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Reviews

Potential Cardiovascular Applications of Glutamate, Aspartate, and Other Amino Acids

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Summary: Cardioplegic solutions rich in the hydrophilic, basic amino acids, glutamate and aspartate, have enhanced myocardial preservation and left ventricular function. This has been demonstrated in assorted animal preparations involving ischemia with and without reperfusion. Published clinical data, though limited, strongly support the contention that these amino acids have myocardial protective properties. Several biochemical mechanisms exist by which certain amino acids may attenuate ischemic or reperfusion injury. Glutamate and aspartate may become preferred myocardial fuels in the setting of ischemia. They may also reduce myocardial ammonia production and reduce cytoplasmic lactate levels, thereby deinhibiting glycolysis. Some amino acids may become substrate for the citric acid cycle. Glutamate and aspartate also move reducing equivalents from cytoplasm to mitochondria where they are necessary for oxidative phosphorylation and energy generation. A rationale exists for the use of an amino acid-rich cardioplegia-like solution in myocardial infarction. These solutions are safe and inexpensive.

Key words: glutamate, aspartate, cardioplegia

Introduction

Amino acid supplements have been shown to reduce hypoxic injury in various experimental preparations. The evidence is strongest for glutamate, fairly strong for aspartate, and circumspect for some other amino acids. Clinical use of amino acids in myocardial ischemia has been largely restricted to cardioplegia solutions, although the potential for other applications exists. The rationale for cardioplegia is to attenuate the myocardial injuries occurring with ischemia and subsequent reperfusion, which are obligatory in cardiac bypass. These same insults to the heart occur with acute myocardial infarction which is treated with fibrinolytic therapy or primary angioplasty. The chemical structures of glutamate and aspartate are shown in Figure 1.

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Myocardial Amino Acid Metabolism

In an aerobic environment, amino acid oxidation accounts for < 5% of energy production, although there is considerable variation depending on substrate availability.[1] L-glutamate is the only amino acid that is extracted by normal myocardium while alanine and glutamine are produced.[2] In ischemia and reperfusion, glutamate and aspartate become preferential fuels. In the first 4 h following cardiopulmonary bypass, the heart does not use carbohydrate or lipid substrates but does take up amino acids, chiefly glutamate.[3] In the setting of hypoxia, cardiac consumption of glutamate and aspartate increases and their tissue levels fall while production of alanine increases.[4,5] Isolated rat heart preparations exposed to global ischemia show an initial increase in glutamate and malate oxidation rates attributed to an increase in the capacity for reduced nicotinamide dehydrogenase (NADH) oxidation.[6] Rabbit heart preparations exposed to anoxia with a glutamate-enriched buffer demonstrate increased oxygen consumption and energy generation that occur because of increased oxidation of glutamate to succinate.[7] Myocardial alanine production and consumption of glutamate appear to be linked and are inversely proportional to the availability of oxygen. In patients undergoing cardiac catheterization, those with coronary artery disease take up more glutamate and release more alanine than those with normal coronary arteries.[8,9] These differences are exaggerated with pacing stress. Magnetic resonance studies in normal controls and patients with coronary artery disease have also shown augmented extraction efficiency for glutamate in the setting of flow reduction.[10] Tissue levels of succinate and

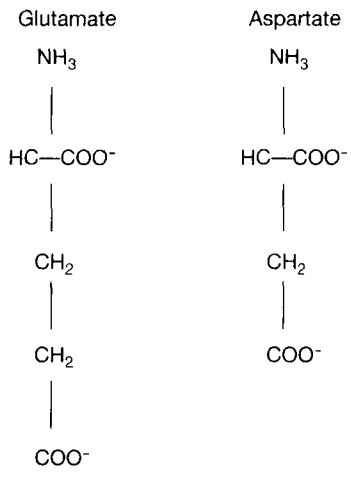

FIG. 1 Chemical structure of glutamate and aspartate.

alanine, which are the anaerobic end products of glutamate and aspartate metabolism, increase in hypoxic injury.[4, 11, 12] Skeletal muscle from diving vertebrates is extremely rich in aspartate aminotransferase and alanine aminotransferase, leading to the hypothesis that these animals rely on anaerobic metabolism of glutamate and aspartate.[13–15]

