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Effect of long-term nitrite administration on browning of white adipose tissue in type 2 diabetic rats: A stereological study

Tarlan Varzandi[a,b], Mahammad Amin Abdollahifar[c], Seyed Ali Haeri Rohani[b], Abbas Piryaei[c], Azita Zadeh-Vakili[d], Sajad Jeddi[a,*], Asghar Ghasemi[a,**]

[a] Endocrine Physiology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Department of Animal Biology, School of Biology, College of Science, University of Tehran, Tehran, Iran
[c] Department of Anatomical Sciences and Biology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[d] Cellular and Molecular Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Introduction: Nitric oxide (NO) deficiency is associated with obesity and type 2 diabetes. Nitrite, a NO donor, is considered as a new therapeutic agent in diabetes. This study aims at determining effects of long-term nitrite administration on browning of white adipose tissue (WAT) in type 2 diabetic rats.

Methods: Male rats were divided into 4 groups: Control, control + nitrite, diabetes, and diabetes + nitrite. Sodium nitrite (50 mg/L in drinking water) was administered for 3 months. Body weight was measured weekly. Fasting serum levels of glucose and nitric oxide metabolites (NOx) were measured monthly. Histological evaluations and measurement of cyclic guanosine monophosphate (cGMP) and NOx levels in adipose tissue were done at the end of the study.

Results: Nitrite decreased serum glucose concentration and body weight gain in diabetic rats by 27.6% and 37.9%, respectively. In diabetic rats, nitrite increased NOx and cGMP levels in inguinal WAT by 95.7% and 33.1%, respectively. Numerical density in WAT of nitrite-treated diabetic rats was higher than in diabetic ones (995 ± 83 vs. 2513 ± 256 cell/mm^3, $P < 0.001$); in addition, total surface area (4.84 ± 0.32 vs. 44.26 ± 9.7, mm^2, $P < 0.001$) and volume of inguinal beige adipose tissue (7.2 ± 0.49 vs. 66.4 ± 14.51 mm^3, < 0.001) were higher in nitrite-treated diabetic rats compared to diabetic ones.

Conclusions: Favorable effects of long-term nitrite administration in obese type 2 diabetic rats is, at least in part, due to browning of WAT and also associated with increased NOx and cGMP level in adipose tissue. These findings may have potential applications for management of diabesity.

1. Introduction

The prevalence of obesity and type 2 diabetes are increasing worldwide [1]. Obesity and type 2 diabetes are closely associated and diabetes occurring in the context of obesity is today called “diabesity” [2]. The risk of developing T2DM increases 3-fold in overweight and 7-fold in obese subjects [3, 4]. In addition to balance food intake and energy expenditure, obesity is associated with the ratio of white-to-brown adipose tissue [5]. Adipose tissues contain white, brown, and beige (brown-in-white) adipocytes; the beige adipocytes, have a white fat-like phenotype, which in response of appropriate stimuli (e.g. cold exposure), can change to a brown fat-like phenotype, a phenomenon called browning [6]. Beige adipocytes exhibit anti-obesity and anti-diabetic effects [7]. Browning of white adipose tissue (WAT) is impaired in diabetes and obesity [7, 8] and brown adipose tissue (BAT) activity is inversely associated with the percentage of body fat [9–12].

Nitric oxide (NO) deficiency has been reported in obesity and diabetes [13]. Nitrate and nitrite, mainly by their generation of NO, have anti-obesity and anti-diabetic properties and are recommended as a nutrition-based therapy for obesity and T2DM [14–17]. Nitrate/nitrite have several beneficial effects in obesity and diabetes including; decreasing body weight [13, 18, 19], visceral fat accumulation [13], and also fasting glucose levels [13, 18, 20]; nitrate/nitrite also improve glucose and insulin tolerance, and lipid profiles [18, 20, 21].

* Correspondence to: S. Jeddi, Endocrine Physiology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, No. 24, Arabi Street, Daneshjoo Blvd, Velenjak, P.O. Box: 19395-4763, Tehran, Iran.
** Correspondence to: A. Ghasemi, Endocrine Physiology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, No. 24, Arabi Street, Daneshjoo Blvd, Velenjak, P.O. Box: 19395-4763, Tehran, Iran.
E-mail addresses: Sajad.jeddi@sbmu.ac.ir (S. Jeddi), Ghasemi@endocrine.ac.ir (A. Ghasemi).

