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Original Contribution

ORAL ADMINISTRATION OF RAC-α-LIPOIC ACID MODULATES INSULIN SENSITIVITY IN PATIENTS WITH TYPE-2 DIABETES MELLITUS: A PLACEBO-CONTROLLED PILOT TRIAL

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Abstract—α-lipoic acid (ALA), a naturally occuring compound and a radical scavenger was shown to enhance glucose transport and utilization in different experimental and animal models. Clinical studies described an increase of insulin sensitivity after acute and short-term (10 d) parenteral administration of ALA. The effects of a 4-week oral treatment with α-lipoic acid were evaluated in a placebo-controlled, multicenter pilot study to determine see whether oral treatment also improves insulin sensitivity. Seventy-four patients with type-2 diabetes were randomized to either placebo ($n = 19$); or active treatment in various doses of 600 mg once daily ($n = 19$), twice daily (1200 mg; $n = 18$), or thrice daily (1800 mg; $n = 18$) α-lipoic acid. An isoglycemic glucose-clamp was done on days 0 (pre) and 29 (post). In this explorative study, analysis was done according to the number of subjects showing an improvement of insulin sensitivity after treatment. Furthermore, the effects of active vs. placebo treatment on insulin sensitivity was compared. All four groups were comparable and had a similar degree of hyperglycemia and insulin sensitivity at baseline. When compared to placebo, significantly more subjects had an increase in insulin-stimulated glucose disposal (MCR) after ALA treatment in each group. As there was no dose effect seen in the three different α-lipoic acid groups, all subjects receiving ALA were combined in the "active" group and then compared to placebo. This revealed significantly different changes in MCR after treatment (+27% vs. placebo; $p < .01$). This placebo-controlled explorative study confirms previous observations of an increase of insulin sensitivity in type-2 diabetes after acute and chronic intravenous administration of ALA. The results suggest that oral administration of α-lipoic acid can improve insulin sensitivity in patients with type-2 diabetes. The encouraging findings of this pilot trial need to be substantiated by further investigations.

Keywords—Insulin resistance, Insulin-stimulated glucose update, Type 2 diabetes mellitus, α-Lipoic acid, Glucose clamp, Radical scavenger, Free radicals

INTRODUCTION

In the pathogenesis of type-2 diabetes mellitus, resistance of insulin-stimulated glucose uptake and impairment of both nonoxidative and oxidative glucose metabolism play important roles [1,2]. Hyperinsulinemia compensates for decreased insulin sensitivity and euglycemia is maintained as long as insulin secretion can be adequately achieved [2]. Most of the type 2 diabetics are hyperinsulinemic when initially diagnosed and insulin treatment is not necessary [2]. Therefore, interventions in type 2 diabetes mellitus should primarily focus on lowering blood glucose by enhancing insulin sensitivity [2,3], as is successfully done with diet, weight loss, and physical activity [2,4,5]. If these measures cannot achieve good glycemic control, a pharmacologic intervention is necessary.

Skeletal muscle is the major tissue responsible for the postprandial uptake and storage of glucose [6]; as this insulin-stimulated glucose uptake in peripheral tissues is impaired in type 2 diabetes mellitus, substrates that aug-

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ment insulin's action on muscular glucose uptake will also lower blood glucose levels.

Oral antidiabetic agents, such as the sulfonylureas, the biguanides, acarbose, and the thiazolidinediones improve hyperglycemia; they all improve insulin sensitivity via direct or indirect mechansims [7–18]. Although sulfonylureas primarily restore first phase insulin secretion, acarbose reduces the postprandial rise in glucose, and metformin mainly has an effect on hepatic glucose output [7,11,13], the newer agents, like the thiazolidinediones, specifically improve insulin sensitivity [11,12,14]. The latter represent a new group of antidiabetic agents, the insulin action enhancers [14]; however their safety for human use has been questioned after serious liver damage had been reported with troglitazone [14]. At present it is unknown whether this is a class effect or a specific effect of troglitazone; therefore, it will have to be demonstrated that the thiazolidinediones are safe drugs, considering that a chronic treatment is necessary.

Preclinical evidence suggests that thioctic acid may exert its beneficial effects by improving several mechanisms: different experimental models describe an increase of glucose uptake and metabolism by thioctic acid in skeletal muscle [19–22], in L6-myotubes [23], and in the heart [24].

