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Type 2 diabetic conditions in Otsuka Long-Evans Tokushima Fatty rats are ameliorated by 5-aminolevulinic acid

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ARTICLE INFO

Article history:
Received 29 January 2014
Revised 4 April 2014
Accepted 18 April 2014

Keywords:
5-Aminolevulinic acid
Mitochondria
OLETF rat
Type 2 diabetes mellitus
Visceral fat

ABSTRACT

A precursor of protoporphyrin IX, 5-aminolevulinic acid (5-ALA) is used as a prodrug for photodiagnosis and photodynamic therapy. Recently, it has been shown that 5-ALA reduces glucose levels during fasting and after glucose loading in prediabetic subjects. We hypothesized that 5-ALA ameliorates diabetic conditions through mitochondrial changes in visceral adipose tissue. In order to explore the metabolic effects on the type 2 diabetic state, we administered ALA hydrochloride in combination with sodium ferrous citrate to Otsuka Long-Evans Tokushima Fatty (OLETF) rats at intragastric doses of 20 and 300 mg kg^{-1} d^{-1} for 6 weeks. The administration of 300 mg kg^{-1} d^{-1} of 5-ALA improved glucose intolerance, hypertriglyceridemia, and hyperleptinemia in OLETF rats more effectively than the administration of an equivalent dose of metformin, in accordance with reductions in food intake and body weight. Furthermore, the weight of the retroperitoneal fat tended to decrease and cellular mitochondrial content of the fat was markedly reduced by the 5-ALA administration, showing a positive correlation. These results suggest that 5-ALA ameliorates diabetic abnormalities in OLETF rats by reducing the visceral fat mass and mitochondrial content of adipocytes in a site-specific manner.

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1. Introduction

The prevalence of diabetes mellitus has been steadily increasing each year, and it has been reported that the global number of diabetic patients reached 371 million in 2012, with more than 90% of these cases being type 2 diabetes mellitus [1]. Visceral adiposity is usually observed in type 2 diabetic patients and is independently linked to the disease [2,3]. In fact, an improvement in insulin sensitivity is accompanied by a decrease in the visceral fat depot, which provides a critical clue for preventive measures for the disease [4].

It has now been proven that white adipose tissue not only is a lipid storage organ but also functions as an active organ involved in the development of insulin resistance. White

Abbreviations: 5-ALA, 5-aminolevulinic acid; GABA, γ-aminobutyric acid; LETO, Long-Evans Tokushima Otsuka; OLETF, Otsuka Long-Evans Tokushima Fatty; PGC1α, peroxisome proliferator–activated receptor γ, coactivator 1α; SFC, sodium ferrous citrate; TNF, tumor necrosis factor.

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http://dx.doi.org/10.1016/j.nutres.2014.04.013
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adipose tissue secretes adipocytokines such as adiponectin, tumor necrosis factor (TNF) α, and leptin, which are associated with insulin action [5,6]. Furthermore, the hypertrophy of adipocytes affects insulin sensitivity; that is, the larger the size of the adipocytes, the lower the insulin sensitivity [7,8].

Mitochondria are responsible for various metabolic reactions and maintaining cellular energy homeostasis. The mitochondrial contents of adipose tissues in subcutaneous, epididymal, and omental regions have been shown to decrease under diabetic states [9–12], whereas no information is currently available concerning the differences in the mitochondrial contents among visceral fat regions (epididymal, mesenteric, and retroperitoneal fat pads).

Recently, 5-aminolevulinic acid (5-ALA), a naturally occurring precursor of porphyrin, was used for photodiagnosis and photodynamic therapy as a prodrug, in which the photosensitizer protoporphyrin IX is accumulated in cancer cells [13]. Alternatively, it has been reported that the plasma glucose profile was improved during fasting and after glucose loading in prediabetic subjects [14,15]. However, the effect of 5-ALA on type 2 diabetic conditions has not been elucidated.

The Otsuka Long-Evans Tokushima Fatty (OLETF) rat is a model of type 2 diabetes mellitus, which shows metabolic syndrome-like characteristics with visceral adiposity. Visceral fats, especially in the retroperitoneal region, are accumulated from 12 weeks of age, when insulin resistance develops in the rats [16,17].

We hypothesized that 5-ALA ameliorates diabetic conditions through mitochondrial changes in visceral adipose tissue. In order to assess this hypothesis, we administered 5-ALA intragastrically to OLETF rats and examined the effects of the compound on glucose tolerance, visceral fat depots, and the mitochondrial content.