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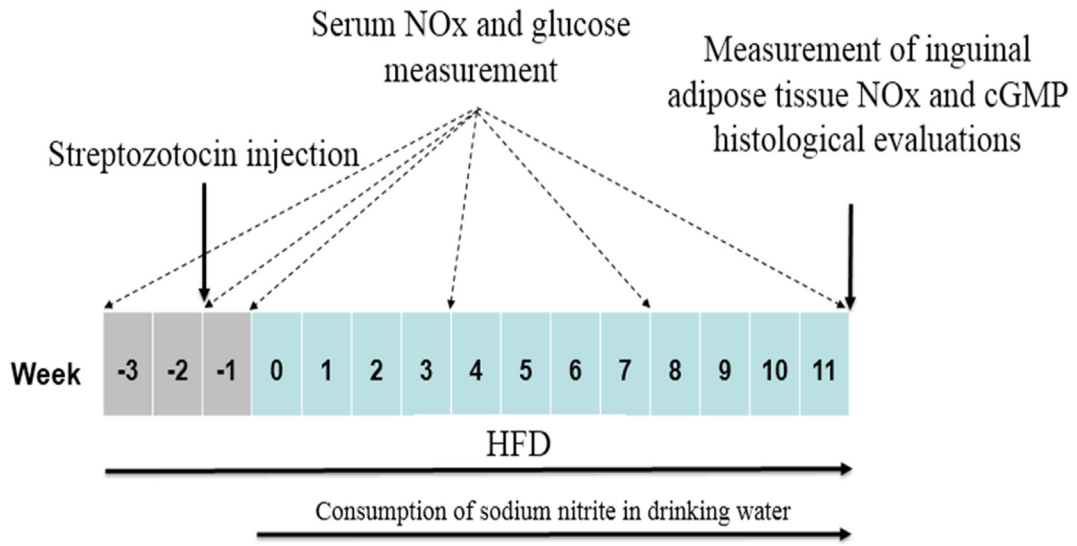

Fig. 1. Timeline of the study. Rats in diabetic groups fed high-fat diet (HFD) throughout the study. Sodium nitrite (50 mg/L in drinking water) was administrated from 3 weeks after HFD and 1 week after Streptozotocin (STZ, 30 mg/kg intraperitonell) injection. NOx, nitrite + nitrate; cGMP, cyclic guanosine monophosphate.

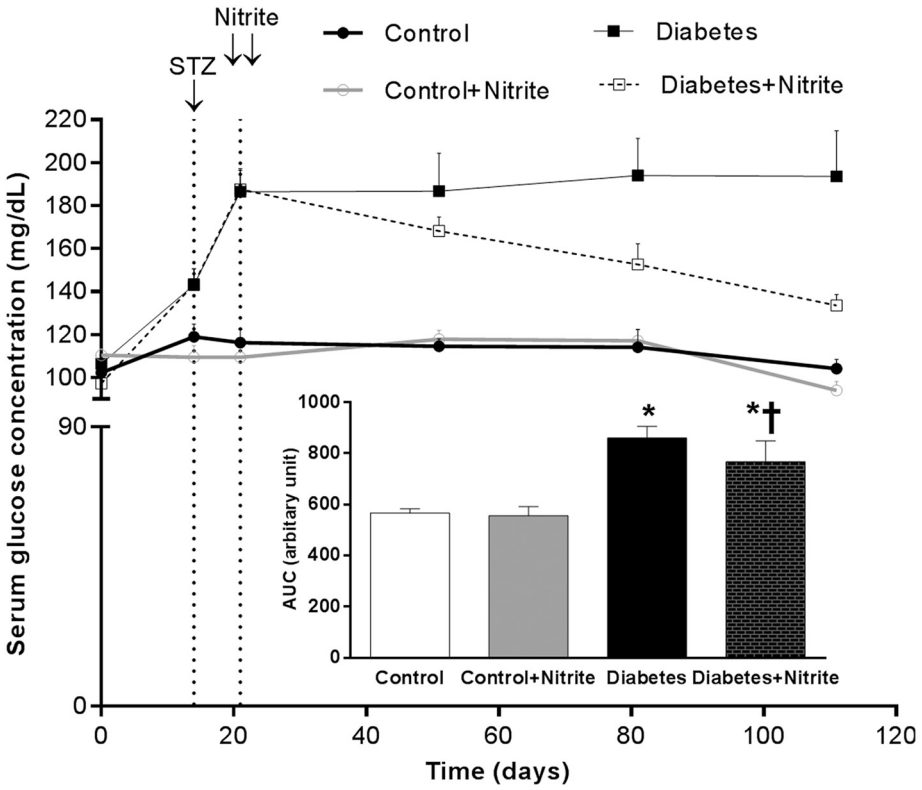

Fig. 2. Effects of sodium nitrite administration on fasting serum glucose. Inset indicates the area under the curves. *, † Statistically significant difference compared to the control and diabetic groups, respectively. Values are mean ± SEM (n = 10/each group). ↓, streptozotocin (STZ) injection (30 mg/kg, intraperitoneally); ↓↓, start of sodium nitrite administration (50 mg/L in drinking water).

According to a recent review, in most animal studies, nitrate and nitrite decrease body weight, without affecting food intake and water consumption [4]; other mechanisms including browning of WAT, may therefore be involved in this decreasing effect; to the best of our knowledge, there is only one study that addresses the effect of nitrate, but not nitrite administration, on the browning of WAT in ob/ob mice [7]. The aim of this study was therefore to assess effects of long-term nitrite administration on browning of WAT in type 2 diabetic rats using a stereological approach.

2. Materials and methods

2.1. Animals and diets

Male Wistar rats (200–220 g) were housed in a rodent facility on a 12 h light/12 h dark cycle under controlled temperature and humidity (23 ± 2 °C and 50 ± 6% respectively), and received ad libitum tap water and standard rat chow and or high-fat diet (HFD). This study was approved by the local ethics committee of the Research Institute for Endocrine Sciences (IR.SBMU.ENDOCRINE.REC.1395.214). Control groups consumed standard rat chow (Pars animal feed) in which 5.7%, 72.2%, and 22.1% of calories are from fat, carbohydrate, and protein, respectively, i.e. a total caloric value of ~3160 kcal/kg. Diabetic