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REVIEW ARTICLE

Selective Adenosine A2A Agonists May Change Myocardial Perfusion Imaging

Kazuya Takehana, MD, PhD

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Abstract

In recent years, the requirement for pharmacological stress myocardial perfusion imaging (SPECT) has increased, and adenosine stress testing is now the mainstream. Selective adenosine A2A receptor agonists will be applied clinically in the future. By selectively activating only A2A receptors, it can reduce complications such as bronchospasm, hypotension, and bradycardia, which have been problems with adenosine stress tests. In addition, since this drug can be administered in bolus injection, it has the advantage of being able to perform the test at one root.

Keywords: Myocardial perfusion imaging, Pharmacological stress agents, Regadenoson, Selective adenosine agonists

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Exercise stress testing is used in symptomatic intermediate-risk patients who can exercise and who have interpretable electrocardiography results. Since its sensitivity is directly related to its ability of increasing myocardial oxygen demand, the amount of exercise must be sufficient for proper evaluation, which may consequently limit its utilization (1). An adequate diagnostic exercise stress test requires reaching 85% of the maximal predicted heart rate (2). In patients who cannot fulfill this target due to abnormalities involving the respiratory system or having ongoing systemic problems limiting their mobility, or when baseline electrocardiogram is abnormal such as with left ventricular hypertrophy, left bundle branch block (LBBB), paced rhythm, Wolff Parkinson White (WPW) syndrome, or greater than 1 mm ST-segment depression, pharmacological stress testing is considered. Pharmacological stress test can replace in patients who cannot exercise. Adenosine, dipyridamole, and adenosine A2A receptor agonist, such as regadenoson, binodenoson or apadenoson (Figure 1), which are coronary vasodilators exert their effect on coronary flow reserve (CFR) directly by increasing the coronary flow. The main purpose of a stress test is to assess the extent and adequacy of the ability to increase the flow of the coronary circulation, reflecting CFR. Ischemic symptoms begin when there is an imbalance in either myocardial supply or demand, resulting in stiffening of the myocardium and abnormal wall motion. Coronary artery disease is diagnosed when there is stenosis of the coronary arteries and a stress test induces hypoperfusion and restricted blood flow. The effect of exercise stress on CFR is mainly indirect: increased heart rate leads to greater oxygen demand in the myocardium, which in turn increases CFR. In contrast to exercise and dobutamine, these agents induce perfusion heterogeneity in stenosed segments rather than inducing flow demand and subsequent ischemia.

Adenosine receptors

Adenosine function is regulated via four G protein-coupled receptors: A1, A2A, A2B, and A3 (Table 1 and Figure 2). Of these four receptors, the A2A receptor is involved in anti-inflammatory and protective effects against cholesterol accumulation. By modulating the cholesterol transport pathway, adenosine can improve cholesterol balance, thereby protecting macrophages from lipid overload and foam cell formation. A2A receptor agonists have both athero-protective and anti-inflammatory effects. The pharmacological effects of methotrexate are mediated by the release of adenosine and the activation of A2A receptors. Some antiplatelet agents also antagonize the adenosine diphosphate-mediated action on P2Y12 receptors, which reduce platelet activation and adhesion, reducing thrombotic occlusion of atherosclerotic

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Division of Cardiology, Department of Medicine II, Kansai Medical University, Osaka, Japan

