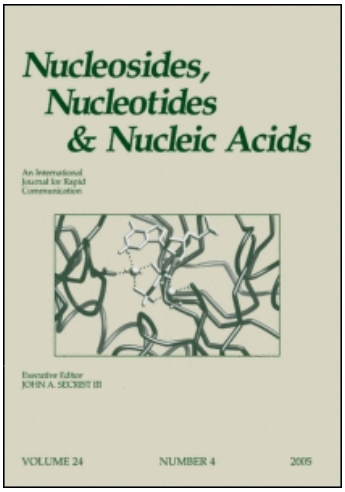

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Role of Adenosine in Energy Supply/Demand Balance

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ROLE OF ADENOSINE IN ENERGY SUPPLY/DEMAND BALANCE

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Abstract. The central paradigm of adenosine research is the idea that adenosine controls energy supply/demand balance. According to this theory, AMP is hydrolyzed to adenosine during conditions of hypoxia, ischemia, or exercise. Adenosine then redresses local energy deficits by reducing energy demand and increasing energy supply.

Scientific Paradigms. A scientific paradigm[1] is an explanatory theory that is accepted by the scientific community. Examples include Maxwell's unified theory of electromagnetism, Einstein's theory of relativity, and Darwin's theory of evolution. To be useful, a paradigm should meet several criteria. It should provide a unified explanation for various related phenomena. These phenomena, however, may not be recognized as related until seen in light of the new paradigm. For example, Maxwell's theory showed that the apparently disparate phenomena of electricity, magnetism, and light were actually different aspects of the single phenomenon of electromagnetism. A paradigm should be logical and internally consistent, as illustrated by each of the above examples. It should also agree with most existing data. Perfect agreement with all existing data may not be possible because of deficiencies in the state of the art. For instance, Darwin's theory of evolution was slow to be accepted because of some very convincing calculations by Lord Kelvin that the Earth was only a few million years old.[2] Only later, with the discovery of radioactivity, was the Earth's age revised to a few billion years, an age that is more consistent with the time-course of evolution. A

paradigm should make verifiable predictions, an example being the predictions of atomic energy and gravitational lensing from special and general relativity, respectively. A paradigm also should suggest new ideas. These may occur as part of an attempt to extend the range of application of a paradigm. For instance, radio waves were predicted from Maxwell's theory by extension of the idea of light waves to lower frequencies. Such new ideas often have important scientific or commercial implications, as illustrated by the above example. Finally, a paradigm is subject to revision as additional information becomes available.

The present article describes the central paradigm of adenosine research, the role of adenosine in energy supply/demand balance.

Metabolic Control of Blood Flow: The Berne Hypothesis. Since the nineteenth century,[3,4,5] it has been known that organs regulate their own blood flow, as illustrated by the phenomenon of reactive hyperemia. In reactive hyperemia, a vessel dilates after the release of a temporary occlusion. To explain this phenomenon, various investigators have proposed the metabolite hypothesis: the idea that blood flow is regulated by a metabolite that accumulates during hypoxia.[4,5,6]

A significant milestone in adenosine research was the proposal in 1963 by Berne[7] and Gerlach *et al.*[8] (anticipated by Lindner and Rigler[9]) that adenosine is the metabolite that increases blood flow during hypoxia. This idea, commonly called the Berne hypothesis, is the forerunner of the current energy supply/demand paradigm. As will be discussed below, this original idea has been both broadened and narrowed over the years: broadened in the sense that it has been expanded from blood flow to energy supply and demand in general; narrowed in that adenosine is not *the* metabolite that regulates energy and blood flow, but one of several such metabolites.

Role of Adenosine in Energy Supply and Demand. The present-day conception of adenosine's role in energy supply/demand[10-12] is illustrated in FIG. 1. An increase in oxygen demand (for instance due to exercise) or a decrease in oxygen supply (for instance due to ischemia or hypoxia) causes net breakdown of ATP. [For the present discussion, oxygen and energy will be used interchangeably; this issue will be discussed further near the end of this article.] Concurrently, levels of ADP and AMP rise. A portion of the AMP is hydrolyzed to adenosine, which diffuses out of the cell and into the surrounding tissue, where it activates A_1 and A_2 adenosine receptors. A_1 receptors, which are usually located on the working cells of a tissue (for instance, neurons and cardiomyocytes), mediate decreases in oxygen demand. A_2 receptors, which in many cases are located on vascular elements, mediate increases in oxygen supply. The net effect of A_1 and A_2 receptor activation is an increase in tissue oxygen levels and a

