubulointerstitial fibrosis. The involvement of connective tissue growth factor, epidermal growth factor in the mechanism of mesangial cell fibrosis is assessed. The data of the effect of serotonin on mesangial cells and the processes of glomerulosclerosis and tubulointerstitial fibrosis are given.

Keywords: glomerulosclerosis, tubulointerstitial fibrosis, mesangial cells, serotonin, serotonergic system.

Introduction

All forms of progressive disease processes are based on excessive proliferation and follow-up renal cells' fibrosis [1]. The fact that serotonin stabilizes structure functional characteristics of mesangial cells without parasympathetic innervation indicates possible compensatory effect of serotonin and serotoninergic innervation on optimal renal functioning level maintenance accompanying extraorganic regulation disturbance [2].

Fibrosis

Transforming growth factor-β (TGF-β) is a key to fibrosis processes in renal glomeruli and other tissues. TGF-β is a basic part of a large pleiotropic cytokine family, playing a crucial role in embryogenesis, extracellular matrix proteins synthesis, transformations in immune system, cells' proliferation and apoptosis [3]. The most numerous is a TGF-β1 isoform of transforming growth factor. Mesangial cells can be one of the main sources of transforming growth factor-β1. mRNA and factor TGF-β1 proteins are fixedly replicated on models of glomerulosclerosis [4] and progressive human renal diseases [5]. Except proper synthesis autoinduction, TGF-β1 controls cells' expression of reactive oxygen species (ROS), which participate in fibrosis processes. Reactive oxygen species (ROS) participate in serotoninergic control of transforming growth factor-β1 expression [6]. Reactive oxygen species act as mediators of kinases ERK (extracellular signal regulated kinases) activation in various types of cells [7,8]. E.L. Greene E.L. et al. (2000) и S.H. Lee et al. (1999) pointed out transmitter implication of serotonin induced superoxide in ERK kinases activation both in mesangial renal cells and hamster's lungs fibroblasts. Serotonin G-protein associated receptors can also suscitate ERK of mesangial cells [9]. Oxidants play an essential role by mediating interleukin-1 suscitated activation of MAPK kinases (mitogen-activated protein kinases) in human glomerular mesangial cell culture [7]. Serotonin activation of p42/44 MAPK-kinase succeeds to protein kinase C activation, forming calmodulin-dependent CaM-kinase excitation independent signaling pathway [10]. Serotonin induces transforming growth factor and facilitates ERK kinases activation in various types of cells.

Connective tissue growth factor

Connective tissue growth factor (CTGF) belongs to low-related insulin like growth factor of cohesion proteins family; to this family also belong Mac25, nov-oncogenes and cyr61. Transforming growth factor-β is the most intense connective tissue growth factor inductor in fibroblasts [11]. Serotonin and lysophosphatidic acid also induce connective tissue growth factor expression in mesangial renal cells. Experiments in aortic smooth muscle cells and mammary cancer tissue cells have shown that connective tissue growth factor can act as a cell stunt and apoptosis transmitter. Connective tissue growth factor intensifies fibroblasts' proliferation and appears to be an intense extracellular matrix stimulant [12]. While fibrosis developing connective tissue growth factor level increase; it is supposed that the given factor is etiological, participating in fibrosis diseases development and progression. For instance, in kidney connective tissue growth factor mRNA level was increased in the majority of biopsy samples, taken from pa-

tients with glomerulosclerosis and tubule interstitial fibrosis [13]. In podocytes of glomerulus epithelium basal expression of connective tissue growth factor was revealed. In case of inflammation connective tissue growth factor level in proliferating glomerular epithelium, cells increase; this growth factor also occurs in mesangial cells [14], expressing basal mRNA connective tissue growth factor level, which further increases due to transforming growth factor effect, as well as increased glucose level. Glucose-induced connective tissue growth factor level increase is blocked by transforming growth factor antibodies; that reveals that connective tissue growth factor is the main target for regulatory effect in mesangial cells [15]. Connective tissue growth factor is capable of inducing its own mRNA. In such a way, mesangial cells are target-cells for connective tissue growth factor, which can be seen from connective tissue growth factor extracellular matrix proteins (fibronectin and collagen type I and IV) induction [16].