Recently, clinical glucose clamp studies also indicate an improvement of insulin sensitivity after acute and chronic parenteral administration in type 2 diabetics [25–27]. It was, therefore, of interest to see whether these beneficial effects can also be found after the oral administration of the agent.

SUBJECTS AND METHODS

In this pilot trial the metabolic effect of three different dosages of α-lipoic acid (600, 1200, 1800 mg/d; i.e., 600 mg once, twice, or thrice daily) was assessed in a placebo-controlled, randomized multicenter design.

Seventy-four well-controlled subjects with type-2 diabetes participated in this study; they were otherwise healthy, did not suffer from any infectious or malignant disease, or any acute illness. The patients were recruited by their family doctors who followed up on them during the study. They reported to one of the three study centers, located in academic teaching hospitals (Munich and Baden-Baden, Germany) or the department of clinical pharmacology (Asta Company, Frankfurt, Germany) only at the day of the metabolic investigation (glucose clamp).

As standardization of diet and lifestyle is difficult to achieve in an outpatient study population, all participants were asked to maintain their usual lifestyle habits or (concomitant) medication. The impact of changes in diet, weight, and in physical activity on insulin sensitivity was explained to the patients.

Patients on insulin treatment were excluded. Oral antihypoglycemic treatment and other concomitant medication (such as antihypertensives) was continued and was not supposed to be changed. A substantial part of the study subjects were, however, on diet alone. About 20% of the patients already had signs of diabetic complications, such as retinopathy, or polyneuropathy.

Study design

All patients underwent a hyperinsulinaemic isoglycaemic glucose clamp (see below) on two occasions: the first before the initiation of treatment (day 0, PRE), and the second 28 d later (day 29, POST). After the first glucose clamp, they were randomly assigned to either placebo ($n = 19$) or active treatment in various doses of 600 mg once daily ($n = 19$), twice daily (1200 mg; $n = 18$), or thrice daily (1800 mg; $n = 18$) α-lipoic acid (Thioctacid; Asta Medica, Frankfurt, Germany).

Glucose clamp procedure

The glucose clamp was done according to the protocol of DeFronzo et al. [28] with some minor modifications, as described previously [26]. Basically, the fasting blood glucose was held constant (+7%, i.e., "isoglycaemia") during the period of the investigation. The amount of glucose needed to maintain isoglycaemia, the glucose infusion rate (GIR), is an indirect indicator of insulin sensitivity. To determine the efficacy of the glucose utilization, i.e., the metabolic clearance rate for glucose (MCR), GIR is divided by the plasma glucose during the steady state (SSPG). To correct for differences in the steady state plasma insulin (SSPI) achieved during the clamp, GIR is divided by SSPI to obtain the insulin sensitivity index (ISI). In this study, MCR was taken as the main indicator of insulin sensitivity.

Additional measurements

Routine laboratory parameters were determined before each glucose clamp in all the study subjects. They were analyzed with commercially available test kits, as described previously [29].

Ethics

Each subject had been informed about the purpose and the risks of the study and had given their written consent. The study protocol was in accordance with the Declaration of Helsinki, and was accepted by the independent ethical committees of the General Medical Councils of Hesse, Bavaria, and Baden-Württemberg.

Table 1. Patient Description—Anthropometric Data

		Placebo	Thio 600	Thio 1200	Thio 1800	Active treatment
N		19	19	18	18	55
Age	Mean ± SEM	60.4 ± 2.4	58.1 ± 2.8	60.9 ± 2.2	62.1 ± 3.0	60.3 ± 1.5
Sex	Male	12	10	11	10	31
	Female	7	9	7	8	24
BMI	Mean ± SEM	28.9 ± 1.0	29.9 ± 1.3	29.2 ± 0.9	29.2 ± 0.9	29.4 ± 0.6

Statistics

Values are indicated as mean + SEM, unless otherwise stated. Statistical analysis was done according to intent to treat, but when analysis was done per protocol, results were essentially the same (data not shown). In this explorative study, treatment group comparison was done according to the number of subjects who experienced an improvement of insulin sensitivity after treatment using cross tabulation and Chi-square test. The target parameter was the change in insulin sensitivity as measured by the MCR. As there was no effect of the different dosages in the three treatment groups, these groups were taken together as the "active" group for further analysis. The latter was compared to the placebo treated control group. The Kruskal-Wallis analysis of variance was used.