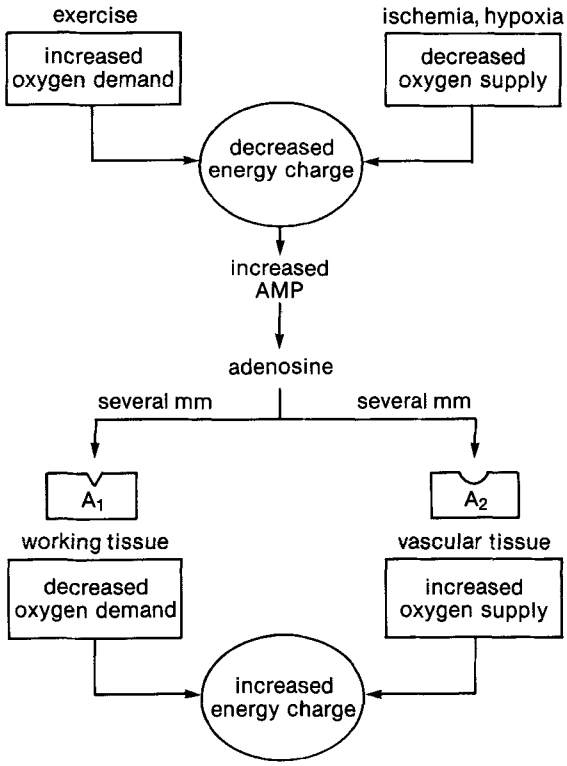

FIG. 1. Role of adenosine in energy supply/demand balance. Modified from reference 12.

return to energy supply/demand balance. The remainder of this article describes the details of the energy supply/demand paradigm and the evidence for (and against) this hypothesis.

Sources of Adenosine. Numerous studies have shown that extracellular adenosine levels rise during hypoxia and exercise. The levels of adenosine produced under these conditions are sufficient to account for reactive hyperemia and other responses to oxygen deficit (reviewed in reference 13). What is the metabolic source of the adenosine that is produced during hypoxia? Several possible sources exist. The longest-studied is the ecto-5'-nucleotidase. This enzyme, which exists in high amounts on the surface of many different cell types, hydrolyzes 5'-AMP to adenosine. Several factors, however, make it unlikely that the ecto-5'-nucleotidase is involved in the breakdown of intracellular AMP. The enzyme is located on the extracellular face of the

plasma membrane, and therefore requires extracellular AMP as substrate. Also, ADP is a powerful inhibitor of the ecto-5'-nucleotidase,[14] so that if any of the enzyme were to be somehow misrouted to the inside of the cell, it would be inactive. The ecto-5'-nucleotidase may be involved in production of adenosine from extracellular ADP and ATP released by platelets and purinergic nerves (see below).

Another potential source of adenosine is from the action of S-adenosylhomocysteine hydrolase. This enzyme, which is intracellular and partly membrane-bound, produces adenosine and homocysteine from S-adenosylhomocysteine (SAH), a side-product of methylation by S-adenosylmethionine. Because biological methylation is not closely linked to the energy status of the cell, it seems unlikely that hydrolysis of SAH is the source of the adenosine that is released during hypoxia. Deussen *et al.*[15] have concluded that SAH hydrolase contributes to basal adenosine release but not to the increase seen with hypoxia.

ATP is released from purinergic nerves,[16] from muscle tissue,[17] and (with ADP) from platelets.[18] Experimental evidence also implies that extracellular ATP is not the main source of adenosine during hypoxia. In depolarized brain slices, the production of adenosine is not blocked by inhibitors of extracellular 5'-nucleotidase, which catalyzes the final step in the breakdown of extracellular ATP to adenosine.[19] Similar results are seen in leukocytes and heart cells.[20,21] Also, adenosine accumulates intracellularly during hypoxia if transport out of the cell is blocked.[21] If the main source of adenosine were extracellular, adenosine would accumulate extracellularly during transport blockade. The adenosine that is produced from extracellular ATP may be involved in negative feedback control of neurotransmitter release (see below).

Only recently has a credible source of hypoxia-released adenosine been identified.[22] A 5'-nucleotidase from pigeon heart has a cytosolic location and shows a 15-fold preference for AMP compared to IMP. Most importantly, the enzyme is *activated* by ADP. Since concentrations of the activator ADP and the substrate AMP rise in parallel during net hydrolysis of ATP, adenosine production should increase in a more-than-linear fashion. Such a system has obvious advantages in an engineering sense: under normoxic conditions, futile cycling due to AMP hydrolysis followed by rephosphorylation of adenosine would be low. Yet during hypoxia high adenosine production would allow a more complete restoration of energy balance.

