Adenosine in exercise adaptation

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By influencing the regulation of the mechanisms of angiogenesis, erythropoietin production, blood flow, myocardial glucose uptake, glycogenolysis, systolic blood pressure, respiration, plasma norepinephrine and epinephrine levels, adenosine may exert a significant effect on the body's adaptation response to exercise. However, adenosine's possible influence over the vasodilatory response to exercise in skeletal muscle is controversial and more research is required to resolve this issue. Various popular exercise training methods, such as cyclic training, interval training, and the 'warm down' from training may increase adenosine levels and thereby might enhance the response of adenosine-influenced adaptive mechanisms. Among the several classes of drugs which may enhance extracellular adenosine levels and thereby might augment adenosine-influenced adaptive mechanisms, are the anabolic steroidal and some readily available non-steroidal anti-inflammatory drugs (NSAIDs).

Keywords: Anabolic steroids, angiogenesis, erythropoiesis, non-steroidal anti-inflammatory drugs

Adenosine formation and metabolism

Adenosine, a purine, is a metabolic product of ATP with a half-life in human blood¹ of about 10 s. It is reformed into adenosine triphosphate (ATP) and excess amounts are enzymatically converted via the purine catabolic pathway sequence, to inosine, hypoxanthine, xanthine and finally uric acid (*Figure 1*). Many cell types produce adenosine, including heart², skeletal muscle³ and brain⁴.

Adenosine can be derived from AMP and ultimately ATP (*Figure 1*) and because it has a short half-life, its release parallels metabolic activity in many cell types including heart² and skeletal muscle⁴. These characteristics make this purine an ideal barometer of the local activity of exercising muscle tissue. A high rate of ATP breakdown, such as occurs during exercise, results in high levels of adenosine^{3,5}. This adenosine can overwhelm the purine catabolic pathway (*Figure 1*) in the cell and the excess moves out, accumulating in the extracellular space and blood. Adenosine's enzymatic breakdown continues

in the blood, its brief half-life resulting in a localization of higher adenosine concentrations in the areas experiencing the most adenosine synthesis. Lowering the rate of ATP use results in a net re-uptake of adenosine by the cells and subsequent enzymatic breakdown or reformation into ATP. High blood and extracellular levels of adenosine give this purine access to the body's extracellular regulatory receptors, through which adenosine may exert various regulative effects on the body's complex adaptation response to exercise.

Immediate responses to exercise

In many tissues, including skeletal muscle, heart and brain, adenosine is a potent vasodilator⁶. It dilates blood vessels in response to anoxia (low oxygen concentration)^{3,7} and possibly in response to hypercapnia (high blood carbon dioxide concentration)⁸. This dilatory response takes place during even short bouts of hypoxia or hypercapnia (< 1 min) and is part of the body's initial response to metabolic stress. Since the half-life of adenosine is relatively short, those tissues that produce adenosine would be the primary target of benefits which may be derived from enhanced adenosine levels. This allows the body to make an appropriate, localized and graded, adaptive response to exercise stress. The effects of adenosine on skeletal muscle vasodilation are found to be dose-dependent and ischaemic exercise increases the plasma concentration of adenosine⁹. Furthermore, ischaemic contraction of skeletal muscle increases the venous concentration of adenosine within the

Figure 1. A summary of the breakdown of ATP and the formation of adenosine with its subsequent reformation into ATP or enzymatic breakdown via the purine catabolic pathway (ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate)

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vaso-active range¹⁰. Interestingly, dipyridamole, an adenosine agonist which inhibits cellular re-uptake of this purine and thereby promotes elevated extracellular levels of adenosine^{11,12}, produces coronary blood flow effects which approximate exercise¹³⁻¹⁵ and is used in thallium-201 (²⁰¹Tl) perfusion scintigraphy in the detection of coronary artery disease in patients unable to exercise^{16,17}. However, tissue blood flow is a complex response and other vasodilator responses are involved as demonstrated by the adenosine antagonist caffeine which attenuates, but fails to abolish, the increased blood flow response to anoxia (low oxygen concentration)⁷ and hypercapnia (high carbon dioxide concentration)⁸ in rat brain where blood flow is thought to be largely influenced by adenosine under the above conditions⁴.

