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Editorial Open Access

Purinergic P2X7 Receptors and Chronic Kidney Disease

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Editorial

Intracellular adenosine triphosphate (ATP) is the most important source of energy for intracellular reactions. Cytoplasmic ATP does not cross the plasma membrane, but a small fraction of ATP is released from the cells into extracellular space through the series of finely tuned processes such as exocytosis, ion channels, and nucleotide transporters. The release of intracellular ATP can be triggered by various stimuli like mechanical stress, cell membrane damage, inflammation, hypoxia, cell growth and death. Adenosine triphosphate in extracellular compartment, albeit at 1000 times lower concentration than intracellular ATP, serves as a signaling molecule by binding and activating nucleotide receptors called purinergic receptors in cell membrane [1].

Purinergic signaling has been intensively studied since its discovery in the 1970s [2] and has been shown to affect virtually any field in biomedical science. At the present time, purinergic signaling has been accepted as a crucial component in the pathogenesis of various diseases, mediating a vast array of biological processes such as neuronal transmission, signal transduction in cardiovascular system, exocrine and endocrine functions, immunity, inflammation and cancer. One of the fields of interest is also Chronic Kidney Disease (CKD). Purinergic signaling involvement has been described in several important intrarenal regulatory mechanisms, including tubuloglomerular feedback, the autoregulatory response of the glomerular and extraglomerular microcirculation, and the control of renin release. Furthermore, purinergic signaling influences water and electrolyte transport in all segments of the renal tubule. There is an autocrine/paracrine release of ATP from epithelial and endothelial cells, as well as the release of a cotransmitter from sympathetic nerves [3]. Many authors study the mechanisms of purinergic signaling in wide range of renal pathology, including polycystic kidney disease, nephritis, diabetic nephropathy, hypertension as well as other systemic diseases characterized by renal inflammatory response. Moreover, clinically relevant therapeutic strategies are being developed.

Purinergic receptors are subclassified as P1 receptors activated by the ATP metabolite adenosine and P2 receptors activated by ATP and/or other nucleotides. The P2 receptors are ubiquitously expressed throughout the kidney on both cortical and medullary vascular and tubular compartments. On the basis of their signaling properties, P2 receptors can be further subdivided into metabotropic P2Y receptors (P2YRs) that are G-protein-coupled, and ionotropic P2X receptors (P2XRs) that are nucleotide-gated ion channels. Seven P2XRs have been identified (P2X1-P2X7) which are involved in a variety of biological responses, mainly related to inflammation, tissue damage and cell proliferation [4,5].

One of these receptors is P2X7R which is scarcely expressed in physiological conditions but can be upregulated by inflammation. The P2X7R expression was originally defined in macrophages and monocytes and thereafter in different cell types including the kidney. During inflammation, several cell types release ATP from intracellular storage compartments into the extracellular space being a potent stimulus for P2X7R activation. This results in opening the cation channel followed by forming a non-specific pore. The channel opening induces Na^+ and Ca^{2+} influx and K^+ efflux leading to plasma membrane depolarization, increase of intracellular Ca^{2+} level and activation of Ca^{2+} signaling cascades [6].

In our studies, more than 40% of cation channels of surface P2X7Rs were open and the permeability of their pores was increased already in early stages of CKD. The activated P2X7Rs on peripheral blood mononuclear cells of patients with CKD had a significantly reduced sensitivity to P2X7R antagonism and their functionality was altered [7,8]. The increased expression of P2X7Rs and thereby altered cellular signaling in monocytes was also manifested already in early stages of CKD. These changes can be related to systemic inflammatory state, thus influencing the immune and vascular systems. Monocytes are essential immune system cells with unique roles during inflammatory response. Immunodeficiency and increased frequency of infections are known in CKD patients. Moreover, the P2X7Rs expression was significantly increased also in lymphocytes of CKD patients, but the increase was less pronounced when compared to monocytes, and manifested mainly in B-cells [9]. Experimental studies have not only revealed a pathogenetic role of P2X7Rs, but also pointed out potential therapeutic use of a selective antagonist in the treatment of inflammatory renal diseases.

Clinical interventions involving purinergic signaling are just beginning. Several clinical trials (Phase 1 and 2) using P2X7R antagonists in the treatment of various inflammatory diseases (inflammatory bowel disease, rheumatoid arthritis and chronic obstructive pulmonary disease) have failed to show benefit thus far, although the drugs have been well tolerated [10]. Menzies et al. analyzed factors why P2X7R antagonists have failed in clinical trials. Human P2X7R has at least 10 splice isoforms, the functions of which have not been elucidated. Furthermore, it is evident that P2X7R does not act alone because P2X4R can also modulate the efficacy of P2X7R-mediated inflammation [6]. Recent studies exhibit a functional relationship between these two receptors [11]. Preclinical data suggest that genetic variation in P2X7R will increase the population-wide variance of both the agonist and antagonist binding affinities. The tissue distribution, regulation and function of these splice isoforms in the healthy kidney is just beginning to be explored. The pharmacogenomics of P2X7R and the impact on the disease are largely unknown. With better understanding of purinergic signaling and more subtype-specific agonists and antagonists, the prospect for P2X7Rs targeted therapies is still promising.

References

1. Solini A, Usuelli V, Fiorina P (2015) The dark side of extracellular ATP in kidney disease. J Am Nephrol 26: 1007-1016.
2. Burnstock G (1972) Puerinergic nerves. Pharmacol Rev 24: 509-581.
3. Burnstock G, Evans LC, Bailey MA (2014) Purinergic signalling in the kidney in helth and disease. Purinergic Signalling 10: 71-101.
4. Ralevic V, Burnstock G (1998) Receptors for purines and pyrimidines. Pharmacol Rev 50: 413-492.
5. North RA (2002) Molecular physiology of P2X receptors. Physiol Rev 82: 1013-1067.
6. Howarth AR, Conway BR, Bailey MA (2015) Vascular and inflammatory actions of P2X receptors in renal injury. Auton Neurosci 191: 135-140.
7. Lajdova I, Oksa A, Chorvat D Jr, Topor P, Spustova V (2012) Purinergic P2X7 receptors participate in disturbed intracellular calcium homeostasis in peripheral blood mononuclear cells of patients with chronic kidney disease. Kidney Blood Press Res 35: 48-57.
8. Lajdova I, Spustova V, Oksa A, Kaderjakova Z, Chorvat Jr D, et al. (2015) The impact of vitamin D3 supplementation on mechanisms of cell calcium signaling in chronic kidney disease. BioMed Res Int: Pgs 12.
9. Lajdova I, Oksa A, Horvathova M, Spustova V (2017) Expression of purinergic P2X7 receptors in subpopulations of peripheral blood mononuclear cells in early-stage chronic kidney disease. J Physiol Phrmacol 68: 779-785.
10. Arulkumaran N, Unwin RJ, Tam FWK (2011) A potential therapeutic role for P2X7 receptor (P2X7R) antagonists in the treatment of inflammatory diseases. Expert Opin Investig Drugs 20: 897-915.
11. Menzies RI, Tam FW, Unwin RJ, Baliley M (2017) Purinergic signaling in kidney disease. Kidney Int 91: 315-323.