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Anti-obesity and anti-diabetic effects of nitrate and nitrite

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ABSTRACT

Prevalence of obesity is increasing worldwide and type 2 diabetes to date is the most devastating complication of obesity. Decreased nitric oxide bioavailability is a feature of obesity and diabetes that links these two pathologies. Nitric oxide is synthesized both by nitric oxide synthase enzymes from L-arginine and nitric oxide synthase-independent from nitrate/nitrite. Nitric oxide production from nitrate/nitrite could potentially be used for nutrition-based therapy in obesity and diabetes. Nitric oxide deficiency also contributes to pathogeneses of cardiovascular disease and hypertension, which are associated with obesity and diabetes. This review summarizes pathways for nitric oxide production and focuses on the anti-diabetic and anti-obesity effects of the nitrate-nitrite-nitric oxide pathway. In addition to increasing nitric oxide production, nitrate and nitrite reduce oxidative stress, increase adipose tissue browning, have favorable effects on nitric oxide synthase expression, and increase insulin secretion, all effects that are potentially promising for management of obesity and diabetes. Based on current data, it could be suggested that amplifying the nitrate–nitrite–nitric oxide pathway is a diet-based strategy for increasing nitric oxide bioavailability and the management of these two interlinked conditions. Adding nitrate/nitrite to drugs that are currently used for managing diabetes (e.g. metformin) and possibly anti-obesity drugs may also enhance their efficacy.

Contents

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1. Introduction

Obesity, as a major, fast increasing pandemic, is a preventable disease that along with overweight affects one-third of adult populations worldwide [1–3]. Prevalence of obesity in adults increased from 13% to 36% during 1962–2010 [4] and has doubled in the past two decades [5]. By 2030, 38% and 20% of these populations are expected to be overweight and obese, respectively [1]. In the past four decades, mean body mass index has increased by 0.45 kg/m^2 per decade [6].

Type 2 diabetes mellitus (T2DM) is the most devastating complication of obesity [7]. The worldwide prevalence of T2DM among adults was about 6.4% in 2010 [8] and based on estimations, will rise to 7.7%, affecting 439 million people, by 2030 [9–11]. Between 2010 and 2030, increases of 20 and 69% are expected among adults with T2DM in the developed and developing countries, respectively [10].

Obesity and T2DM are tightly linked and compared to normal weight subjects, the risk of developing T2DM increases in overweight and obese subjects by three and seven fold, respectively [1]. In both T2DM and obesity, endothelial dysfunction leads to insufficient production of nitric oxide (NO) [12,13].

NO plays an important role in regulating systemic metabolism, food intake, energy balance, and insulin sensitivity [4,14]. NO may be the linking molecule in clustering different components of metabolic syndrome [15–17] and also between obesity and T2DM [14]. Endothelial dysfunction, i.e. impaired NO-dependent vascular function or loss of bioavailable NO [18], seems to be a mechanism common to the development of metabolic syndrome and insulin resistance [19,20].

Defects in endogenous endothelial NO synthase (eNOS)-derived NO synthesis and its bioavailability along with increased oxidative stress play a role in linking metabolic and cardiovascular disease [21–23]. In addition, an association of polymorphisms in NOS isoforms with insulin resistance and T2DM has been reported [4]; eNOS$^{-/-}$ mice have insulin resistance [24] and display features of metabolic syndrome [21], indicating that eNOS regulates insulin sensitivity [24].

Inorganic nitrate/nitrite, mainly, but not per se, by converting to NO, have anti-diabetic and anti-obesity effects [25,26] and could be potential therapies for obesity, T2DM, and metabolic syndrome [16,19,25,27–29]. The long-term effect of low levels dietary nitrite/nitrate in mice causes the metabolic syndrome, endothelial dysfunction and vascular complications [30]. The aim of this study is to review the anti-obesity and anti-diabetic effects of nitrate/nitrite and to determine possible mechanisms involved in producing such effects.

2. Nitric oxide synthesis

In all tissues, NO is produced via enzymatic and non-enzymatic pathways [31–34]. (Fig. 1). NO is mostly produced from L-arginine (the L-arginine-NO pathway) by enzymes known as NOS [4,35–37]. Three isoforms of NOS including constitutive neuronal (nNOS/NOS1), inducible (iNOS/NOS2), and constitutive eNOS (NOS3) have been identified [12,38–42]. NO could be protective or toxic depending on the level, location, source, and environment [43]. Both exogenous and NOS-derived NO could act as negative feedback modulators of NO synthesis [44–46]. In addition, local NO overproduction by iNOS could inhibit constitutive NOSs [4,44]. NO

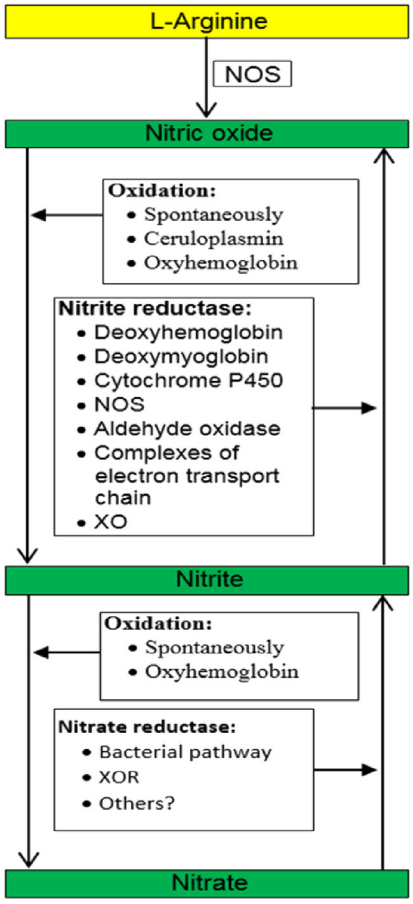

Fig. 1. Nitric oxide (NO) production; both NO synthase (NOS)-dependent and independent pathways are shown. XOR, xanthine oxidoreductase; XO, xanthine oxidase.