In addition, adenosine's role as a physiological vasodilator in skeletal muscle is not clearly established. Some observers have suggested that adenosine can contribute up to 40% of the vasodilation observed during isometric twitch contraction of the cat gracilis muscle¹⁸. However, other observers have reported that exercise hyperaemia of dog hindlimb is not reduced by the antagonism of adenosine receptors¹⁹. Furthermore, some observers have suggested that adenosine influences skeletal muscle blood flow in high-oxidative-slow-twitch fibres but not in low-oxidative-fast-twitch fibres²⁰ while others suggest that more adenosine is released from low-oxidative-fast-twitch fibres than from high-oxidative-slow-twitch fibres of skeletal muscle²¹. Several other reports have indicated that adenosine either is²²⁻²⁵ or is not²⁶⁻²⁹ involved in the hyperaemic response to exercise. More investigation is needed on adenosine's possible role as a skeletal muscle vasodilator.

Adenosine also acts as a respiratory stimulant in man as was first demonstrated in 1985³⁰. Further experiments have revealed that the increase in respiration is principally due to an increase in tidal volume with the inspiratory flow rate increased and the expiratory duration decreased during adenosine infusion³¹.

Subjects who receive high intravascular doses of adenosine experience pain and discomfort, with maximal pain or discomfort preceding maximal blood flow rates⁹. Adenosine was confirmed as the source of pain or discomfort when glycerol trinitrate was used to provoke a similar increase in flow to that of adenosine, in the same subjects, but failed to produce any subject distress. These results suggest that adenosine acts to alert an individual, via pain and discomfort, to the approach of maximal work levels and that further large work increases are not possible. Additionally, elevated adenosine levels are found to potentiate insulin-stimulated myocardial glucose uptake in a dose-response dependent manner with myocardial glucose uptake response to adenosine more sensitive than the vasodilator response³². This allows the myocardium to use glucose in the manufacture of ATP at a faster rate and as a result forestalls exhaustion. Adenosine also stimulates glycogenolysis (glycogen breakdown) in the isolated perfused rat liver³³, promoting glucose formation, and thereby helps to maintain the energy supply to the cell.

Other investigators have demonstrated that adenosine also increases heart rate, systolic blood pressure, plasma norepinephrine and epinephrine and it is hypothesized to be a part of the activation of the sympathoadrenal response³⁴.

Long-term responses to exercise

After exercise metabolic rate falls but for some time remains higher than in the basal condition. Since in skeletal and heart muscle tissue extracellular adenosine levels parallel metabolic activity, adenosine levels also fall, but for some time remain higher than in the pre-exercise state. These elevated postexercise adenosine levels may continue to exert an influence on the body's adaptation to exercise.

One of these adaptations may be angiogenesis (new blood vessel formation). Adenosine enhances new blood vessel growth in both normal and hypoxic conditions^{35,36}. Adenosine-induced angiogenic growth in these studies was abolished by agents which antagonize the action of adenosine. Further evidence of adenosine's regulatory action in angiogenesis was demonstrated with dipyridamole, an adenosine re-uptake inhibitor. Chronic administration of dipyridamole results in angiogenic growth in both the heart³⁷⁻³⁹ and skeletal muscle^{40,41}.

Another action of adenosine may be in the regulation of the production of the hormone erythropoietin. Erythropoietin is produced in the kidney and stimulates erythropoiesis (red blood cell production) in the bone marrow. Increased adenosine levels enhance erythropoietin production in mice⁴²⁻⁴⁴. Theophylline, a chemical relative of caffeine, and an adenosine antagonist (as is caffeine), abolishes adenosine-induced increases in erythropoietin production⁴⁴ and reduces erythropoietin production in normal individuals as well as in patients with erythrocytosis (excess red blood cell production) after renal transplant⁴⁵.

Exercise adaptive mechanisms

The role of adenosine in influencing the above adaptive mechanisms has some important implications in the field of exercise training.

First, athletes in training may receive the greatest erythropoietic and angiogenic adaptive benefits by creating high systemic levels of adenosine. Since adenosine production is dependent on the energy stress level and the rate of use of ATP, it follows that stressful training with high levels of ATP use per unit of time would increase adenosine levels and thereby enhance adenosine-influenced adaptive responses. This may be, in part, an explanation for the necessity of interval training. All athletes, even those whose sport requires an effort for a period of hours (i.e. marathon runners, triathletes, marathon cross-country skiers and road-race cyclists), require interval training to achieve peak performance. The higher levels of adenosine produced as a result of the increased rate of ATP utilization per unit of time during interval training may promote adenosine-influenced adaptive responses necessary for the enhancement of performance.