Local Hormone Role of Adenosine. As a local hormone, adenosine differs from classical neurotransmitters and circulating hormones. Classical neurotransmitters are produced specifically by neurons, are stored in synaptic vesicles, and are released by exocytosis. Many neurotransmitters (for instance, acetylcholine at the neuromuscular

junction) are very short-acting (milliseconds to seconds) and are inactivated inside the synapse (less than 1 micron from the site of release). At the opposite end of the scale, classical circulating hormones are produced by glands and distributed by the circulation, and act for long periods of time (minutes to hours) and at distant locations (in humans, the target can be more than 1 meter from the source of the hormone). In contrast to both of the above, adenosine is produced by many cell types (it is difficult to name a cell that does not produce adenosine), is produced on demand rather than being stored in vesicles, and is released by facilitated diffusion rather than exocytosis. Adenosine's half-life of a few seconds in the circulation ensures that it acts locally, diffusing perhaps a millimeter from the cell in which it was produced.

Roles of Adenosine Receptor Subtypes in Energy Supply and Demand. The two major adenosine receptor subtypes, A_1 and A_2, differ in both structure-activity relationships[23] and effector coupling. The A_1 receptor mediates inhibition of adenylate cyclase,[24,25] opening of potassium channels,[26] closing of calcium channels,[27] and stimulation[28] or inhibition[29] of phosphatidylinositol turnover. Contrariwise, the A_2 receptor stimulates adenylate cyclase;[24,25] it is not clear yet whether the A_2 receptor may also have effects unrelated to adenylate cyclase. The two subtypes also appear to have distinct and complementary roles in regulating energy supply and demand (TABLE 1). A_1 responses almost invariably cause decreases in oxygen demand (reviewed in references 12 and 23). In a few cases (inhibition of breathing, constriction of preglomerular arterioles, inhibition of erythropoietin production), A_1 activation also causes a decrease in oxygen supply. In each case, however, these effects are counteracted by larger A_2 responses increasing oxygen supply. Although most A_2 effects increase oxygen supply (TABLE 1), a few (for instance, inhibition of locomotor activity and relaxation of gut smooth muscle) decrease oxygen demand. These latter effects are still consistent with adenosine's role in energy supply/demand balance. The stimulation of renin release by A_2 agonists increases oxygen demand, but this effect is counteracted by a more powerful A_1 inhibition of renin release.

Many of the effects of adenosine are cytoprotective. Thus, the role of adenosine is not only to control energy supply and demand but also to protect against damage from inadequate tissue oxygenation.[45] Although decreasing oxygen demand and increasing oxygen supply would have protective effects *per se*, several responses to adenosine appear to provide protection independent of oxygen. The A_2-mediated inhibition of neutrophil activation prevents the production of damaging oxygen radicals during reperfusion.[43] Inhibition of excitatory amino acid release[46] protects against neuronal death due to overexcitation. The A_1-mediated inhibition of calcium uptake in the

TABLE 1. Effects of adenosine A_1 and A_2 receptor activation on oxygen supply and demand.

A_1 Receptor Activation

Response	O_2 Demand	O_2 Supply	Reference
Central Nervous System			
↓ locomotor activity	↓		30
↓ neuronal firing	↓		31
↓ transmitter release	↓		32
↓ body temperature	↓		30
↓ breathing (CNS)	↓	↓	33
Cardiovascular System			
↓ heart rate	↓		34
↓ heart force	↓		34
Kidney			
constrict preglomerular arterioles	↓	↓	35
↓ renin release	↓		36
↓ erythropoietin production		↓	37
Adipocyte			
↓ lipolysis	↓		38

A_2 Receptor Activation

Response	O_2 Demand	O_2 Supply	Reference
Central Nervous System			
↓ locomotor activity	↓		39
Peripheral Nervous System			
↑ breathing (carotid chemoreceptor)		↑	40
angina pain	↑		41
Cardiovascular System			
vasodilation		↑	34
↓ platelet aggregation		↑	42
↓ neutrophil activation		↑	43
Kidney			
dilate postglomerular arterioles	↓	↑	35
↑ renin release	↑		36
↑ erythropoietin production		↑	37
Gastrointestinal System			
relax gut smooth muscle	↓		44

heart[47] and brain[27] protects against damage from calcium overload. The angina pain caused by adenosine[41] prevents overexertion that could cause cardiac damage. This presumed A_2 effect thus indirectly causes a decrease in oxygen demand. Inhibition of lipolysis (A_1),[38] inhibition of vascular smooth muscle proliferation (A_2),[48] and stimulation of angiogenesis (A_2)[49] by adenosine hint of a long-term antiatherogenic role for adenosine.[45]

