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Editorial Open Access

ATP Metabolism as Biomarker Target for Cardiovascular Protection

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Cardiovascular disease including stroke is the leading cause of death and disability worldwide and an enormous economic burden to our societies [1]. Based on the latest statistics released for heart and stroke disease, an estimated 83,600,000 adults in the United States (US) (>30%) have one or more types of Cardiovascular Disease (CVD) of whom more than 90% have hypertension, 18% have Coronary Heart Disease (CHD), close to 10% have Myocardial Infarction (MI) and 8% have stroke. The total direct and indirect cost in the US alone for treatment of cardiovascular diseases (hospitalization, drugs, home healthcare, etc.) and lost of productivity and morbidity is estimated at close to $315 billion US per year [2]. Thus prevention by better diagnosis and drug treatment could provide a huge saving for the health care cost worldwide. Despite advancement in modern cardiovascular medicine, the prevalence of hypertension, Ischemic Heart Disease (IHD) and stroke is still on the rise, and that finding an optimum therapy to slow disease progression remains a therapeutic challenge.

In our laboratory, we have been embarking on the concept to study the potential of circulatory concentrations of adenosine and ATP and their metabolites as biomarkers for cardiovascular protection and as targets for anti-ischemia drugs [3,4]. The importance of adenosine and ATP in regulating many biological functions has long been recognized, especially for their effects on the cardiovascular system [5,6]. It is known that adenosine and ATP are key factors in regulation of coronary blood flow [7], inhibiting platelet aggregation [8], protection of myocardium [9], neuromodulation [10], attenuating tissue necrosis [6], ischemic preconditioning [11], immunomodulation [12], energy metabolism [13], and pain mediation [14] which together maintain the homeostasis of the cardiovascular system. It has been shown that patients with effort angina and essential hypertension have altered adenosine metabolism compared to healthy individuals [15], and that plasma concentration of adenosine increase in patients with Congestive Heart Failure (CHF) [16], which could be a physiologic response to heart failure and help to reduce the severity of the disease [17]. Thus it has been postulated that adenosine and ATP may be used as sensitive biomarkers to quantify myocardial and endothelial ischemia [18], and for monitoring therapeutic effects of anti-ischemia drugs [19,20].

In response to ischemia, ATP is broken down to release adenosine. The activity of adenosine is very short lived because it is rapidly taken up by myocardial and endothelial cells, erythrocytes (RBC), and also rapidly metabolized to inosine and subsequently to hypoxanthine, adenine, S-Adenosyl Homocysteine (SAH), and other adenine nucleotides [15]. There are also evidences to indicate that ATP is a neurotransmitter and released together with adenosine to maintain the homeostasis within the cardiovascular system and for neuroprotection [21]. Extracellular ATP is broken down rapidly to ADP and AMP and finally to adenosine by 5'-nucleotidase [15]. These metabolic events are known to occur in the myocardium as well as in erythrocytes (RBC), but it is not clear whether or not they are regulated by similar mechanism [22,23].

There is a host of evidence to indicate that many clinically useful therapeutic agents act by altering the normal physiologic functions of adenosine [24]. For example, dipyridamole exerts its vasodilating effect by inhibiting the uptake of endogenous adenosine thereby prolonging its effect in the circulation [25,26]. On the other hand, theophylline and the methylxanthines are competitive inhibitors of adenosine binding to its receptors and hence they antagonize the effects of adenosine and dipyridamole [24]. Adenosine and ATP and their association with energy metabolism are increasingly exploited as targets for drug discovery and development for a wide variety of clinical conditions [27]. For example, adenosine A2A receptor agonists are currently developed as anti-inflammatory agents or for stress test [28], the P2Y12 receptor antagonists for coronary artery disease [29], and the A1 receptor agonists and P2X7 antagonists have potential for cardiovascular and neuroprotection [30]. There are now also evidences both from our laboratory and others to indicate that while many cardiovascular drugs such as nucleoside transport inhibitors, calcium antagonists (CCBs), sotalol, and amiodarone inhibit the uptake of adenosine, others such as propranolol and enalapril are practically devoid of any inhibitory activity [19,31]. Thus adenosine and ATP transport and metabolism are clinically relevant therapeutic targets for cardiovascular and neuroprotective agents [30,32,33].

In summary, ATP and adenosine metabolism are key regulators affecting cardiovascular homeostasis. They could be exploited as biomarker targets for drug development and management of cardiovascular diseases which have affected millions of patients worldwide.

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