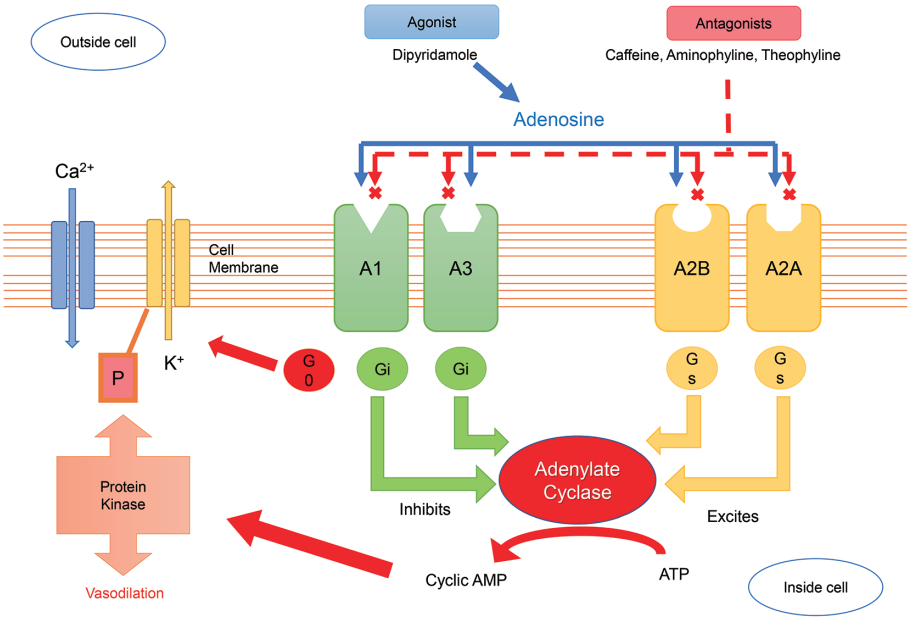

Figure 1　Chemical structures of adenosine and the selective A2A receptor agonists.

Table 1　Distribution and action of each adenosine receptors (modified from Zoghbi and Iskandrian (5))

Receptor type	Location	Action	Distribution
A1	SA node	Negative dromotropic, inotropic and chronotropic effects	SA block, AV block
	AV node	Preconditioning	Cardiovascular protection
	Atrial myocyte	Chest pain production	
	Ventricular myocyte	Tachypnea production	
A2A	Smooth muscle cells	Coronary vasodilatation	Increase of coronary blood flow
		Peripheral vasodilation	Flushing
		Anti-inflammatory effect	Hypotension
		Sympathetic stimulation	
A2B	Smooth muscle cells	Vasodilation in most vascular beds	Bronchoconstriction
		Vasoconstriction in renal afferent arterioles and hepatic veins	Angiogenesis
		Bronchiolar constriction	Gastrointestinal discomfort
	Mast cell degranulation		
A3	Ventricular myocyte	Preconditioning	Cardio protection
		Bronchospasm	

SA: sinoatrial, AV: atrioventricular

arteries (3).

Adenosine is a naturally occurring, non-selective agonist of all subtypes of adenosine receptors. It is inhibited by dipyridamole, thus increasing the intrinsic adenosine concentration since the widespread actions of adenosine include effects on multiple organs and systems including the heart (4, 5), nervous system (6), adenosine deaminase is the enzyme responsible for its degradation. This non-selectivity produces multiple undesirable side effects, notably, bronchoconstriction via adenosine A2B receptor subtype stimulation, and bradycardia and atrioventricular block via adenosine A1 receptor stimulation (Table 1). In contrast, A2A agonist administration produces coronary vasodilation because only A2A action is activated, thus these side effects do not logically occur, and the test can be performed with a safer and better tolerability profile. Additionally, in contrast that the adenosine must be administered by a continuous intravenous infusion because of its ultrashort half-life, these agents are administered as a single bolus, weight-unadjusted dose, unlike the weight-adjusted infusion dose of adenosine and dipyridamole (7–9).

Pharmacokinetics of regadenoson are triphasic, with coronary blood flow increasing to more than twice baseline at 30 seconds post-dose and decreasing to less than twice baseline at 10 minutes (10). The most common protocol for injection of regadenoson is injected as a bolus and radiotracer