Mechanisms of Potential Benefit

Several different mechanisms exist by which glutamate might protect against hypoxia (Table I). It does not have significant effects on hemodynamic parameters, although small increases in cardiac output as well as decreases in vascular resistances and heart rate have been observed.[16] Glutamate stimulates insulin secretion and gluconeogenesis.[17] Glutamate is essential for the function of the malate-aspartate shuttle (Fig. 2). The malate-aspartate shuttle effectively moves reducing equivalents (NADH) from the cytoplasm to the mitochondrial matrix where they enter the respiratory chain generating adenosine triphosphatase (ATP). At the same time, cytoplasmic NAD is regenerated permitting glycolysis to continue. Exogenous glutamate in isolated rat hearts has increased transport of NADH into mitochondria while improving glycolysis rates in a postischemic model.[18] Glutamate and pyruvate may undergo transamination, wherein the amino group of glutamate is exchanged for the keto moiety of pyruvate forming alpha-ketoglutarate and alanine. There is at least theoretical benefit to this in anaerobic conditions since lactate is a potent inhibitor of glycolysis. Myocardial ischemia results in the accumulation of free ammonia which inhibits a number of metabolic reactions.[19, 20] Glutamate decreases myocardial ammonia formation and enhances production of glutamine.

TABLE I Theoretical beneficial effects of glutamate in hypoxia

* Increased flux through malate-aspartate shuttle
* Decreased myocardial ammonia production
* Increased alpha-ketoglutarate formation leading to adenosine triphosphatase production in citric acid cycle
* Decreased lactate levels by shunting pyruvate to alanine

Glutamate may also undergo transformation to intermediates in the citric acid cycle. Levels of these intermediate substances decrease normally in ischemia. As the endogenous citric acid cycle intermediates are depleted in ischemia, oxidative phosphorylation may be less efficient when oxygen is restored (reperfusion). Adding amino acid precursors—or citric acid cycle intermediates—counteracts their depletion and has improved postischemic myocardial metabolism, including the function of complex I of the respiratory chain.[21, 22] Alpha-ketoglutarate, the transamination product of glutamate, may be converted to succinate and ATP without molecular oxygen. Alpha-ketoglutarate may also participate in an aminotransferase reaction, with aspartate generating oxaloacetate which is metabolized through malate and fumarate to succinate with the generation of ATP. These two reactions, alpha-ketoglutarate dehydrogenase and fumarate

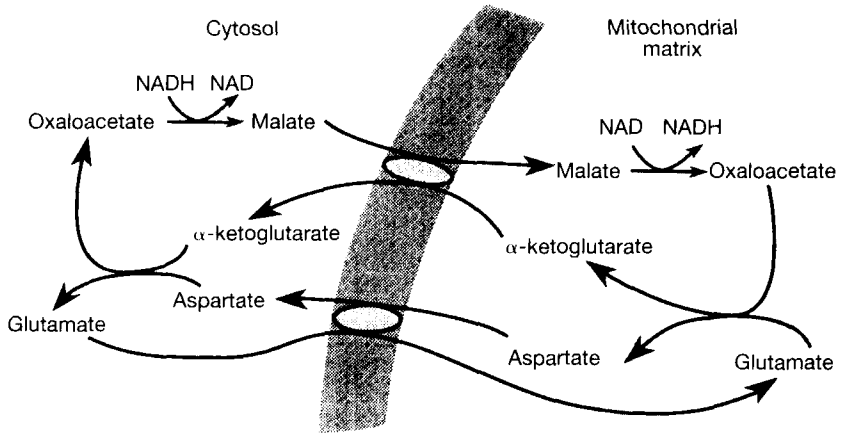

FIG. 2 Malate-aspartate shuttle. NADH = reduced nicotinamide-adenine dinucleotide, NAD = nicotinamide-adenine dinucleotide.

reductase, are in redox balance and lead to succinate production and substrate level phosphorylation in the citric acid cycle. The aminotransferase inhibitor, aminooxyacetic acid, eliminates glutamate consumption and alanine accumulation in hypoxic animal models.[4,23,24] This suggests that the mechanism of action of exogenous glutamate is by intermediary metabolism in the citric acid cycle. Although subject to less study, exogenous aspartate may also undergo anaerobic conversion to succinate, generating ATP independent of the respiratory chain.

Anti-Ischemic Properties—Animal Data

In isolated perfused animal hearts subjected to periods of anoxia, glutamate has attenuated injury and preserved mechanical function. Penney and Cascarano reported improved contractile function and maintenance of tissue levels of glycogen and ATP when rat hearts were anoxically perfused with a fumarate, malate, glutamate solution as opposed to glucose.[25] A comparable benefit was achieved with oxaloacetate and alpha-ketoglutarate. Both amino acid solutions stimulated glucose uptake and lactate output, but the energy expenditure per unit of lactate was increased.

