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Brief Rapid Report

Trimetazidine Therapy Prevents Obesity-Induced Cardiomyopathy in Mice

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ABSTRACT

Obesity is a significant risk factor for the development of cardiovascular disease. Inhibiting fatty acid oxidation has emerged as a novel approach for the treatment of ischemic heart disease. Our aim was to determine whether pharmacologic inhibition of 3-ketoacyl-coenzyme A thiolase (3-KAT), which catalyzes the final step of fatty acid oxidation, could improve obesity-induced cardiomyopathy. A 3-week treatment with the 3-KAT inhibitor trimetazidine prevented obesity-induced reduction in both systolic and diastolic function. Therefore, targeting cardiac fatty acid oxidation may be a novel therapeutic approach to alleviate the growing burden of obesity-related cardiomyopathy.

RÉSUMÉ

L'obésité est un facteur de risque important de la manifestation de la maladie cardiovasculaire. L'inhibition de l'oxydation des acides gras est apparue comme une nouvelle approche de traitement de la cardiopathie ischémique. Notre but était de déterminer si l'inhibition pharmacologique de la 3-kétoacyl-Coenzyme A-thiolase (3-KAT), qui catalyse l'étape finale de la oxydation des acides gras, pourrait améliorer la cardiomyopathie de l'obèse. Un traitement de 3 semaines par la trimétazidine, un inhibiteur 3-KAT, prévenait la réduction de la fonction systolique et de la fonction diastolique induite par l'obésité. Par conséquent, le ciblage de l'oxydation cardiaque des acides gras peut constituer une nouvelle approche thérapeutique pour alléger le fardeau croissant de la cardiomyopathie liée à l'obésité.

Rates of obesity are growing at an alarming rate worldwide and are now a threat not only to developed nations but to developing nations as well. Furthermore, obesity is a significant risk factor for cardiovascular diseases such as ischemic heart disease and heart failure.[1] Therefore, there is a growing need to better understand how obesity contributes to cardiac dysfunction so that novel therapies can be developed to target this patient population. One such novel approach involves targeting cardiac energetics, specifically by inhibiting fatty acid oxidation, which has been shown to improve left ventricular (LV) function in patients with both ischemic heart disease and heart failure.[2,3]

Whether inhibiting fatty acid oxidation rates in the heart can improve obesity-induced cardiac dysfunction is unknown, but previous studies in mice have demonstrated that obesity increases the heart's reliance on fatty acid oxidation for energy production,[4] a finding also observed in obese women, which contributes to reductions in cardiac efficiency.[5] Elevated fatty acid oxidation rates in the heart decrease cardiac efficiency through a number of mechanisms, with corresponding reductions in glucose oxidation (oxidation of glucose consumes less oxygen than does oxidation of a fatty acid) and subsequent intracellular acidosis potentially being key contributors to this effect.[6]

Conversely, peripheral inhibition of fatty acid oxidation has been proposed to be a key driver of the lipid accumulation in muscle and liver of obese individuals.[7] If excess fatty acids in obesity are not oxidized, they can be partitioned into lipid intermediates such as ceramide and diacylglycerol, which have been shown to induce skeletal muscle insulin resistance through various mechanisms.[8,9]

A number of studies have now demonstrated that inhibiting fatty acid oxidation rates may actually improve skeletal muscle insulin resistance.[10-12] Furthermore, we have shown that treatment with trimetazidine, an inhibitor of 3-ketoacyl-coenzyme A thiolase (KAT-3) (the last enzyme involved in mitochondrial fatty acid oxidation), does not exacerbate obesity-induced insulin resistance.[13] Because trimetazidine is used clinically in more than 80 countries as a treatment for angina,[3] the aims of this study were to determine whether trimetazidine's metabolic effects may also impart benefit in the setting of obesity-induced cardiomyopathy and support recent findings showing that trimetazidine improves contractile efficiency in obese humans.[14]

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See page 943 for disclosure information.

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Methods

For a detailed description of methods used, please refer to Supplemental Appendix S1.

Results

Treatment with trimetazidine decreases fatty acid oxidation in the isolated heart and in cardiac myocytes

Similar to our findings in the rat heart,[15] treatment of the isolated working mouse heart with 100 μM trimetazidine over the course of a 60-minute aerobic perfusion significantly decreased palmitate oxidation rates (Fig. 1A). These findings were repeated in primary cultures of neonatal rat cardiac myocytes treated with 10 μM trimetazidine (Fig. 1B).

Treatment with trimetazidine does not affect obesity-induced insulin resistance but prevents the development of obesity-induced cardiomyopathy