Second, exercise adaptation through adenosine-influenced regulatory mechanisms may also explain the success of cyclic training. Cyclic training is the practice of following a high-stress training period with one or more low-stress training period(s). Adenosine's influence is dependent on a high rate of ATP use. Glycogen is the chief carbohydrate storage molecule in animals. Glycogen is converted to glucose via glycogenolysis (glycogen breakdown) with the resulting glucose being converted to ATP via aerobic glycolysis (glucose breakdown) and the citric acid (Krebs) cycle (manufactures ATP). Although the levels of intramuscular ATP are never fully depleted, presumably as a cellular protective mechanism, glycogen stores are much more variable. Several consecutive days of high-stress training bouts can deplete skeletal muscle glycogen reserves⁴⁶ and blood glucose levels⁴⁷ thereby limiting the rephosphorylation of ATP ($\text{ADP} + \text{P} \rightarrow \text{ATP}$; Figure 1) which reduces the rate of ATP resynthesis and potentially results in an ultimate decline in both ATP and adenosine levels. Indeed, in a recent study, 3 days of consecutive running or cycling at 75% of $\dot{V}\text{O}_{2\text{max}}$ resulted in a reduction of skeletal muscle glycogen stores, blood glucose and uric acid synthesis (an adenosine metabolite; Figure 1) in human subjects⁴⁷. This can result in the exhaustion stage of the general adaptation syndrome, described by Selye as a stage where further resistance to stress becomes impossible⁴⁸, and results in a failure to adapt. Following a high-stress training session with one or more low-stress training sessions gives the body an opportunity to replenish the glycogen stores from which adenosine can ultimately be derived.

Third, the above evidence also supports the practice of exercise 'warm down'. Exercise 'warm down' is the practice of continuing to exercise for a short time at a low level of stress immediately following a high-stress bout of exercise. This reduced activity would presumably produce some adenosine adding to the high-stress postexercise adenosine levels and extending their recovery time to basal levels thereby promoting adenosine-influenced adaptive responses.

Finally, no discussion of chemistry and athletics would be complete without acknowledging the potential for abuse. Many chemical agents reduce the cellular re-uptake of adenosine in animals⁴⁹ and they probably act in the same manner in humans. Inhibition of the cellular re-uptake of adenosine is effective in increasing adenosine levels as demonstrated by dipyrindamole, an adenosine re-uptake inhibitor, which increases adenosine levels when administered orally to human subjects¹¹. Drugs which reduce the cellular re-uptake of adenosine include some of the drugs in each of the following categories: (1) anabolic and corticosteroids; (2) anti-convulsants; (3) antidepressants; (4) antihistamines; (5) coronary vasodilators; (6) non-steroidal anti-inflammatory drugs (NSAIDs); and (7) some antibiotics⁴⁹. The two most likely categories to be involved in athlete abuse are anabolic steroids and NSAIDs.

Anabolic steroids are drugs which enhance athletic performance and are banned in international athletic contests. They have many actions, one of which is the

reduction of adenosine cellular re-uptake by some of these agents⁴⁹. With regard to adenosine's activation of mechanisms which promote endurance performance (i.e. angiogenesis and erythropoiesis), it has been observed that androgenic hormone therapy increases erythropoiesis in humans⁵⁰. It is also interesting to note that when rats were 'sprint trained' to deduce whether or not Ben Johnson received benefits from anabolic steroid use in his 1988 Olympic 100-m run, researchers from South Africa concluded that he may have received endurance but not speed benefits⁵¹. Whether or not he may have gained benefits in acceleration was not addressed by these observers and will require further investigation. Many authors have written about the abuse of steroids in athletics. Some of the more undesirable side-effects of steroid abuse are altered liver function⁵² and possible myocardial infarction⁵³. A current approach to the steroid abuse problem is to educate abusers and younger potential abusers about the undesirable side-effects of the misuse of steroids and provide alternatives such as strength training and appropriate nutrition⁵⁴.

