Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 495–502

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

The beta-1 adrenergic antagonist, atenolol, decreases acylation stimulating protein, exercise capacity and plasma free fatty acids in men with type 2 diabetes

J. Smith, A. Ferland, J. Méthot, P. Brassard, S. Lacroix, P. Poirier, K. Cianflone*

Y2186, 2725 Chemin Ste-Foy, Institut universitaire de cardiologie et de pneumologie de Québec, Université Laval, Québec, Canada G1V 4G5

Received 21 December 2009; received in revised form 22 June 2010; accepted 18 August 2010

KEYWORDS
Atenolol;
β-blocker;
Acylation stimulating protein;
Exercise;
Type 2 diabetes mellitus

Abstract *Background and aims:* Atenolol is a beta-1 adrenergic antagonist commonly prescribed for the treatment of systemic hypertension or coronary artery disease yet its use in individuals with type 2 diabetes mellitus (T2DM) is controversial due to potentially negative side effects on insulin resistance. Non-esterified fatty acid (NEFA) metabolism is altered in T2DM especially under conditions of metabolic stress such as exercise or the postprandial state. We evaluated atenolol effects on circulating NEFA and related hormones in men with T2DM during acute cardiorespiratory exercise in both the fasting and postprandial state, including the adipokine acylation stimulating protein (ASP) which stimulates adipose tissue NEFA uptake.

Methods and results: Ten men with T2DM underwent four 1-h exercise sessions at 60% of their maximal oxygen uptake (VO_{2max}) under the following conditions: 1) fasting (F), and 2) 2 h postprandial (PP) without medication; and 3) fasting (F-Atenolol), and 4) 2 h postprandial (PP-Atenolol) after a one-week treatment with atenolol. Results were tested for the effects of atenolol via two-way ANOVA for the F vs F-Atenolol and PP vs PP-Atenolol states separately. Atenolol treatment decreased fasting and postprandial glycerol ($p < 0.0001$) and NEFA ($p < 0.0001$), postprandial epinephrine ($p = 0.048$), postprandial cortisol ($p = 0.02$), postprandial ASP ($p = 0.04$) and postprandial dopamine ($p < 0.004$).

* Corresponding author. Tel.: +1 418 656 8711x3731; fax: +1 418 656 4602.
E-mail address: katherine.cianflone@crhl.ulaval.ca (K. Cianflone).

0939-4753/$ - see front matter
doi:10.1016/j.numecd.2010.08.008

Conclusion: Atenolol alters fatty acid metabolism and associated metabolic hormones including ASP during exercise in men with T2DM and its effects are more apparent during conditions of stress such as the postprandial state, acute exercise and obesity.

Introduction

Approximately 5.5% of the population in Canada and 8% of the population in the United States have been diagnosed with type 2 diabetes mellitus (T2DM) [1,2]. T2DM is a complex and pervasive disease causing widespread morbidities in those affected: it is often associated with, or causes, obesity, systemic inflammation, dyslipidemia, micro- and macrovascular damage and hypertension [3]. The risk for systemic hypertension and coronary heart disease are approximately increased two-fold in those with T2DM, compared with the general population [4] and it is estimated that 35%—75% of severe diabetic complications, cardiovascular and renal disease in patients with T2DM may be attributed to hypertension [5].

T2DM is also known to affect adipose tissue function and to change the circulating levels of not only energy substrates, such as non-esterified fatty acids (NEFA), but also several adipose tissue secreted hormones including acylation stimulating protein (ASP) [6]. ASP is produced by adipose tissue and correlates positively with body weight, hyperglycemia and dyslipidemia [7]. It signals through the C5L2 receptor on adipocytes to stimulate the uptake of dietary TG and glucose and decreases lipolysis causing the net effect of increased dietary TG storage. ASP secretion increases within the adipose tissue milieu in response to a meal and decreases with long-term exercise training in healthy young men [8].

Standard treatment and management of T2DM involves a combination of pharmacologic therapy and lifestyle changes [2]. Regular cardio-pulmonary exercise has been shown to be one of the most effective therapies to improve glucose metabolism and insulin sensitivity. However, lifestyle interventions are often implemented in conjunction with drug treatment. Long-term treatment with beta-blockers has been shown to be highly effective in reducing the risk of cardiovascular events and death in T2DM patients post myocardial infarction [9]. Atenolol is a beta-1 adrenergic antagonist which shows more cardioselectivity than general beta-adrenergic antagonists thereby minimizing the unwanted side effects and is one of the most widely prescribed beta-blockers. While the long-term effects of both exercise and beta-blocker treatment have been studied, the acute metabolic effects are just as relevant to the patients' long-term outcomes. Several studies in healthy volunteers have shown that atenolol reduces circulating NEFA and glycerol concentrations and also reduces exercise capacity as measured by time-to-exhaustion [10—12]. However, NEFA metabolism during acute atenolol treatment has not been evaluated in individuals with T2DM where NEFA metabolism is already dysfunctional.

Previous results have shown that acute treatment with beta-blockers (i.e. atenolol 100 mg id for 5 days) was not sufficient to decrease fasting and postprandial insulin concentrations in patients with T2DM, who were free of hypertension and cardiovascular complications [13]. Under the same conditions, beta-blockers had no effect on plasma insulin modulation during sub-maximal aerobic exercise. However, the effects on fatty acid metabolism and adipose tissue hormone secretion were not evaluated.

Acute conditions can exacerbate the metabolic disturbances of T2DM. Many individuals with severe insulin resistance/T2DM may have normal fasting glucose concentrations for several years with severely disturbed postprandial glucose handling [14] . Further, exercise can also cause metabolic stress, causing some individuals with T2DM to experience hypoglycaemia during acute endurance exercise sessions. It is not known how the addition of a pharmaceutical agent, in particular, atenolol, will further alter the metabolic responses during these stressors.

The aim of this study was to evaluate the effect of atenolol on the acute NEFA and ASP response during two metabolic stresses: the postprandial state and an exercise session. We hypothesized that atenolol would attenuate the NEFA release during exercise and the postprandial state and ASP would similarly decrease. The results of this study provide insight into the acute functioning of adipose tissue in T2DM during several metabolic stressors including pharmacotherapy, exercise and food intake.

Methods

Study population

The protocol was approved by the Ethics Committee of Laval Hospital. Ten sedentary men ranging in age from 36 to 64 years with T2DM but free of cardiovascular complications were studied after having given informed consent. Patients were recruited to assess the impact of acute beta-blockade on energy substrate utilization and related hormones during submaximal exercise performed at 60% of their respective maximal oxygen uptake (VO_{2max}), with and without the use of atenolol. Subjects were treated by diet and or oral hypoglycemic agents, which were not taken on the days of the experimentation. No subject was receiving insulin therapy nor was engaged in a regular exercise program for up to 3 months before entering the study. All subjects were instructed to maintain their usual dietary habits, to prevent fluctuations in their weight, until the protocol was completed. Standard clinical and preliminary laboratory examinations showed no evidence of diabetic complications. Previous data on glucose and insulin metabolism during exercise has been previously published on this study population [13].

Measurement of maximal oxygen uptake and baseline plasma values

Two assessments of maximal oxygen uptake (VO_{2max}) were performed in the fasting state, one with and one without the five-day treatment with atenolol, prior to the experimental exercise sessions. The exercise intensity used