RESULTS

All four groups were comparable regarding age, sex, body weight (Table 1), concomitant disease, and medication (data not shown). However, as a group, the whole study population was quite heterogeneous and represented a wide range of age (34–81 years), weight (50–129 kg), and duration of diabetes (3 months to 30 years). Late complications (polyneuropathy or retinopathy) were present in 14(19%) of 74.

Safety

The study medication was well tolerated and no serious adverse events were reported; the rate of side effects was somewhat higher in the placebo group. Some patients reported symptoms similiar to minor hypoglycemic episodes. In a few subjects, oral antidiabetics, such as glibenclamide dosage, had to be reduced due to hypoglycemic symptoms.

Anthropometric data

During the study, mean body weight and the hemodynamic parameters (blood pressure or heart rate) remained stable in all groups. However, in some subjects, body weight was modified (range: −4.0 kg vs. +7.0 kg).

Laboratory parameters measured before and after treatment revealed no difference.

Metabolism

At baseline, all groups had a similar quality of long-term metabolic control (HbA1c), degree of fasting hyperglycemia and insulin resistance (Table 2). However, in each group these values varied considerably over a wide range within each group.

At baseline, insulin stimulated glucose disposal was markedly impaired in the patients (Table 2), as indicated by a lower MCR for glucose when compared to a healthy group [26].

After treatment, glucose uptake improved significantly more often in those groups that had active treatment (Fig. 1). While the MCR decreased by −10% in the placebo group, insulin sensitivity increased by +15% after 600 mg, +14% after 1200 mg and +22% after 1800 mg (NS). Due to the small sample size and the considerable variations in the insulin sensitivity, however, the treatment induced changes in each group, failed to reach a statistical significance when considered separately. Fasting plasma glucose revealed no change, whereas fasting insulin showed a trend towards lower levels (NS).

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Table 2. Patient Description—Metabolic Data at Baseline

Baseline (mean ± SEM)	Placebo	Thio 600	Thio 1200	Thio 1800	Active treatment
Fasting Glucose (mg/dL)	143.9 ± 7.6	141.3 ± 7.5	143.6 ± 7.3	136.5 ± 8.0	140.4 ± 3.1
MCR (ml/kg*min)*100	3.02 ± 0.3	3.25 ± 0.4	3.40 ± 0.3	3.30 ± 0.6	3.35 ± 0.16

