

## Therapeutic Potential of Adenosine Transport Modulators for Cardiovascular Protection

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### Introduction

Cardiovascular disease including stroke is the leading cause of death and disability worldwide [1] and an enormous economic burden to our societies [2]. Based on the latest statistics released for heart and stroke disease, an estimated 83,600,000 adults in the United State (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 loss of productivity and morbidity is estimated at close to \$315 billion US per year [3]. Thus prevention by improving diagnosis and drug treatment strategies could provide a huge saving for the health care cost worldwide.

The importance of adenosine in regulating many biological functions has long been recognized, especially for their effects on the cardiovascular system [4, 5]. It is known that adenosine metabolism is a key factor in regulation of coronary blood flow [6], inhibiting platelet aggregation [7,8] protection of myocardium [9], neuromodulation [10], attenuating tissue necrosis [11], ischemic preconditioning [12], immunomodulation [13], energy metabolism [14], and pain mediation [15] which maintain the homeostasis of the cardiovascular system. Adenosine modulates these actions by interacting with adenosine receptors (AR), which are distributed ubiquitously throughout the body [16]. It is believed that metabolic condition of the myocardium may be assessed quantitatively by the level of adenosine production which maintains a healthy balance between energy supply and demand in the cardiovascular system [17].

Under pathologic and stressful conditions such as those associated with ischemia, hypoxia, trauma, seizure, inflammation and pain, there is an increased demand for energy triggering an increased catabolism of ATP to AMP and subsequently to adenosine, resulting in elevated levels of adenosine in both extracellular and intracellular space which protects against tissue damage [18]. There have been many studies both in animal models and humans to explore the cardiovascular protective effects of adenosine in the past few decades. These studies have laid the ground work and set the pace for future research on adenosine, adenosine agonists and adenosine re-uptake inhibitors as cardiovascular protective agents.

### Adenosine production and metabolism under normal physiological and hypoxic conditions in the cardiovascular system

Under normal physiological conditions the main source of adenosine is from catabolism of ATP to ADP and then to AMP, which is further catabolized by ecto and endo 5' nucleotidase to produce adenosine [19]. Another source of adenosine is from hydrolysis of S-adenosylhomocystein which is derived from the transmethylation pathway utilizing S-adenosylmethionine [20]. Intracellular adenosine can undergo rephosphorylation to form AMP and other adenine nucleotides by adenosine kinase [21] or metabolized to inosine

by adenosine deaminase respectively [22], which maintain low concentrations of adenosine under basal or normal physiologic condition [19]. However, during ischemia/hypoxia or in extremely heavy workloads, there is an increased demand of energy which triggers a breakdown of ATP and release of adenosine locally and into systemic circulation [23]. The adenosine released is taken up rapidly by endothelial cells and red blood cells via nucleoside transporters and subsequently metabolized to ATP [24] to maintain the low basal level of adenosine.

### Importance of ATP synthase and adenylate kinase in cardioprotection

ATP synthase is a mitochondrial enzyme involved in oxidative phosphorylation during ATP synthesis [25]. It is a key enzyme directly involved in cellular energy metabolism and the widely conceived theory of ischemia preconditioning and a target for cardioprotection [26,27]. Pharmacologic agents which activate ATP synthase or maintain its integrity in adversary conditions such as demonstrated for the tetracyclines [28] may help to preserve intracellular ATP in ischemia. On the other hand, adenylate kinases are abundant phosphotransferases catalyzing the inter-conversion of adenine nucleotides and thus regulate the adenine nucleotide ratios in different intracellular compartments. The enzymes are present ubiquitously in various tissues in the body including the RBC [29], and involved in regulating energy metabolism and energy signaling in the cardiovascular system as well as in the body [30,31]. Thus both enzymes are critically important working together to maintain an optimum balance of energy supply and demand for cardiovascular homeostasis.

### Adenosine transport modulators for cardioprotection

It is clear that adenosine plays a pivotal role in cardioprotection not only by its receptor mediated actions, but also as a source of supply for intracellular AMP [9] which is a substrate as well as an important signaling mechanism for ATP synthesis [26]. It has been reported that inhibiting nucleoside transporter by R75231 improves the functional recovery from ischemia/reperfusion injury in an isolated rabbit heart model [32]. Similarly, dipyridamole and other nucleoside transporter inhibitors (NTI) such as dilazep have been shown to be protective in various animal models of myocardial ischemia, which may be mediated via adenosine A(1) receptor [33]. It was suggested that the order of

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potency inhibiting adenosine uptake by erythrocytes is draflazine  $\geq$  dilazep  $>$ R 75 231  $>$ NBMPR  $>$  mioflazine = dipyridamole  $>$  lidoflazine [34]. Using mammalian cardiac myocytes, it was shown that adenosine attenuated the stimulatory effects of isoproterenol via blockade of calcium influx [35], which may explain at least partly the cardiovascular protective effect of calcium channel blockers [36], although these agents may also have a direct effect modulating the transport and metabolism of adenosine [37-39].

## Future Direction

The role of adenosine in cardiovascular protection in ischemia and reperfusion injury is well established. Pharmacologic agents such as the NTI have been used successfully in animal models and patients to increase extracellular adenosine concentrations and enhance the protective effect of endogenous adenosine. While adenosine kinase which metabolizes adenosine to adenosine monophosphate (AMP) has been advocated as a target for drug development for cardiovascular and metabolic diseases [21], the adenosine transporters, ATP synthase as well as adenylate kinase may also be exploited as drug targets to develop selective agents for cardiovascular prevention and protection. A better understanding and refinement of adenosine transporters and these energy metabolism enzymes can improve the safety and efficacy of the NTI as a therapeutic strategy for management of ischemic heart disease and related cardiovascular conditions. While most of the earlier studies have focused on the effect of NTI on extracellular adenosine or adenosine metabolism in cardiac myocytes, little is known of the effect of these agents on ATP/adenosine metabolism in erythrocytes (RBC) *in vivo* under normal or in ischemia conditions. It is probable that the increase in plasma concentrations of adenosine during ischemia could be attributed at least in part to metabolic breakdown of ATP in the RBC [40]. Blockade of the reuptake of adenosine by the NTI could moderate ATP metabolism and the nucleotide pool in the RBC which may be an important factor affecting the safety and efficacy of these therapeutic agents. The relationship between the nucleotide concentrations in the RBC and those of the endothelium and myocardium, and the potential of ATP metabolism in the RBC as a surrogate biomarker for energy balance in the body warrants further studies. Understanding these concepts and the inter-play of ATP metabolism in these different tissues would enable us to explore the future potential of NTI and other modulators of the nucleoside transporters for management of myocardial ischemia.

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