2. Methods and materials

2.1. Animals and diet

At 5 weeks of age, male OLETF rats and Long-Evans Tokushima Otsuka (LETO—used as the nondiabetic control) rats were purchased from Hoshino Laboratory Animals, Inc (Ibaraki, Japan). Throughout the experimental periods, the rats were fed an AIN93G diet containing vitamin mix, mineral mix, vitamin-free casein, cellulose (Oriental Yeast Co, Ltd, Tokyo, Japan), L-cystin, soybean oil (Wako Pure Chemical Industries, Ltd, Osaka, Japan), *tert*-butylhydroquinone (Sigma-Aldrich, St Louis, MO, USA), cornstarch (Matsutani Chemical Industry Co, Ltd, Hyogo, Japan), and sucrose (Itochu Sugar Co, Ltd, Aichi, Japan; Table 1) [18].

Table 1 – Ingredient composition of the diet (AIN93G) fed to LETO and OLETF rats

Ingredient	g/kg diet
Cornstarch	529.5
Vitamin-free casein	200
Sucrose	102.486
Soybean oil	70
Cellulose	50
AIN93G mineral mix (listed below)	35
AIN93G vitamin mix (listed below)	10
L-Cystine	3
tert-Butylhydroquinone	0.014

AIN93G mineral mix (in g/kg mix): calcium carbonate, anhydrous, 357; potassium phosphate, monobasic, 196; potassium citrate, tri-potassium, monohydrate, 70.78; sodium chloride, 74; potassium sulfate, 46.6; magnesium oxide, 24; ferric citrate, 6.06; zinc carbonate, 1.65; manganous carbonate, 0.63; cupric carbonate, 0.3; potassium iodate, 0.01; sodium selenite, anhydrous, 0.01025; ammonium paramolybdate, 4 hydrate, 0.00795; sodium meta-silicate, 9 hydrate, 1.45; chromium potassium sulfate, 12 hydrate, 0.275; lithium chloride, 0.0174; boric acid, 0.0815; sodium fluoride, 0.0635; nickel carbonate, 0.0318; ammonium vanadate, 0.0066; sucrose, 221.026.
AIN93G vitamin mix (in g/kg mix): nicotinic acid, 3; calcium pantothenate, 1.6; pyridoxine-HCl, 0.7; thiamin-HCl, 0.6; riboflavin, 0.6; folic acid, 0.2; D-biotin, 0.02; vitamin B_{12}, 2.5; vitamin E, 15; vitamin A, 0.8; vitamin D_3, 0.25; vitamin K, 0.075; choline bitartrate, 250; sucrose, 724.655.

2.2. Animal treatments

All experimental procedures were approved by the Kyoto Prefectural University Experimental Animal Committee. The rats had free access to feed and distilled water while they were kept in an environment with a 12-hour light/dark cycle at 22 ± 2°C. The body weight and food consumption of the rats were measured every morning. The food efficiency ratio was calculated by dividing the average change in body weight by the average food intake during the 6 weeks of administration.

5-Aminolevulinic acid hydrochloride and sodium ferrous citrate (SFC; kindly provided by SBI Pharmaceuticals Co, Ltd, Tokyo, Japan) were dissolved in distilled water (mole ratio 1:0.05). Metformin hydrochloride (Metogluco; Dainippon-Sumitomo Pharmaceutical Co, Ltd, Osaka, Japan) was suspended in the distilled water. At 28 weeks of age, the OLETF rats were divided into the following 4 groups after evaluation by an oral glucose tolerance test: (1) the control group, receiving distilled water (n = 6); (2) the 5-ALA20 group, receiving 20 mg kg^{-1} d^{-1} of 5-ALA hydrochloride and 3.14 mg kg^{-1} d^{-1} of SFC (n = 7); (3) the ALA300 group, receiving 300 mg kg^{-1} d^{-1} of 5-ALA hydrochloride and 47.1 mg kg^{-1} d^{-1} of SFC (n = 7); and (4) the Met300 group, receiving 300 mg kg^{-1} d^{-1} of metformin hydrochloride (n = 6). The LETO rats (n = 7) were administered distilled water. All of the treatments were performed every morning and continued for 6 weeks (from 29 to 35 weeks of age).

2.3. Oral glucose tolerance test

The oral glucose tolerance test was performed 1 week before (28 weeks of age; Fig. 2A, upper panel) and after 5 weeks of the 5-ALA administration (34 weeks of age). Briefly, after overnight fasting, the LETO and OLETF rats were intragastrically loaded with glucose (2 g/kg), which was followed by blood sampling from the tail vein at 0, 30, 60, 90, and 120 minutes. The blood glucose concentration was measured by the glucose oxidase electrode method (Glucocard; ARKRAY, Inc, Kyoto, Japan).

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