

Purinergic Signaling in Cardiovascular System: A Fertile Ground of Investigation

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Abstract

Purinergic signaling is a primitive and highly conserved system between animals. Nucleotides (e.g. ATP, ADP) and nucleosides (e.g. adenosine) may act as cellular messengers when getting the extracellular space and binding purinoceptors. In the cardiovascular system, nucleotides may either lead to vasoconstriction when activating VSMC P2 receptors or vasorelaxation by the activation of endothelial P2. Ectonucleotidases, especially NTPDase1 and ecto-5'-nucleotidase, are able to hydrolyse purine nucleotides in order to finish ATP signaling. Our research group has focusing in clarifying the mechanisms of ectonucleotidases' contribution to the development and progression of hypertension. However, there is a big lack in selective inhibitors for ectonucleotidases which restricts the use of purinergic therapies. At the same time, this scarcity may characterize the nucleotides' signaling as a very fertile ground of investigation in the cardiovascular system.

Keywords: Purinergic signaling; Purinoceptors; Ectonucleotidases; Hypertension disease; Neurotransmitters

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Tel: 3438233714

Received: September 10, 2015; **Accepted:** September 14, 2015; **Published:** October 07, 2015

Citation: Fürstenau CR. Purinergic Signaling in Cardiovascular System: A Fertile Ground of Investigation. *Biochem Mol Biol J.* 2016, 1:1.

Introduction

The purinergic signaling concept was firstly proposed by Burnstock in the early 1970s [1]. At that time, the idea that ATP could act as a neurotransmitter besides its well established role as energy source for several metabolic processes faced intense resistance. Nowadays, the nucleotides' signaling is widely accepted as a primitive and highly conserved system and distinct roles for nucleotides (e.g. ATP, ADP) and nucleosides (e.g. adenosine) as extracellular transmitters are now extensively described in a range of tissues [2]. It is remarkable that nucleotides and nucleosides must reach the extracellular space in order to function as cellular messengers. This may either occur by cellular lysis or under mechanical stimulus (shear stress, hypoxia) as well as release from nerve terminals together with other neurotransmitters [3]. Once they get the extracellular space, nucleotides will bind purinergic P2 receptors (P2X, ion channels exclusive responsive to ATP or P2Y, G-coupled receptors that may respond to ATP, ADP, UTP, UDP and UDP-glucose) while adenosine will be recognized by a class of purinoceptors named P1 [4].

After passing their message inside the cell, these molecules must be metabolized to finish purinergic signaling. The hydrolysis of nucleotides and nucleosides is guaranteed by a cascade of ectonucleotidases, which are ectoenzymes able to regulate the agonist availability as well as the purinoceptors activation [5]. Among all ectonucleotidases already described, the families ecto-nucleotide-triphosphate diphosphohydrolase (E-NTPDase1-8) and ecto-5'-nucleotidase (CD73, E-5'-N) seem to be the most important. Acting in concert, both E-NTPDase and CD73 may at the same time finish with ATP signaling and promote adenosine signaling activation. The role of purinergic signaling in the regulation of cardiovascular system has becoming more and more important. Importantly, the activation of endothelial P2 receptors induces a local vasorelaxation by the release of nitric oxide (NO), prostacyclin (PGI2) and endothelium-derived hyperpolarizing factor (EDHF) [6]. In an opposite way, the VSMC purinoceptors activation promotes a vasoconstriction via P2 and P2Y [7]. A broad range of studies has showing the importance of purines in the cardiovascular regulation. Our group has focused in the investigation of ectonucleotidases, mainly NTPDase1 and ecto-5'-

nucleotidase, in distinct pathophysiological scenarios of vascular biology. In this regard, we have already kinetically characterized the presence of soluble NTPDases in serum fraction, as well as in circulating platelets [8,9]. Ultimately, we have putting a big effort to clarify the role of these enzymes in the development and progression of hypertension disease. From the literature, we know that NTPDase1, expressed in both VSMC and EC, is the main ectonucleotidase in the vasculature that is able to modulate the availability of nucleotides and the activation of specific purinergic receptors, controlling the vascular tone and blood pressure [10]. Presently, we are investigating if there is a “standard behavior” for ectonucleotidases activities in response to different hypertension models (chemical, genetic and diet-induced). Purinergic signaling components are expressed in all animal

biological systems. More than this, some of purinergic elements are being already manipulated in clinics as is the case for thienopyridines that are selective irreversible P2Y₁₂ platelet antagonists, used as anti-platelet drugs. Also, the importance of this signaling pathway has been compared to other classical regulators of cardiovascular processes, such as sympathetic and renin-angiotensin systems. The scarcity of selective agonists and antagonists to purinergic receptors as well as the lack of specific inhibitors to ectonucleotidases still restricts the use of purinergic therapies. Nonetheless, this paucity also strengths the purinergic signaling studies as a very fertile ground of investigation to be used as a new approach in the understanding and treatment of cardiovascular processes and pathologies.

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