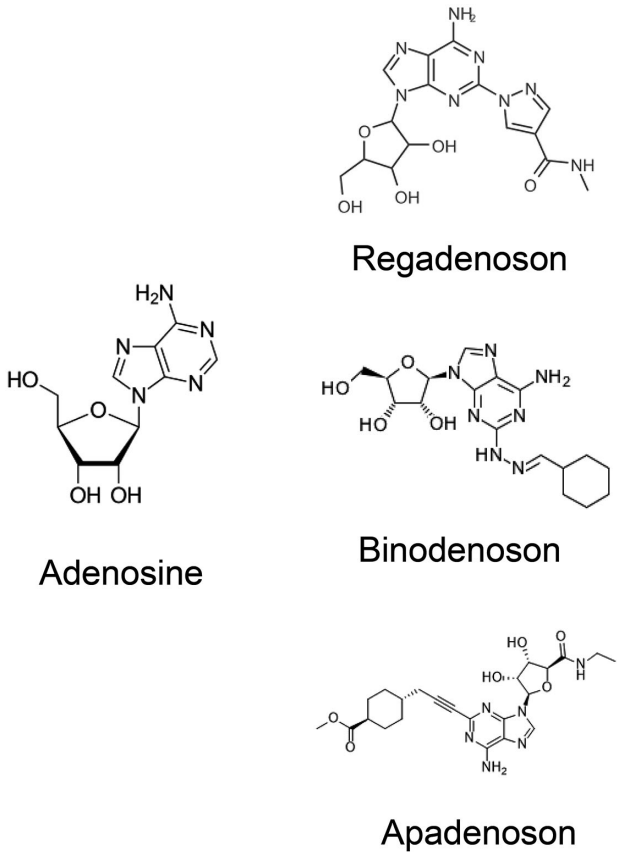

Figure 2 Adenosine receptor subtypes and mode of action.

inject at 30 seconds after vasodilator injection. Although there is no metabolism in the liver and 57% appears unchanged in urine, no dose adjustment is required when regadenoson is used in patients with impaired renal function and/or on dialysis. This ease of administration and the reproducible, comparable efficacy to adenosine with fewer side effects made regadenoson the most widely used pharmacological agent for stress testing in the United States.

It is important to remember, though, that these side effects are not eliminated because the selectivity is not perfect in practice. Regadenoson selectively acts on adenosine A2A receptors and preferentially vasodilates coronary arteries, making it an alternate to adenosine for patients with bronchospastic or bronchoconstricting lung diseases, but the U.S. Food and Drug Administration (FDA) warns against its use in patients with bronchospastic diseases such as asthma and cautions against its use in patients with obstructive lung diseases such as chronic obstructive pulmonary disease (COPD) (11). Brink et al. reported that a significantly higher percentage of patients who received regadenoson experienced at least one side effect compared to patients who received an adenosine stress test (12). It is reasonable to assume that the differences in tolerability are mostly related to the short half-life of adenosine (less than 10 seconds). Regadenoson has a triphasic half-life, usually lasting 15 to 30 minutes.

It has been reported that unpredictable side effects of regadenoson include coronary spasm, cardiac arrest, bradycardia, hypotension, and epileptic seizures (5,13–15). These side effects are not thought to involve the above receptors. Although there are only a few reported cases, all of them are serious events that directly affect the patients prognosis, and therefore, strict monitoring of the patients' conditions is necessary during the use of regadenoson.

Clinical studies

Pharmacological stress myocardial perfusion SPECT imaging used dipyridamole in the last century, but the clinical use of adenosine was approved in Japan in 2005. The use of A2A agonists in animal studies of myocardial perfusion imaging began in the 1990s, and it was shown that the use of A2A agonists resulted in coronary vasodilation with less blood pressure variability (16, 17). Based on these results, the clinical use of A2A agonist was first introduced in the U.S. in 2008, and as of 2013, 83.8% of patients with pharmacological stress testing were loaded with regadenoson (18). Regadenoson, on the other hand, has been approved in the EU for the measurement of fractional flow reserve of a single coronary artery stenosis during invasive coronary angiography in 2019. (https://www.ema.europa.eu/en/documents/product-information/rapiscan-epar-product-information_en.pdf). In Japan, up to Phase II trials have been completed and Phase III trials are currently being conducted for regadenoson. Clinical use of A2A agonists is expected to make pharmacologic stress myocardial perfusion imaging possible in a safer and simpler manner.

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Conflicts of interest

None declared.

Reprint requests and correspondence:
Kazuya Takehana, MD, PhD
Division of Cardiology, Department of Medicine II, Kansai Medical University, 2-5-1 Shinmachi, Hirakata, Osaka, 573-1010 Japan
E-mail: takehana@hirakata.kmu.ac.jp

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