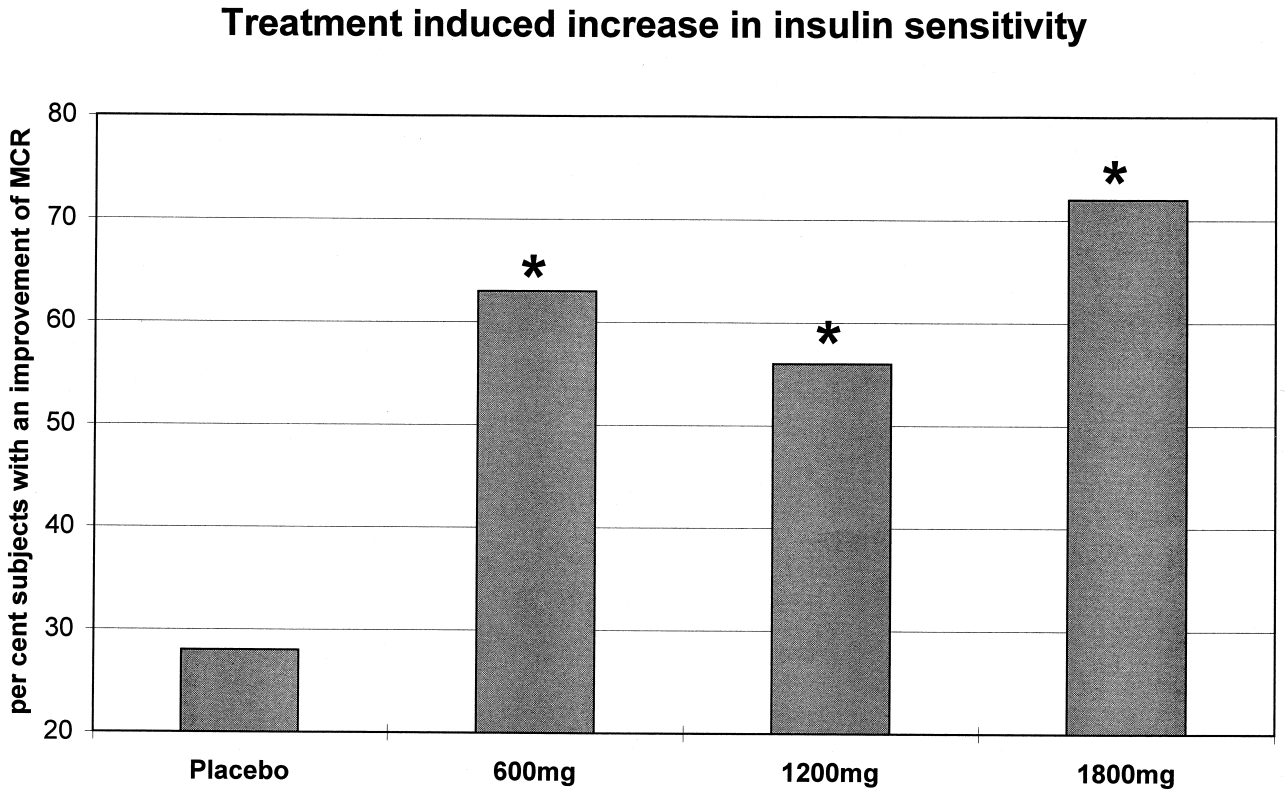

Fig. 1. Treatment induced changes in insulin sensitivity as measured by the glucose clamp method: percent of subjects in each group showing an improvement of MCR; *$p < .05$.

α-lipoic acid on MCR were analyzed, there was no significant difference between these treatment groups. Therefore, all patients receiving α-lipoic acid were combined in the "active" treatment group. When this combined active group was compared to the placebo treated diabetics, there was a significant difference in the change of MCR: while it decreased by -10% in the placebo group, it increased by $+17\%$ after α-lipoic acid (active vs. placebo $+27\%$, $p < .01$, Fig. 2).

DISCUSSION

This pilot trial suggests that a 4-week oral administration of α-lipoic acid can augment insulin sensitivity in type-2 diabetics. The number of patients who showed an improvement of insulin resistance was significantly greater after α-lipoic acid than in the placebo-treated group. When the absolute effects of the active treatment were compared to placebo, the data indicate that while insulin sensitivity decreased slightly in p value, there was a (nonsignificant) increase of MCR in each active group ($+15$–20%); the lack of statistical significance might be due to the small sample size, the short treatment period, and the heterogeneous groups. When the combined active groups were compared with placebo, however, there was a significant difference in the change of insulin sensitivity between active and placebo treatment ($p < .01$).

This explorative study confirms the beneficial metabolic effects of α-lipoic acid previously described: two placebo-controlled studies in type 2 diabetes subjects reported an improvement of insulin sensitivity after acute intravenous infusion with α-lipoic acid 500 mg [27] or 1000 mg [26]. Furthermore, in an open study, insulin sensitivity was also enhanced after 10 d of parenteral treatment with α-lipoic acid (500 mg/d) [25]. In another open study with oral adminsitration (2×600 mg/d) in lean and obese type 2 diabetic patients, α-lipoic acid decreased both serum lactate and pyruvate and improved glucose effectiveness and insulin sensitivity after only 4 weeks of treatment [30].

The data of this present placebo-controlled pilot trial suggest, that α-lipoic acid can enhance insulin-stimulated whole body glucose disposal also after oral administration.

As the study population showed a large variability in age, body weight, duration of diabetes, etc., and as there was no standardization of diet, one could speculate that the treatment effects might have been more pronounced in a more homogeneous study group.