Evidence for a protective role of endogenous adenosine is also beginning to emerge. Inhibition of adenosine deaminase protects gerbils from ischemic brain damage[50] and improves the recovery of ATP levels in the ischemic rat kidney.[51] Conversely, selective adenosine antagonists have proconvulsant effects[52] and prevent the hypoxia-induced depression of electrical activity in hippocampal slices.[53] Adenosine antagonists and exogenous adenosine deaminase accelerate the breakdown of ATP and the onset of ischemic contracture in the oxygen-deficient rat heart.[54,55]

Evolutionary Origin of the Adenosine System. Phosphorylation potential is the ratio of ATP concentration to the product of the concentrations of ADP and inorganic phosphate:

$$\text{phosphorylation potential} = [ATP] / [ADP]x[P_i].$$

The phosphorylation potential determines whether coupled ATPase reactions go in the forward or reverse direction. Since maintaining ATPase reactions in the forward direction is important for long-term cellular viability, a mechanism for buffering phosphorylation potential during stress could contribute to survival. Such a mechanism could be provided by the sequential actions of adenylate kinase and 5'-nucleotidase. ADP is maintained in equilibrium with ATP and AMP by the adenylate kinase reaction:

$$2\ ADP \longleftrightarrow ATP + AMP.$$

If AMP is removed, the net effect of the adenylate kinase reaction is to convert two molecules of ADP to one molecule of ATP, simultaneously reducing the denominator and increasing the numerator of the ratio that defines phosphorylation potential. Based on the above, it seems reasonable to speculate that adenosine production may have originated as a way of buffering phosphorylation potential by breaking down AMP. The survival value of this mechanism would even apply to unicellular organisms, suggesting that systems for producing adenosine may have preceded a signaling role for the nucleoside.

Relative Importance of Glucose and Oxygen in Short-Term Energy Balance. Aerobic energy metabolism requires both oxygen and a carbon source, commonly glucose. What are the relative contributions of oxygen and glucose to the production of adenosine and the maintenance of energy balance? Oxygen is more important for short-term energy balance. Cellular oxygen stores (in the form of hemoglobin and myoglobin) are only sufficient for a few minutes, and a high percentage of oxygen can be extracted in a single pass through an organ. In contrast, cellular stores of glucose (in the form of glycogen) can last for hours, and a low percentage of glucose is extracted in a single pass. Since the main role of adenosine is to prevent cellular damage from short periods of energy deficit, this role should be more closely related to oxygen than to glucose.

Role of Adenosine in Glucose Metabolism. The above considerations notwithstanding, adenosine does have several actions on glucose metabolism. Most of these actions have the common feature of protecting critical organs (*i.e.*, the heart and brain). Adenosine stimulates glucagon release,[56] thus protecting against hypoglycemia and consequent brain damage. Adenosine stimulates glucose uptake in the heart[57] and adipocytes,[58] the effect in the heart presumably being cardioprotective. In contrast, adenosine inhibits glucose uptake in skeletal muscle.[59] In an engineering sense, the difference between heart muscle and skeletal muscle may stem from the fact that glucose uptake in skeletal muscle should increase lactate output and deplete glucose and oxygen from the blood. Such effects would be antiprotective for the heart and brain. Adenosine also stimulates glycolysis in the heart.[60] By shifting the heart to an anaerobic route of metabolism, this response conserves oxygen at the expense of glucose utilization.

Other Regulators of Short-Term Energy Balance. The importance of adenosine in reactive hyperemia and other responses to short-term energy imbalance can be tested using adenosine antagonists and adenosine deaminase. Although results vary widely from one preparation to the next (reviewed in references 6, 13, 61, and 62), the most common observation is a partial block of reactive hyperemia (30-50%). Occasionally, the outcome is full blockade or no blockade at all. The degree of blockade is highly dependent on tissue, species, stimulus (*i.e.*, hypoxia, exercise, etc.), time, and degree of oxygen deficit. From these results, it is clear that adenosine is not the only regulator of energy supply and demand. Teleologically, such redundancy makes sense, since it would be dangerous to entrust such a critical role to a single substance. Other mediators that may serve in this role include prostacyclin, nicotinic acid, low pH, extracellular potassium, extracellular ATP or ADP (via endothelium-derived relaxing factor), neuropeptides (via the axon reflex), and ATP-inhibited potassium channels. Nicotinic acid may be of particular interest, since it mediates responses analogous to

adenosine A_1 and A_2 responses (inhibition of lipolysis, vasodilation),[63] and could be produced from NAD under metabolic stress much as adenosine is produced from AMP. [Interestingly, NAD may also be an indirect source of adenosine.[64]]