Epidermal growth factor

Mesangial cells bear EGF-receptor on their surface [17] and express heparin-binding EGF-like growth factor (HB-EGF). Tumor necrosis factor-α (TACE (ADAM17)) converting enzyme and heparin-binding EGF-like growth factor play a crucial role in epidermal growth factor receptors transactivation by 5-HT2A-receptors in renal mesangial cells and cellular proliferation. 5-HT2A-receptors stimulation rapidly excites tumor necrosis factor-α converting enzyme and heparin-binding EGF-like growth factor and activates epidermal growth factor receptors (EGFR). EGFR transactivation in turn leads to phosphorylation and proliferation of mesangial cells [18]. Mesangial cells serotonin induced proliferation signaling pathway can be represented in the following way: 5-HT 5-HT2A-receptor tumor necrosis factor-α converting enzyme heparin-binding EGF-like growth factor epidermal growth factor receptors extracellular signal regulated kinase proliferation [19]. G-protein coupled receptor (GPCR) and metalloproteinase participate in epidermal growth factor receptors transactivation in cells. Metalloproteinase contribution to epidermal growth factor receptors transactivation and extracellular signal regulated kinase phosphorylation strongly depends on type of cell and GPCR [20]. Metalloproteinase activation occurs in such important processes as Helicobacter pylori-induced disorder, motility of tumor cells, hypercardia [21], neovascularity and cystic fibrosis [22]. Naturally mesangial matrix contains fibronectin, laminin, collagen and other macromolecules. Mesangial cells play an important role in type IV collagen metabolism by modulating its synthesis and breakdown [23]. In vitro experiments in rat's mesangial cells have shown, that type IV collagen secretion is induced by high doses of glucose [24] and external growth factor TGF-β [25]. Serotonin and low-molecular lysophosphatidic acid control involution, proliferation and induction of mesangial cells genes. Consequently, serotonin and lysophosphatidic acid can control glomerular hemodynamics and glomerular nephritis progression. More than that, serotonin facilitates extracellular matrix production by mesangial cells, inducing transforming growth factor and enhancing type IV collagen synthesis [26], activating successively protein kinase C and transforming growth factor TGF-β1.

Protein kinase C participates in agonists induced reactions of various types of cells [27, 10]. The enzyme activates by high doses of diacylglycerol (DAG) and calcium in cell membrane. In rat's glomerular mesangial cell culture serotonin with the participation of phospholipase C facilitates these cells' proliferation and their prostaglandin synthesis. This metabolic chain includes transient cytosolic calcium level increase, which is followed by protein kinase C activation. According to M. Kasho et al. (1998), serotonin induced increase of type IV collagen production by human mesangial cells is mediated successively by phospholipase C activation, diacylglycerol and calcium level increase and protein kinase C activation together with phospholipase C initiating by serotonin [28]. Serotonin stimulant effect on type IV collagen secretion is blocked by calphostin C. Serotonin have enhanced membrane protein kinase C activity. Phorbolester, a well-known membrane protein kinase C activator, facilitated type IV collagen production. These facts prove protein kinase C mediating role in serotonin induced type IV collagen secretion increase in mesangial cells. Serotonin, enhancing type IV collagen production in mesangial cells, simultaneously increases transforming growth factor-β active form level. TGF-β antibodies have completely suppressed type IV collagen production; injection of TGF-β exogenous factor have enhanced type IV collagen production. Hence it appears that transforming growth factor-β possibly participates in type IV collagen synthesis in mesangial cells [26].

Mitogenic effect of serotonin

5-HT2A–receptors expressed by mesangial cells mediate serotonin mitogenic effect and immediate early response genes induction. Hence, these effects are toxin-insensitive due to 5-HT2A–receptors and Gq/11 –proteins association and are connected with TGF-β1 growth factor and collagen synthesis by means of protein kinase C (PKC)-dependent mechanism. 5-HT2A–receptor of mesangial cells with the involvement of protein kinase C trans activates endothelial growth factor receptors (EGFR) [29]. Serotonin, interleukin-1 and platelet-derived growth factor produced by glomerulus cells, activated macrophages and platelets respectively facilitate mesangial cell's proliferation. In this regard, it is revealing that macrophages and platelets' presence in affected glomeruli was brought out in histologic studies. Endothelial cells and glomerular basement membrane damage is supposed to facilitate thrombocyte adhesion and aggregation. Serotonin time- and dose-dependently stimulates DNA synthesis in rat's glomerular mesangial cell culture acting synergistically with insulin and presenting in kidneys [30] epidermal growth factor, which appears to be a strong mesangial cells' mitogen. Serotonin stimulates phospholipase C and protein kinase C as well as initiates rat's kidney mesangial cells mitogens is apparently by means of 5-HT2-receptors activa-

tion. Serotonin induces phosphoinositide hydrolysis in normal rat kidney cells (NRK-cells), activating 5-HT2-receptors. However, signaling pathways with the participation of 5-HT2A-receptors in glomerular mesangial cells are much more diverse: Ca2+ release from intercellular depots [31], protein kinase C (PKC) activation, vasodilate prostaglandins synthesis stimulation, Cl-associated membrane depolarization and mitogens is activation [32].

