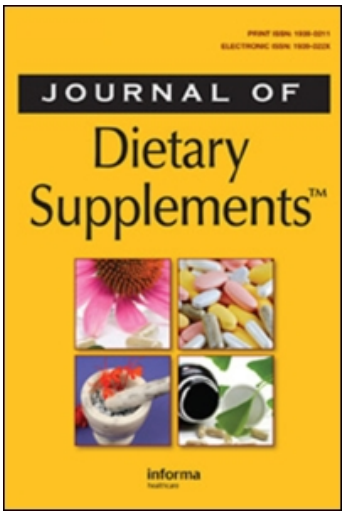

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Ribose in the Heart

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ABSTRACT. Every cell needs energy, i.e., adenosine triphosphate (ATP), to carry out its function. Decreased oxygen levels, decreased blood flow, and other stressful conditions can drastically effect the intracellular concentrations of these energy compounds. Skeletal muscle, unlike the heart, can address this drop in ATP by employing the myokinase reaction, ultimately producing ATP with a subsequent elevation in adenosine monophosphate (AMP). Ribose, a naturally occurring 5-carbon monosaccharide, is a key component of RNA, DNA (which has deoxyribose), acetyl coenzyme A, and ATP. Each cell produces its own ribose, involved in the pentose phosphate pathway (PPP), to aid in ATP production. States of ischemia and/or hypoxia can severely lower levels of cellular energy compounds in the heart, with an associated compromise in cellular processes, ultimately reflected in altered function. Ribose appears to provide a solution to the problem in replenishing the depressed ATP levels and improving functional status of patients afflicted with cardiovascular diseases.

KEYWORDS. Ribose, heart function, ATP

Every cell needs energy, i.e., adenosine triphosphate (ATP) to carry out its function. Decreased oxygen levels, decreased blood flow, and other stressful conditions can drastically effect the intracellular concentrations of these energy compounds. Skeletal muscle, unlike the heart, can address

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TABLE 1.

Energy Needed to Fuel Physiological Function in the Heart Under Controlled Conditions	Relative Need for Maximal Energy the Cell		Effect of Ischemia and Hypoxia on Heart Energy Levels	
Calcium pumps	−52 kJ/mol	High	Control	−58.4 kJ/mol
Sodium/potassium pumps	−48 kJ/mol	Medium	12-minute hypoxia ($pO_2 \sim 20$ Torr)	−51.6 kJ/mol
Contraction	−46 kJ/mol	Low	12-minute zero-flow ischemia	−43.7 kJ/mol

Adopted from Ingwall (2002).

this drop in ATP by employing the myokinase reaction, ultimately producing adenosine triphosphate (ATP) with a subsequent elevation in adenosine monophosphate (AMP) (Ingwall, 2002; Zimmer, 1996). AMP can be catabolized to nucleosides (such as inosine and hypoxanthine), which leak from the cell, limiting the restoration of adenine nucleotides (Ingwall, 2002). When adequate levels of oxygen are reestablished, a concerted effort to regenerate ATP levels sets in motion, halting any further losses. However, adenine nucleotide concentrations return very slowly because of the loss of ATP precursors from the cell and low activity of key pathway enzymes within the cell (Ingwall, 2002).

Are concentrations of ATP important? They are critical! The integrity, cellular chemical reactions, and the intended function of each cell are directly dependent upon quantifiable levels of ATP. Insufficient levels of ATP can severely affect intracellular processes and function (Table 1). For example, low ATP levels are found in chronic myocardial ischemia, including congestive heart failure (CHF). This state of deficiency leaves the heart energy-starved, which many have referred to as a "metabolic disaster" (Ingwall, 2002).