ATP Release and Cotransmission. Presynaptic inhibition by adenosine A_1 receptors may be related to two distinct roles, one in purinergic nerves and the other in all neurons with A_1 receptors. In purinergic neurons (those that use ATP as a neurotransmitter), ecto-nucleotidases in the synaptic cleft break down ATP to adenosine. Via activation of an A_1 receptor, adenosine then inhibits further release of ATP and its cotransmitters, such as acetylcholine, norepinephrine, and neuropeptide Y.[65] In this negative feedback loop, the A_1 receptor essentially acts as an autoreceptor for ATP. All neurons (purinergic and nonpurinergic) have two other potential sources of presynaptic adenosine: intracellular adenosine produced from the surrounding tissue, and ATP released from postsynaptic sources. Many types of muscle tissue release ATP upon stimulation.[17] Intracellular adenosine release would signal the local energy state, while the postsynaptic release of ATP might signal the degree of activation of the target tissue, allowing the organ to respond to future energy demands before an actual energy deficit occurs ("anticipatory hyperemia"). Since all of the above roles protect against overexcitation, they are not incompatible and therefore could have evolved concurrently.

Role of the Low-Affinity A_2 Receptor (A_{2b}). Two subtypes of A_2 receptor have been proposed,[66] a high-affinity receptor whose distribution in the brain is confined to the striatum, nucleus accumbens, and olfactory tubercle, and a low-affinity receptor with a more widespread distribution in the brain. These two receptors, called A_{2a} and A_{2b} respectively, appear to be different proteins.[67] The A_{2a} receptor has nanomolar affinity for adenosine, and virtually all of the A_2-mediated physiological responses cited earlier are attributable to the A_{2a} subtype. What, then, is the role of the A_{2b} receptor? Solid evidence on this point is lacking, so at present it is only possible to speculate, based on what little is known about this receptor. The affinity of adenosine for the A_{2b} receptor is low, generally around 10 μM, or far above the nanomolar concentrations that would occur physiologically. Under what conditions could this receptor be activated? It would appear that quite a severe stimulus might be necessary to attain sufficient levels of adenosine: for instance, complete ischemia or a major systems failure such as cardiac arrest. Another important aspect of this receptor is its wide distribution, including most brain areas, the heart,[68] and many cultured cell lines. Interestingly, the A_{2b} receptor is often colocalized with A_1 receptors, for instance in neurons[66] and cardiomyocytes.[68] Its biochemical actions, however, are opposite to those of the A_1

receptor, since it causes an increase rather than a decrease in cyclic AMP. Putting these different actions together, it is possible to assemble a highly speculative picture of the role of this receptor. The A_{2b} receptor may exist to reactivate the heart and brain during a life-threatening systems failure such as cardiac arrest. Under such an immediate peril, the protective role of the A_1 receptor would be unimportant and the A_1-mediated depression of function would be counterproductive. The A_{2b} receptor may therefore exist to override such protective mechanisms and marshal all remaining resources toward resuscitation. The above hypothesis, although consistent with what is known about the A_{2b} receptor, has meager factual evidence to support it at present. Even if this speculation is incorrect, however, it will have served a useful purpose if it focuses attention on the role of this poorly understood receptor.

Conclusion: Evaluation of the Energy Supply/Demand Paradigm. How well does the energy supply-demand paradigm fulfill the criteria of a useful paradigm? A strong point of the theory is its unification of the diverse actions of adenosine, which have little in common except protection against hypoxia. The paradigm even appears to encompass some of the more unusual responses to adenosine, such as renal vasoconstriction and stimulation of the carotid chemoreceptor. The energy paradigm also appears to be logical and internally consistent, since the role of adenosine makes sense in an engineering respect and should contribute to the survival of the individual. The paradigm also agrees with the vast majority of existing data. The few exceptions (for instance, stimulation of renin release by A_2 agonists) could be due to developmental or evolutionary constraints. The paradigm also makes verifiable predictions, and tools are becoming available to test these predictions. Agents that interfere with the role of adenosine, such as adenosine deaminase and adenosine receptor antagonists, should have antiprotective effects. [However, such agents may still be therapeutically useful in situations where adenosine causes an undesired depression of function.] Conversely, agents that potentiate adenosine, such as nucleoside uptake blockers and allosteric receptor enhancers, should bolster the protective role of adenosine. Confirmation of these predictions is beginning to appear. Finally, the paradigm suggests new approaches, such as the use of adenosine potentiators for treatment of ischemia.

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