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STATE-OF-THE-ART PAPER

Adenosine

Physiology, Pharmacology, and Clinical Applications

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Adenosine is a ubiquitous extracellular signaling molecule with essential functions in human physiology. Due to the widespread expression of adenosine receptors, it has far-reaching effects across many different organ systems. With a prominent role in the cardiovascular system, it has been extensively studied for both its therapeutic and diagnostic abilities. One of the key areas of use is in the coronary circulation whereby adenosine produces a hyperemic response. An important target of adenosine is the coronary microcirculation whereby adenosine acts as a prominent vasodilator with many of the beneficial effects of adenosine reflected in its capacity to affect the microvessels. Adenosine also has an important role in the pre-conditioned state and also in the attenuation of ischemia-reperfusion injury. This review examines the physiology, pharmacology, and therapeutic applications of adenosine in the human cardiovascular system and provides a brief overview of important aspects of the adenosine-cardiac interaction. It also examines the role of adenosine in the coronary hyperemic response and discusses the use of adenosine for this purpose. After recent concerns about the use of adenosine, a discussion regarding safety of this drug is provided. A brief review of novel agents used to initiate coronary hyperemia is also provided.
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Adenosine is a ubiquitous extracellular signaling molecule with essential functions in human physiology. From providing the backbone for basic energy transfer through its adenosine triphosphate (ATP) and adenosine diphosphate interactions to its role in cell signaling, adenosine is a fundamental component of human biology (1). Adenosine has far-reaching effects as an extracellular signaling molecule inducing vasodilation in most vascular beds, regulating activity in the sympathetic nervous system, having antithrombotic properties, and reducing blood pressure and heart rate. Such properties are some of the reasons why adenosine and its derivatives have therapeutic effects in most organ systems.

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Although adenosine has pleiotropic effects, much of our understanding of adenosine has come through observations of its action in the cardiovascular system. Pioneering work by Drury and Szent-Gyorgyi (2) in the past century pointed to the fact that an adenine compound caused disturbances in heart rate when injected intravenously. It is likely that this adenine compound was in fact adenosine. However, it was not until ~60 years later that the use of this property of adenosine was used clinically to treat patients presenting with supraventricular tachycardia (3).

One of the most common reasons for using adenosine in the cardiovascular system is for the production of vasodilation in the coronary microcirculation to produce hyperemia (4). This property of adenosine to modify microcirculatory function has been used for diagnostic and therapeutic effects for many years and is widely adopted as the gold-standard method of diagnosing ischemia invasively and noninvasively.

This review examines the physiology, pharmacology, and therapeutic applications of adenosine in the human cardiovascular system and provides a

brief overview of important aspects of the adenosine-cardiac interaction.

Adenosine Pharmacology

Adenosine is a naturally occurring endogenous purine nucleoside composed of an adenine molecule attached to a ribose sugar moiety (1) (ribofuranose) via a beta-N9-glycosidic bond (6-amino-9-β-D-ribofuranosyl-9-H-purine) (Fig. 1). It is the nucleoside base of both ATP and the signaling molecule cyclic adenosine monophosphate (cAMP). Adenosine is rapidly transported into vascular endothelial cells and erythrocytes where it is catabolized by adenosine deaminase to inosine (5). Dipyridamole, a commonly used vasoactive medication (6) exerts its effects through inhibition of adenosine deaminase. Adenosine is (re)phosphorylated by adenine kinase forming adenosine monophosphate, which is incorporated into the high-energy phosphate pool (7). Adenosine levels can rise rapidly in ischemic tissue due to adenosine kinase inhibition (1).

Abbreviations and Acronyms

AF = atrial fibrillation

ATP = adenosine triphosphate

AV = atrioventricular

cAMP = cyclic adenosine monophosphate

FFR = fractional flow reserve

IC = intracoronary

IV = intravenous

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

In the intracellular space, adenosine can be synthesized de novo during purine biosynthesis or accumulate as a result of ATP breakdown. Intracellular adenosine concentrations increase when there is a mismatch between ATP synthesis and use as in ischemia or hypoxia (8,9). Adenosine does not freely pass across the cell membrane and requires the use of nucleoside transporters to facilitate the process. Extracellular adenosine arises from active transport of intracellular stores or from breakdown of adenine nucleotides outside the cell (1).

Adenosine binds with 4 evolutionary well-conserved receptor subtypes that are ubiquitously expressed: A1, A2A, A2B, and A3 (10,11). These receptors interact with G-protein receptors. Activation of the G_i protein–bound A1 and A3 receptors reduces adenyl cyclase activity and decreases intracellular cAMP. Activation of the G_s protein–bound A2A and A2B receptors increases adenyl cyclase activity and cAMP levels. Adenosine has highest affinity for the A1 and A2a receptors.

Activation of A2A and A2B adenosine receptors produces potent vasodilation of most vascular beds including the coronary circulation, resulting in an increase in myocardial blood flow (12). However, A2A and A2B activation produces vasoconstriction in renal (13) and splenic afferent arterioles and hepatic veins.

A1 receptors generally have an inhibitory function on most tissues. Activation of cardiac A1 receptors has a myocardial depressant effect with negative chronotropic and dromotropic effects. A1 receptor activation also mediates inhibition of atrioventricular (AV) node conduction and prolongation of the refractory period via inhibition of cAMP-mediated calcium influx and enhances potassium conduction (14) (Fig. 2).

A2A receptor activation also produces anti-inflammatory effects and acts as a major target of caffeine. A2B receptors are found on human mast cells and are thought to produce mast cell degranulation and bronchial constriction (15). A3 receptors are mainly peripherally located but are thought to play a role in mediating pre-conditioning.

The use of adenosine for stress testing and induction of systemic (and coronary) hyperemia is primarily related to the activation of A2A receptors and the resultant increase in myocardial blood flow.

The Human Coronary Microcirculation and Adenosine

The coronary microcirculation is a key regulator of myocardial blood flow. Through alterations in microvascular resistance, the microcirculation controls the delivery of blood to the myocardium over a wide range of perfusion pressures and myocardial oxygen demand through the process of autoregulation (16). In humans, coronary blood flow can increase up to 5 times the basal flow to meet increased demand (17). Such an increase in blood flow is referred to as a hyperemic response and in humans is commonly observed in response to ischemia and exercise (18,19). Quantifying the hyperemic response is a critical step in understanding the coronary circulation and is applied in most physiological assessments of myocardial blood flow. Maximal hyperemia can be achieved through a variety of methods. Exercise is commonly used, but the ability of some patients to exercise is limited. Vessel occlusion to produce ischemia (20) (and thus reactive hyperemia) is another method used in animal models but is not practical or safe to be used in humans not undergoing percutaneous coronary intervention (PCI) due to the inherent risk of vessel injury. Pharmacologically induced vasodilation is a commonly used method of achieving hyperemia in the noninvasive and catheter laboratory settings. Available agents include adenosine, papaverine, sodium nitroprusside, adenosine 5′-triphosphate, and dobutamine (Table 1). Practically, the ideal hyperemic agent should have a rapid onset of action, short duration of action, low cost with no significant side effects (21). For these reasons, adenosine, administered via either the intracoronary or IV route, has become the most widely used method of achieving hyperemia in clinical practice.

The Case for Adenosine

Despite extensive use of adenosine in animal experiments, there was some reluctance to use it for interrogating the