Serotonin by 5-HT2A-receptors activating effectively blocks forskolin-induced cAMP synthesis in mesangial cells. This is proved by the given effect inhibition by 5-HT2A-receptors antagonists ketanserin, ritanserin and spiperone; 5-HT2A-receptors role is indicative of cAMP synthesis blocking serotonin effect sensitivity to pertussis toxin [33,34]. There was mRNA of 5-HT2A-, but not of 5-HT1A- or 5-HT2C-receptors, which were discovered in renal mesangial cells. Mitogenic effect of locally synthesized or thrombocyte-released serotonin occurs with the help of bioamine activated mesangial renal cells 5-HT2A-receptors [34] and protein kinase C. Proliferative serotonin effect is partly and reversibly blocked by lithium chloride. Serotoninergic system participation in mesangial cells' mitogens is provides basic matrix components including laminin and collagen synthesis regulation; glomerular blood flow control along with angiotensin, vasopressin and histamine and local glomerular immune-inflammatory reaction implementation regulation (since macrofagic-type mesangiocytes bear Fc-receptors and other structures, including Ia-antigen on their surface).

According to M.N. Garnovskaya et al. (1995) factors facilitating intracellular cAMP level increase in mesangial cells at the same time appear to be antiproliferative and relaxation inducing. On the contrary, Ca2+ mobilizing or protein kinase C stimulating phospholipase C activators usually facilitate proliferation and/or cause contraction. Therefore, due to simultaneous blocking of cAMP accumulation in mesangial cells by 5-HT2A-receptors and phospholipase C activation one can suppose associated action of appropriate signaling pathways in mitogenic reaction stimulation and contraction induction. So, 5-HT2A-receptor can be a component of two nearby proceeding signaling effects integration. In other words, this is an especial case of serotoninergic system integrative activity [35]. Serotonin, histamine, eicosanoids and platelet-derived growth factor influence glomerular microcirculation by altering arteriolar smooth muscle and mesangial cells contractile condition.

Aggregated thrombocytes participation in glomerular inflammation is accompanied by several growth factors release, especially epidermal growth factor. Renal-produced epidermal growth factor intensifies serotonin action or enhances serotonin sensitivity of mesangial cells, reducing by that amine effect threshold from 10-5 M (in experiments in mesangial cells culture) to 10-7 M and less. Insulin stimulation of mesangial cells along with epidermal growth factor leads to moderate but steady increase of inositol phosphates and 1,2-diacylglycerol level. Serotonin induced increase of type IV collagen production in human mesangial cells is mediated successively by phospholipase C activation, diacylglycerol and calcium level increase and protein kinase C activation along with phospholipase C serotonin initiation, which is likely to determine serotonin participation in glomerulosclerosis [26]. However, according to Varshavsky V.A. (2001), type I and III collagen participates in glomerulosclerosis development as well [36].

Glomerulonephritis

Extracellular signal regulated kinase family (ERK) mitogen-activated protein kinases (MAPK) (Davis R.J., 1993) participate in proliferative glomerulonephritis pathogenesis, experimental glomerulonephritis and human renal cell carcinoma [37]. ERK kinases are activated by MAPK/MEK protein kinases. ERK kinases phosphorylation gives them an opportunity to phosphorylate in turn various targets including excitatory kinases and transcription factors that is to control several mitogenesis-related genes expression. P2X7-receptors expression can be observed in experimental glomerulonephritis and in clinical picture. Purine P2-receptors PPADS blocker effectively suppresses mesangial cells proliferation in rat's mesangial proliferative glomerulonephritis experimental mode [38]. Connective tissue growth factor induction by serotonin and lysophosphatidic acid proves their mediator role in development and progression of such diseases as renal fibrosis, retroperitoneal fibrosis, carcinoid heart disease and lung hypertensive aortic valve disease, related to 5-HT2-agonist fenfluramin and phentermin [39].

Conclusion

Thus, serotonin intensifies type IV collagen synthesis in human renal mesangial cells, and bioamine action is mediated by protein kinase C activation along with succeeding factor TGF-β level increase. Heptahelical serotonin receptors activation related to pertussis toxin insensitive G-protein coupled receptors induces early response genes, through p42/44 MAP-kinase mediation. Early response genes can be serotonin target in mesangial cells.

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