Ribose, a naturally occurring 5-carbon monosaccharide, is a key component of RNA, DNA (which has deoxyribose), acetyl coenzyme A, and ATP. Each cell produces its own ribose, involved in the pentose phosphate pathway (PPP), to aid in ATP production (Zimmer, 1996). Normally, ribose is available to produce these necessary compounds, which is not the case in disease, hypoxia, or stressful states. Further, not all tissues have the same ability to drive the PPP. Liver, mammary glands, and adrenal glands have an abundance of the enzymes that drive the PPP. These enzymes are present in the heart; however, their activity is much slower (Ingwall, 2002;

Zimmer, 1996). This sluggish activity is not an issue for DNA or RNA but is important for the production of ATP. Through the Krebs cycle, ATP is generated by the rephosphorylation of ADP, as glucose and oxygen are converted to CO_2 and water, provided there is an adequate supply of oxygen (Ingwall, 2002). However, when oxygen is insufficient, the cell ceases to function effectively, and production of ATP is compromised. Ribose, on the other hand, has been shown to play a key role by synthesizing new ATP, independent of oxygen availability (Ingwall, 2002; Pauly & Pepine, 2000; Zimmer, 1996).

Supplemental ribose is well tolerated and rapidly absorbed, reaching peak blood levels within 30–45 minutes. Ribose is transported into each cell through phosphorylation by ribokinase to ribose-5-phosphate, as it crosses the cell membrane. Excess available ribose not transported into the cell is excreted by the kidneys unchanged (Gross, Reiter, & Zollner, 1989; Segal & Foley, 1958). Ribose has been reported to have some adverse effects. Even as a sugar, ribose may induce a mildly transient, usually asymptomatic state of hypoglycemia (Segal & Foley, 1958). Gastrointestinal symptoms, such as nausea, loose stools, and, rarely, diarrhea, have been reported, as well as lightheadedness if consumed on an empty stomach (Pliml, von Arnim, Stablein, et al., 1992). With meals or with another carbohydrate, there are fewer occurrences of these potential side effects.

Clinical studies have reported significant functional improvements and subjective benefits in patients with cardiovascular diseases. Omran, Illien, MacCarter, et al. (2003) reported in a double-blind, randomized, crossover (dextrose vs. ribose) trial among class II and class III CHF patients that a significant improvement in diastolic function ($p \leq .02$), quality of life, and exercise tolerance ($p \leq .01$) occurred by taking 5gm/ per dose (tid) of ribose. Pliml et al. (1992) found significant benefits in 20 men (45–69 years of age) with documented stable coronary artery disease, who consumed 15 gm (qid) of ribose. Following 3 days of supplementation with ribose, unlike placebo, patients found a significantly longer treadmill-exercise time interval before demonstrating S-T segment depression or the development of angina. No significant subjective or objective changes were found in the placebo group. Carter, MacCarter, Mannebach, et al. (2005) assessed $VO_{2(max)}$and ventilatory efficiency in class II and class III CHF patients in a double-blind crossover study. Ribose or dextrose, 5 gm (tid), was provided for 8 weeks with a 2-week interval between the crossover arms. The patients who were given ribose maintained their $VO_{2(max)}$ measurement and significantly improved their ventilatory efficiency; both parameters did not improve in the placebo. Vijay, MacCarter, Washam, et al. (2005),

also assessing ventilatory efficiency in class III and class IV CHF patients, found the benefits of ribose by using a daily dose of 5 gm/ per dose (tid). Submaximal exercise testing demonstrated a significant improvement in ventilatory efficiency ($p < .01$), stroke volume ($p < .05$), and oxygen uptake ($p < .028$) with supplemental ribose. Further, Perkowski, Wagner, Marcus, et al. (2005) reported a functional benefit of ribose in patients undergoing off-pump coronary artery bypass revascularization. Preoperatively, patients were given oral ribose, 5 gm/ per dose (tid) and showed a 55% improvement in their cardiac index compared to a similarly matched group of patients who did not receive ribose ($p < .01$).

In summary, adequate ATP levels are essential to maintain each cell's integrity and function. States of ischemia and/or hypoxia can severely lower these levels of cellular energy compounds in the heart, with an associated compromise in cellular processes, ultimately reflected in altered function. Ribose appears to provide a solution to this problem in replenishing these depressed ATP levels and improving the functional status of patients afflicted with cardiovascular diseases.

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