In contrast to steroids, NSAIDs are not banned in international competition and many are available over the counter at a reasonable price. NSAIDs inhibit the enzyme cyclo-oxygenase, responsible for the production of prostaglandins (local hormones)⁵⁵. This mechanism was first proposed by Vane in 1971 who, in 1982, received the Nobel Prize partially in recognition of this discovery. Since 1971, inhibition of prostaglandin synthesis has been found to be the common denominator in NSAID actions with their potency of inhibition *in vitro* paralleling their anti-inflammatory potency *in vivo*. NSAIDs are usually abused in connection with relief from the pain of injury, e.g. those marathon runners who use NSAIDs to relieve pain from overuse injuries enabling them to carry on training⁵⁶. The potential exists for further abuse of NSAIDs by using them to enhance adenosine levels and thereby realize an improved response to the adenosine-influenced adaptive mechanisms involved in exercise. Although it has not been directly demonstrated that NSAIDs increase adenosine levels, it is likely that some do since several are adenosine re-uptake inhibitors⁴⁹, and inhibition of cellular re-uptake is an effective means of increasing adenosine levels^{11,12}. Furthermore, dipyrindamole acts as an analgesic⁵⁷ as do NSAIDs. Dipyrindamole's analgesic effect is probably due to adenosine's ability to depress the firing of central neurones⁵⁸. Finally, increasing blood flow is a primary action of adenosine⁶ and the NSAIDs indomethacin and meclofenamate have also been shown to increase blood flow following sustained, maximal isometric contractions in dog gracilis muscles⁵⁹. Similarly, the NSAIDs indomethacin and ibuprofen enhance anoxia-induced hyperaemia (increase in blood flow) in rat brain, an action likely to be mediated by adenosine⁶⁰.

Athletes might now have the ability to obtain an agent (NSAIDs) which may enhance athletic performance, that is available over the counter, and easier to obtain than alcohol or tobacco. Furthermore, over-the-counter NSAIDs are commonly viewed by the

general public as being largely without risk.

An example of the problems this may generate is the recent concern over the possible use of epoetin by athletes as a form of 'blood doping'⁶¹⁻⁶³. Epoetin (Epogen, Amgen, Thousand Oaks, California, USA) is a recombinant DNA-derived form of human erythropoietin which can increase haematocrit levels (red blood cell density)⁶⁴ and thereby enhance the performance of athletes who participate in endurance events⁶¹⁻⁶³. Since elevated adenosine levels stimulate erythropoietin production⁴²⁻⁴⁴ and many common NSAIDs reduce the cellular re-uptake of adenosine⁴⁹ and therefore are likely promoters of adenosine levels, performance in athletic endurance events could be augmented with NSAID use during training. This could present a unique dilemma for those involved in athletics. The interesting idea that NSAIDs may, over time, augment performance via their agonistic effect on adenosine is unproven and requires more research with exercising humans.

All commonly available NSAIDs, including acetylsalicylic acid (Aspirin), acetaminophen (Tylenol) (McNeil Consumer Products, Fort Washington, Pennsylvania, USA) and ibuprofen (Advil (Whitehall Laboratories, New York, USA) or Motrin (Upjohn, Kalamazoo, Michigan, USA)) reduce extracellular adenosine re-uptake by the cell⁴⁹. They can cause gastrointestinal microbleeding and the chronic NSAID abuser risks serious side-effects including anaemia⁶⁵, hepatopathy (liver damage)⁶⁶, nephropathy (kidney damage)⁶⁷ and hearing loss⁶⁸. Furthermore, a higher incidence of urothelial cancer (cancer of the urinary tract) is exhibited by NSAID abusers⁶⁹.

However, the association between urothelial carcinoma and NSAID abuse is not well defined and may ultimately be associated with other factors. The possible long-term side-effects of NSAIDs make their administration most acceptable for short-term use and indeed, the adenosine-mediated blood flow-enhancing effects realized with NSAID use⁵⁹ may speed the healing of injuries⁷⁰.

Adenosine is likely to play a major role in the body's complex adaptation to exercise. Although other adaptive regulators may exist, adenosine's short half-life and the fact that its formation parallels the rate of local metabolic activity make it an ideal modulatory agent for many of the mechanisms regulating adaptive processes. Since the current work on angiogenesis and erythropoiesis is based on non-exercising animal and human models additional research using exercising humans is required to confirm the effects of adenosine enhancement or inhibition on the adaptive mechanisms of angiogenesis and erythropoiesis. Future research may reveal other roles for this purine in the human body's complex adaptation to exercise.

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