Effect of selective 3-ketoacyl coenzyme A thiolase inhibition on glucose metabolism in cardiac patients

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Abstract

It has recently been shown that trimetazidine, a 3-ketoacyl coenzyme A thiolase inhibitor, improves overall glucose metabolism in diabetic patients with left ventricular dysfunction. Forearm glucose and lipid metabolism and forearm release of endothelial vasodilator and vasoconstrictor factors during prolonged partial inhibition of fatty acid oxidation by trimetazidine have recently been evaluated in patients with postischemic left ventricular dysfunction. Trimetazidine significantly improved both insulin-induced forearm oxidation of glucose and release of cyclic guanosine monophosphate, whereas forearm release of endothelin-1 was decreased. Although these findings need further confirmation, the combined beneficial effects of trimetazidine on left ventricular function and glucose metabolism make the use of this drug particularly attractive, especially in those cardiac patients in whom abnormalities of both myocardial and glucose metabolism coexist.

Keywords: Trimetazidine, diabetes, glucose metabolism, left ventricular function, endothelial function, 3-ketoacyl coenzyme A thiolase inhibition

Introduction

Regulation of glucose metabolism is an important target in the control of cardiovascular risk factors. Abnormalities of glucose homeostasis range from frank diabetes to a state of insulin resistance, a definition used to indicate a need to increase insulin concentrations in order to maintain normal glycemic conditions. Recent studies have identified a direct relationship between endothelial dysfunction and insulin resistance [1]. Endothelin-1 (ET-1) concentrations have been shown to correlate significantly with fasting insulin concentrations, systolic and diastolic blood pressure, visceral obesity, and triglyceride concentrations, confirming a close relationship between insulin resistance and endothelial function [2]. When present, insulin resistance has been found to be operative in both cardiac and skeletal muscles [3]. Different degrees of endothelial dysfunction associated with a state of insulin resistance have been reported in most cardiovascular diseases, such as hypertension [4], coronary artery disease [5,6], microvascular angina [7], and heart failure [8]. In contrast, insulin resistance is a pathological condition that is rarely diagnosed as a distinct entity. In a recent study, our group showed that more than 50% of patients submitted to coronary stenting for ischemic heart disease and with normal baseline blood glucose concentrations exhibit abnormal hyperglycemia after an oral glucose tolerance test [9]. This abnormality is associated with a higher probability of restenosis [9]. Our results are supported by previous studies showing...

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Effects of selective 3-ketoacyl coenzyme A thiolase inhibition on glucose metabolism

Decreasing increased plasma triglyceride and FFA concentrations could be the first therapeutic option for decreasing the reliance of the heart on fatty acids and overcoming the fatty acid inhibition of myocardial glucose utilization. Indeed β-blockers, by reducing peripheral lipolysis, should reduce FFA availability. Interestingly enough, a recent study has shown that one of the main effects of the β-blocker, carvedilol, is the reduction of FFA utilization in favor of greater utilization of glucose in patients with stable New York Heart Association functional class III heart failure [14]. This change in myocardial energetics could provide a potential mechanism for the decreased myocardial oxygen consumption and improved energy efficiency that is seen with β-adrenoceptor blockade in the treatment of heart failure.

Another approach is to induce muscles directly to reduce FFA utilization in favor of glucose oxidation. In this context, the use of a partial fatty acid inhibitor could have a very specific role. Trimetazidine [1-(2,3,4 trimethoxybenzyl-piperazine dihydrochloride)] has been reported to exert several beneficial effects in cardiac patients, without affecting myocardial oxygen consumption and blood supply [15]. This agent has been shown to preserve intracellular concentrations of phosphocreatine and ATP [16] and to reverse the harmful effects of increased triglyceride concentrations, normalizing the impaired myocardial recovery from low-flow ischemia by decreasing myocardial oxidation of lipid and release of citrate [17]. These effects could be a consequence of the main mechanism of action of trimetazidine – ie, inhibition of oxidative phosphorylation by shifting energy production from FFA to glucose oxidation [3]. This beneficial metabolic adaptation is predominantly caused by a selective block of long-chain 3-ketoacyl coenzyme A thiolase activity, the final enzyme involved in β-oxidation [18]. Partial inhibition of fatty acid oxidation may therefore explain the beneficial effects of trimetazidine in cardiac patients.