Rau *et al.* used an amino acid solution containing the L-isomers of glutamate, aspartate, arginine, and ornithine to augment the mechanical performance of isolated rabbit hearts.[22] Benefits were apparent during hypoxia and were more marked upon reperfusion. The addition of glutamate to cardioplegia, given to isolated working rat hearts subjected to 30 min of cardiac arrest, resulted in marked preservation of the cardiac output upon reperfusion.[26] This study by Pisarenko *et al.* also found that glutamate decreased the decline in tissue high-energy phosphates and in tissue aspartate while reducing the accumulation of AMP and ammonia. Both glutamate and aspartate reduced myocardial necrosis assessed enzymatically and by histopathology in rats treated with toxic doses of isoproterenol.[27]

Bittl and Shine have also reported salutary effects of glutamate on the isolated rabbit heart subjected to 30 min of ischemia followed by 30 min of reperfusion.[28] Glutamate significantly improved peak left ventricular (LV) pressure following moderate, severe, and total ischemia. Myocardial oxygen consumption was not altered, suggesting the benefits of glutamate were through an anaerobic pathway.

Striking benefits to a metabolic cocktail consisting of glutamate, aspartate, glucose, insulin, potassium, carnitine, catalase, and mercaptopropionyl glycine were noted by Julia *et al.*[29] In this study, immature puppies received metabolic support prior to and during hypoxia while on bypass. The metabolic support group maintained myocardial levels of glutamate and aspartate. The control animals showed a severe reduction in stroke work index, developed metabolic acidosis, and were prone to circulatory collapse, while the metabolic support group experienced none of these problems.

Lazar *et al.* have documented similar benefits to reperfusion with glutamate.[30] Dogs undergoing 15 min of normothermic arrest followed by 30 min of reperfusion demonstrated high oxygen uptakes, less loss of tissue ATP, and more complete recovery of systolic and diastolic function when 26 mmol/l L-glutamate was added to the reperfusate. In another study, the same authors showed that by rearresting the postischemic dog heart with a blood cardioplegia solution containing L-glutamate, there were significant improvements in subendocardial coronary blood flow, oxygen uptake, stroke work index, and LV relaxation.[31]

In sequential experiments, Rosenkranz *et al.* found significant advantages to cardioplegic solutions containing glutamate and aspartate.[32,33] Dogs were exposed to 45 min of global normothermic ischemia to deplete subendocardial energy reserves, reperfused for 30 min, and then exposed to 2 h of aortic cross-clamping with either cold cardioplegia or normothermic cardioplegia enriched with 26 mmol/l L-glutamate followed by reperfusion.[32] The glutamate-treated animals demonstrated improved oxygen uptake and lactate extraction as well as enhanced stroke work index and lower left atrial pressure during reperfusion. These authors found further benefit when aspartate and glutamate were combined in the cardioplegic solution.[33] In this experiment, dogs were again exposed to 2 h of aortic clamping followed by reperfusion. The aspartate plus glutamate treatment resulted in substantial improvements in oxygen uptake, stroke work index, and left atrial pressure. The combination of aspartate plus glutamate was significantly better than glutamate alone, which was better than multidose blood cardioplegia. In a pig model of a reperfused anterior myocardial infarct, systemic infusion of glutamate and aspartate prior to reperfusion resulted in a 38% reduction in infarct size.[34] Wall motion in the infarct zone was improved with high-dose (13 mmol/l) but not low-dose (3 mmol/l) glutamate/aspartate. Myocardial oxygen consumption in reperfusion was increased in the treated animals, although lactate uptake and glucose extraction did not change significantly.

Beyersdorf *et al.* have shown that metabolic support with glutamate, aspartate, glucose, insulin, potassium, coenzyme Q_{10}, and 2-mercapto-propionyl-glycine improves ventricular function in myocardium remote from the acute infarct.[35] In this experiment, the left anterior descending artery of dogs was completely occluded and a 50% stenosis was created in the circumflex artery. After 2 h of ischemia, the study animals received 4 h of substrate infusion. The untreated dogs showed severe hypocontractility of their posterior wall (48% of control systolic shortening) while the dogs treated with the metabolic solution had hypercontractility in the posterior wall relative to preischemia. Three of nine control animals died, with the others developing severe impairment in systolic function; however, the treated animals maintained a stroke work index 91% of the baseline value. Metabolic therapy also prevented reductions in ATP and creatine phosphate in circumflex territory myocardium.