We placed 26-week-old male mice on a high-fat diet (HFD) for 10 weeks to induce obesity and insulin resistance (data not shown). Starting at week 11, animals received daily intraperitoneal injections of either trimetazidine (15 mg/kg) or vehicle (saline) for a further 3-week period. This treatment protocol did not have further negative effects on body weight gain or obesity-induced glucose intolerance/insulin resistance (Fig. 2, A-C) and did not affect hepatic steatosis (35.50 ± 2.86 [vehicle] vs 35.89 ± 2.87 [trimetazidine] μmol triacylglycerol/g wet weight liver) or plasma lipid profiles (254.89 ± 11.65 [vehicle] vs 258.33 ± 12.26 [trimetazidine] mg/dL fasting plasma triacylglycerol).[13] Using 2-dimensional M-mode ultrasonography/echocardiography, we observed the development of cardiac hypertrophy in obese mice treated with vehicle for 3 weeks as determined by increases in the LV posterior wall and intraventricular septal wall thickness during diastole (Table 1). We also observed mild systolic dysfunction in vehicle-treated obese mice, as indicated by a reduction in LV ejection fraction and fractional shortening (Fig. 2, D and E). Intriguingly, the obesity-induced cardiac hypertrophy and cardiomyopathy were prevented in obese mice treated with trimetazidine (Table 1; Fig. 2, C and D). Assessment of heart weight—tibia length and LV mass—tibia length ratios when the animals were euthanized also demonstrated that trimetazidine treatment reduced obesity-induced cardiac hypertrophy (Fig. 2, F and G). Furthermore, assessment of diastolic function by tissue Doppler echocardiography to measure the early (E) to late (A) ventricular filling velocities revealed diastolic dysfunction in obese mice treated with vehicle for 3 weeks, as seen by a decline in the mitral E′/A′ ratio; however, this was prevented with trimetazidine therapy, suggestive of improved diastolic function (Table 1).

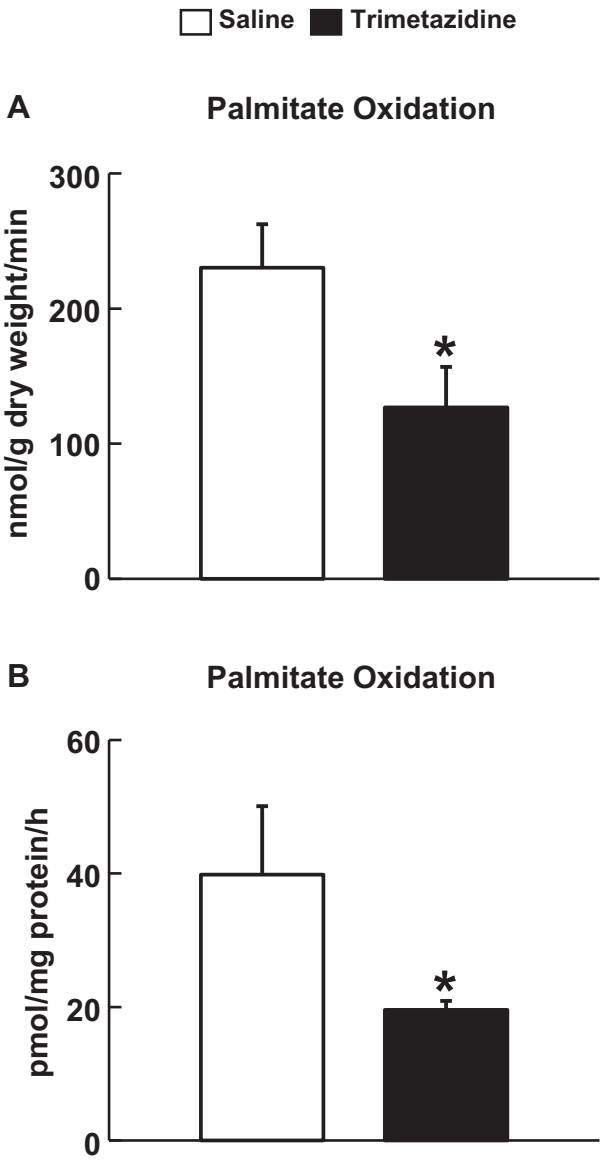

Figure 1. Trimetazidine treatment inhibits *ex vivo* and *in vitro* cardiac palmitate oxidation rates. (**A**) Palmitate oxidation rates were measured in isolated working mouse hearts from C57BL/6 mice perfused for 60 minutes with 5 mM glucose, 0.4 mM [9,10-^{3}H] palmitate prebound to 3% fatty acid free bovine serum albumin (BSA), 100 μU/mL insulin, and either vehicle or 100 μM trimetazidine (n = 5). (**B**) Palmitate oxidation rates were measured in neonatal rat cardiac myocytes cultured for 3 hours in Krebs-Henseleit solution consisting of 11.0 mM glucose and 0.8 mM [1-^{14}C]palmitate bound to 4% fatty acid free BSA and either vehicle or 10 μM trimetazidine (n = 3). Values represent mean ± standard error. Differences were determined with an unpaired 2-tailed Student *t* test. * $P < 0.05$, significantly different from vehicle treated group.

Discussion

This study demonstrates that inhibition of the mitochondrial fatty acid oxidation enzyme 3-KAT with trimetazidine prevents obesity-induced cardiomyopathy. Trimetazidine is used clinically in more than 80 countries to treat patients with angina pectoris because of its metabolic properties.[3] However, because reduced fatty acid oxidation rates in muscle have been proposed to cause insulin resistance in obesity,[7] we initially undertook these studies to determine whether an adverse effect of trimetazidine therapy in humans would be an increased risk of insulin resistance. This question is highly relevant considering that a large portion of patients with ischemic heart disease are also obese and at risk for type 2 diabetes. We have previously reported that contrary to this hypothesis, treatment of obese insulin-resistant mice with trimetazidine did not