Therapeutic approach to abnormal glucose metabolism in cardiac patients

As previously outlined, most cardiac diseases are associated with combined insulin resistance and endothelial dysfunction. In these contexts, improving the cardiac metabolic milieu by partially inhibiting FFA utilization could be particularly effective. In patients with ischemic left ventricular dysfunction, trimetazidine has been shown to exert significant beneficial effects [19,20]. These beneficial effects of the molecule have been incidentally observed to be mainly operative in patients who, in addition to ischemic cardiomyopathy, also have diabetes [21,22] (Figures 1–3). After trimetazidine, there was a clear trend towards a decrease in blood glucose, although the difference compared with placebo was not statistically significant. Conversely, both glycosylated hemoglobin and endothelin were significantly reduced after treatment with trimetazidine. Together, these data indicate a significant trimetazidine-induced improvement in glucose metabolism in cardiac patients. The mechanism of action is related to the property of trimetazidine to facilitate myocardial utilization of glucose instead of FFAs which, in the context of malfunctioning myocardial cells, appear to be deleterious. Interestingly, compounds such as dichloroacetate, which stimulate pyruvate dehydrogenase activity, thereby facilitating glucose oxidation
and inhibiting FFA oxidation, have also been shown to improve left ventricular function in patients with heart failure [23].

Bearing in mind the concept that trimetazidine should, therefore, be able to promote the utilization of glucose and nonfatty substrates by the mitochondria, attention has been focused on this specific issue.

Effects of trimetazidine on endothelial function

It has recently been observed that trimetazidine was able to reduce the release of endothelin in cardiac patients (Figure 3) [21,24]. Growth factors, vasoactive substances, and mechanical stress are involved in the increase in ET-1 concentrations in patients with heart failure. Despite the known adaptive aspect of supporting contractility of the failing heart, persistent increases in cardiac expression of ET-1 in the failing heart have a pathophysiological maladaptive aspect and are associated with the severity of myocardial dysfunction [25].

Trimetazidine-induced reduction in intracellular acidosis in ischemic myocardium [26] could influence, not only myocardial, but also endothelial, membranes. By decreasing endothelial damage, trimetazidine could inhibit ET-1 release — which, in turn, will ultimately decrease myocardial damage. A second hypothesis is that, simply by decreasing the effects of chronic myocardial ischemia, trimetazidine could inhibit the release of ET-1. The observed decrease in ET-1 release that is associated with trimetazidine may therefore be linked to the trimetazidine-induced reduction in myocardial ischemia. Finally, keeping in mind the close relationship between endothelium and insulin sensitivity, the observed effects of trimetazidine on endothelial function could also explain the beneficial action of trimetazidine on glucose metabolism.

Effects of trimetazidine on glucose metabolism

It has recently been shown that, apart from improving left ventricular function in cardiac patients, trimetazidine also improved overall glucose metabolism in the same patients (Figure 1), indicating an attractive ancillary pharmacological property of this class of drug [21]. The known insulin-resistant state in most cardiac patients is certainly aggravated in those patients with overt diabetes. This is particularly relevant in patients with both diabetes and left ventricular dysfunction. In this context, the availability of glucose and the ability of cardiomyocytes and skeletal muscle to metabolize glucose are grossly reduced. Indeed, as a major factor in the development and progression of heart failure is an already reduced availability of ATP, alterations in glucose metabolism could further impair the efficiency of cardiomyocytes in producing energy. By inhibiting fatty acid oxidation, trimetazidine stimulates total glucose utilization, including both glycolysis and glucose oxidation. The effects of trimetazidine on glucose metabolism could therefore be dependent on improved cardiac efficiency, and on improved peripheral extraction and utilization of glucose. Finally, in view of the known relationship between ET-1 concentration and abnormalities of glucose metabolism [1], the observed beneficial effects of trimetazidine on glucose metabolism could also be partly ascribed to the positive effect of the drug on the reduction in ET-1 concentrations.

Animal studies have also suggested that trimetazidine improves blood glucose utilization in rats with fasting hyperglycemia [27]. In this respect, we have recently evaluated both forearm metabolism of glucose and lipid and forearm release of endothelial vasodilator and vasoconstrictor factors during prolonged...
inhibition of β-oxidation by trimetazidine in patients with postischemic left ventricular dysfunction. Trimetazidine increased both insulin-induced forearm glucose oxidation and release of cyclic guanosine monophosphate, whereas forearm release of ET-1 was decreased [28]. Although these findings need further confirmation, the effects of trimetazidine at the skeletal muscle level add a new therapeutic window in the treatment of patients with ischemic heart disease and type 2 diabetes.

Conclusions

Most cardiac diseases are associated with abnormalities of glucose homeostasis, which undoubtedly contribute to the progression of the primary disease. If not adequately treated, in most cardiac patients glucose metabolism abnormalities will contribute heavily to the occurrence of complications, among which severe left ventricular dysfunction is at present one of the most frequent and insidious. In addition to meticulous metabolic control of frank diabetes, special attention should be paid to insulin resistance, a condition that is generally underdiagnosed as a distinct clinical entity. The combined beneficial effects of trimetazidine on left ventricular function and glucose metabolism make the use of this drug particularly attractive, especially in those cardiac patients in whom myocardial and glucose metabolism abnormalities coexist.

* See glossary for definition of these terms.

REFERENCES