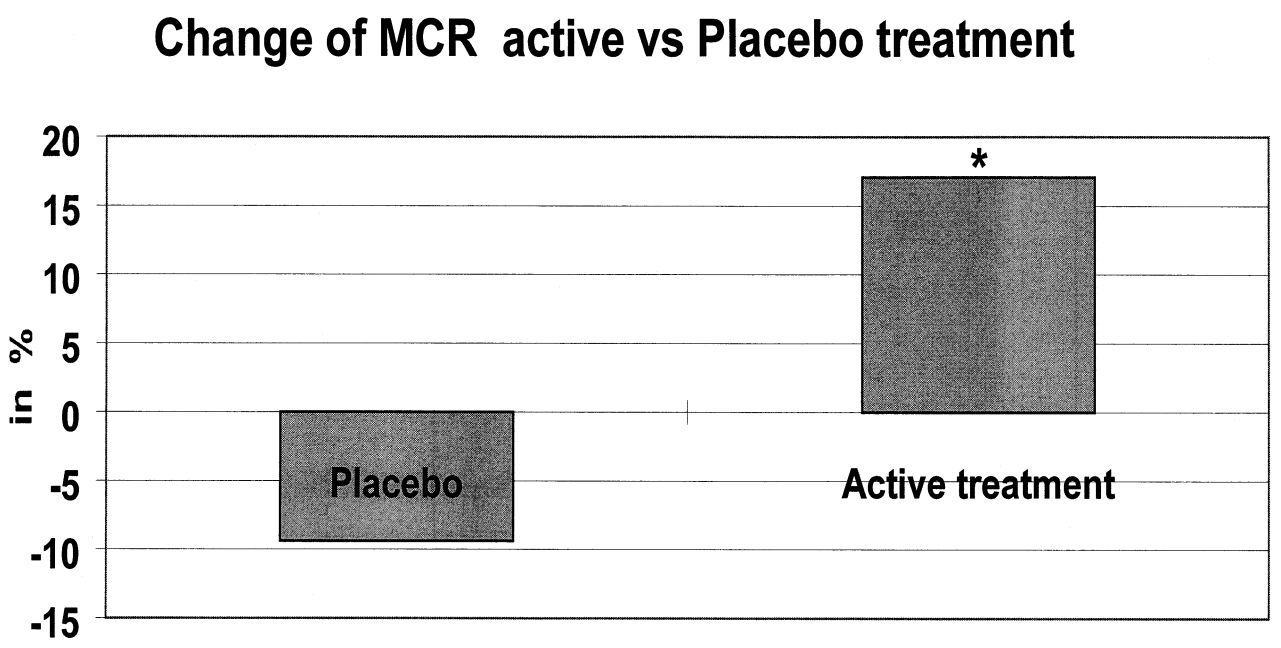

Fig. 2. Absolute effects of active versus placebo intervention on MCR. As there were no differences between the three active treatment groups, they were combined as "active treatment" (see text); $*p < .05$.

Experimental data describe that α-lipoic acid increase glucose uptake in the heart [24,31], in L6-myotubes [23], and in skeletal muscle [19,22,32].

Also, in the obese Zucker rat, chronic administration of α-lipoic acid stimulates the rate of glycogen synthesis, the total amount of glycogen, and insulin-induced glucose oxidation [20,21].

Direct incubation of L6-myotubes or epitrochlearis muscle with α-lipoic acid resulted in an increase of insulin-stimulated glucose uptake, which was additive to insulin [22,23]. When the in vitro incubations were done in the presence of wortmannin, an inhibitor of the pi3-kinase, the effect of α-lipoic acid on glucose uptake was markedly reduced [22,23]. These results indicate that α-lipoic acid uses a part of the insulin-signal-transduction pathway. Very recently it was shown that when erbstatin, an inhibitor of the insulin-receptor tyrosin-kinase was given, α-lipoic acid′s effects on insulin-stimulated glucose uptake are abolished in a similar fashion as insulin′s effect [33]. These data imply that α-lipoic acid uses, in a major part, the insulin signalling chain.

Thus, the preclinical data suggest that α-lipoic acid has an insulin sensitizing potency and are in accordance to the clinical findings in the pilot studies after iv and po administration.

Recent preclinical data suggest that the natural enantiomer [R-(+)-α-lipoic acid] of rac-α-lipoic acid is responsible for the metabolic action of α-lipoic acid. The non-natural enantiomer [S-(−)-α-lipoic acid] even has opposite effects. It downregulates glucose-transporter [23] or increases hyperinsulineamia [21].

Therefore, it is seems more promising to continue further clinical research with the purified pharmacologic active compound.

Currently available data derived from preclinical and clinical studies could serve as a good base for well-controlled clinical studies of sufficient size and duration of treatment to evaluate the antidiabetic potency of chronic administration of the purified metabolic active compound, R-(+)-α-lipoic acid.

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