Glutamate added to glucose and insulin improved postischemic oxygen consumption and reduced lactate production in explanted sheep hearts subjected to 8 h of hypoxia, suggesting that glutamate may be beneficial in transplant organ preservation.[36]

Anti-Ischemic Properties—Clinical Results

Clinical trials of glutamate and aspartate are few but favorable. Kjellman *et al.* have reported beneficial effects with alpha-ketoglutarate (28 g) used as a supplement to cardioplegia in men undergoing aortocoronary bypass surgery.[37] In a randomized trial of 24 patients, those treated with alpha-ketoglutarate had reduced release of CK-MB and troponin T, as well as ultimately reduced lactate release. Robertson *et al.* could not demonstrate any benefit for glutamate-enriched blood cardioplegia as opposed to multi-dose potassium blood cardioplegia without glutamate.[38] However, in this small study both cardioplegia solutions offered nearly complete preservation of coronary flow, LV compliance, and LV systolic function. Pisarenko *et al.* found a significant improvement in cardiac index and stroke volume index with a tendency to lower filling pressures when 10 postoperative patients with cardiac failure were treated with a 15 min infusion of L-glutamate.[19] Thomassen *et al.* examined the effects of glutamate in 20 patients with stable angina, each of whom underwent four exercise tests.[39] Both oral and intravenous glutamate significantly increased exercise duration and delayed the onset of ST depression. Glutamate also resulted in a 15–50% reduction in plasma free fatty acid levels before, during, and after exercise. The same group found benefits to intravenous glutamate (12–25 mg/kg) in stable angina patients undergoing increased pacing.[40] Glutamate increased pacing time until the onset of angina by over 50%, significantly decreased ST-segment depression after pacing, and decreased myocardial lactate release by 50%.

Svedjeholm *et al.* have described 16 patients with immediate postoperative cardiogenic shock treated with glutamate and glucose-insulin-potassium (GIK) with favorable results.[41] These patients were treated with a 0.125 mmol/l glutamate solution infused at 65 cc/kg/l in addition to high-dose GIK. Three patients also received aspartate. Three patients who failed to respond rapidly received intra-aortic balloon pumps but could not be weaned from cardiopulmonary bypass. The remaining 13 showed rapid improvement in cardiac index, were weaned from bypass, and survived. In this report, the metabolic solution was given to patients on cardiopulmonary bypass. A more striking result of the same technique applied to perioperative patients with cardiac arrest has been reported by Beyersdorf *et al.*[42] They treated 14 patients with witnessed cardiac arrest (11 postoperative and 3 in the cardiac catheterization laboratory) by instituting cardiopulmonary bypass and infusing a warm blood cardioplegia solution enriched with hypertonic glucose and high-dose glutamate and aspartate (13 mmol/l each). Prior to institution of bypass, these patients underwent unsuccessful conventional resuscitation attempts for a mean of 59 min. Following 20 min of bypass, spontaneous resumption of sinus rhythm occurred in 11 and the other 3 could be paced. Of this group, 3 patients died prior to discharge but 11 went on to long-term survival. Given the duration and nature of the arrests (refractory ventricular fibrillation, electromechanical dissociation, or ventricular fibrillation progressing to electromechanical dissociation), these results are stunning. Extrapolation of these benefits to other scenarios not involving cardiopulmonary bypass is impossible at this time but worthy of further research.

Tolerability, Sequelae, and Cautions

When given intravenously or orally, glutamate and aspartate appear well tolerated and safe. No hemodynamic changes or adverse effects were reported with intravenous boluses of monosodium glutamate in doses of 1.2 and 2.5 mg/kg.[40] Both glutamate and aspartate are constituents of most amino acid hyperalimenation solutions. Monosodium glutamate is felt to be responsible for the so-called Chinese Restaurant Syndrome consisting of paresthesias and chest discomfort. A more significant but unproven concern about glutamate and aspartate is their role as excitatory neurotransmitters. Limited data have suggested that in the setting of cerebral ischemia glutamate may be neurotoxic and that glutamate antagonists may attenuate neurologic damage.[43,44] While studies showing protective effects of glutamate and aspartate in cardioplegia have been cited, it must be acknowledged that there is no consensus on the ingredients of a cardioplegia solution.

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