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Review Article

Regulation of obesity and insulin resistance by nitric oxide

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ABSTRACT

Obesity is a risk factor for developing type 2 diabetes and cardiovascular disease and has quickly become a worldwide pandemic with few tangible and safe treatment options. Although it is generally accepted that the primary cause of obesity is energy imbalance, i.e., the calories consumed are greater than are utilized, understanding how caloric balance is regulated has proven a challenge. Many "distal" causes of obesity, such as the structural environment, occupation, and social influences, are exceedingly difficult to change or manipulate. Hence, molecular processes and pathways more proximal to the origins of obesity —those that directly regulate energy metabolism or caloric intake—seem to be more feasible targets for therapy. In particular, nitric oxide (NO) is emerging as a central regulator of energy metabolism and body composition. NO bioavailability is decreased in animal models of diet-induced obesity and in obese and insulin-resistant patients, and increasing NO output has remarkable effects on obesity and insulin resistance. This review discusses the role of NO in regulating adiposity and insulin sensitivity and places its modes of action into context with the known causes and consequences of metabolic disease.

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Abbreviations: 3-NT, 3-nitrotyrosine; ADMA, asymmetric dimethyl arginine; Akt, protein kinase B; AMPK, AMP-activated protein kinase; BAT, brown adipose tissue; BH_2, dihydrobiopterin; BH_4, tetrahydrobiopterin; BMR, basal metabolic rate; Cav-1, caveolin-1; CCK, cholecystokinin; cGMP, cyclic guanosine monophosphate; CoA, coenzyme A; EDRF, endothelial-derived relaxing factor; eEF1A1, elongation factor 1-α1; FAD, flavin adenine dinucleotide; FFA, free fatty acid; FMN, flavin mononucleotide; HDL, high-density lipoprotein; HISS, hepatic insulin-sensitizing substance; HSP90, heat shock protein 90; IL-1β, interleukin-1β; IR, insulin receptor; IRS, insulin receptor substrate; KO, knockout; L-NAME, l-N^G-nitroarginine methyl ester; L-NIL, L-N^6-(1-iminoethyl)lysine; LDL, low-density lipoprotein; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NOS, nitric oxide synthase; O-GlcNAc, O-linked *N*-acetylglucosamine; $O_2^{\bullet}-$, superoxide; PGC-1α, PPAR-γ-coactivator-1α; PI3K, phosphoinositide 3-kinase; PKCβII, protein kinase C isoform βII; PPAR, peroxisome proliferator-activated receptor; RNS, reactive nitrogen species; sGC, soluble guanylate cyclase; SIN-1, 3-morpholinosydnonimine; SNO, *S*-nitrosothiol; STZ, streptozotocin; T2D, type 2 diabetes; TLR, Toll-like receptor; TNFα, tumor necrosis factor α; UCP, uncoupling protein

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The obesity epidemic

The recent increase in the prevalence of obesity is cause for alarm. The Centers for Disease Control and Prevention estimate that, from 1962 to 2010, obesity prevalence increased from 13 to 36%. As of 2008, approximately 1.5 billion adults age 20 years or older were overweight, and 10% were obese [1]; more recent data from the United States indicate that >33% of adults and 17% of children are obese [2]. This has led to a dramatic increase in prediabetic states. For example, current estimates indicate that one-third of the population in the United States meets the criteria for prediabetes [3,4], and, in addition to type 2 diabetes (T2D), obesity is closely associated with comorbidities such as cardiovascular disease, hypertension, atherosclerosis, stroke, and cancer [5]. Hence, the current high prevalence of obesity is likely to have a considerable impact on worldwide health. In addition, the economic burden of obesity is substantial and accounts for an estimated $147 billion per year in health care costs [6]. The problem has become so severe that, in 2013, the American Medical Association House of Delegates declared obesity a *disease*.

The principal cause of obesity is energy imbalance: the calories consumed are greater than those utilized by bodily processes, e.g., breathing, digestion, thermogenesis [7]. Indeed, the average consumption of calories in the United States has increased by >200 kcal/day per person, which is partly attributable to the abundance of affordable, widely marketed, energy-dense foods [8–11]. Nevertheless, evidence suggests that the balance between calorie intake and energy expenditure is complex and regulated by many factors. Exposure to increasingly obesogenic environments has been suggested to promote not only overeating, but inactivity as well. For example, the human environment is fraught with both chemical and structural "obesogens." These include, but are not limited to, pollutants that promote adiposity and insulin resistance [12–21]; lack of structural features of the built environment that promote an active lifestyle, such as easy access to parks, sidewalks, and bike paths [22–24]; and the night/day cycles in the natural environment of the individual, which can be altered in those having certain occupations [25–27]. Moreover, the genetic makeup of individuals shows strong associations with the predisposition to become obese [28–30].

Many of these factors influence body composition in an indirect or distal manner and thus could be considered "distal causes" of obesity (Fig. 1). Intervening to address these distal causes is exceedingly difficult. For example, changing the structural environment would probably entail departing from particular types of communities or neighborhoods. Similarly, living under favorable day–night cycles is impossible for workers in some occupations. Even weight loss via caloric restriction faces difficulties, including an evolution-engendered guard against low fat mass [7,31] and the propensity of the body to increase caloric efficiency during dieting [32,33]. The intransigency of these problems has led to a search for causes more proximal to obesity, which may be tangible targets for antiobesity therapies.

Metabolic pathways known to regulate obesity

Understanding the mechanisms that promote adiposity and insulin resistance is critical to stem the growing tide of metabolic disease. In particular, the development of therapies for obesity and T2D requires a better understanding of the biochemical pathways that regulate metabolism and body composition. As a first principle, energy balance must be considered to understand how changes in body composition could occur. Any effective obesity treatment must decrease energy intake, increase energy

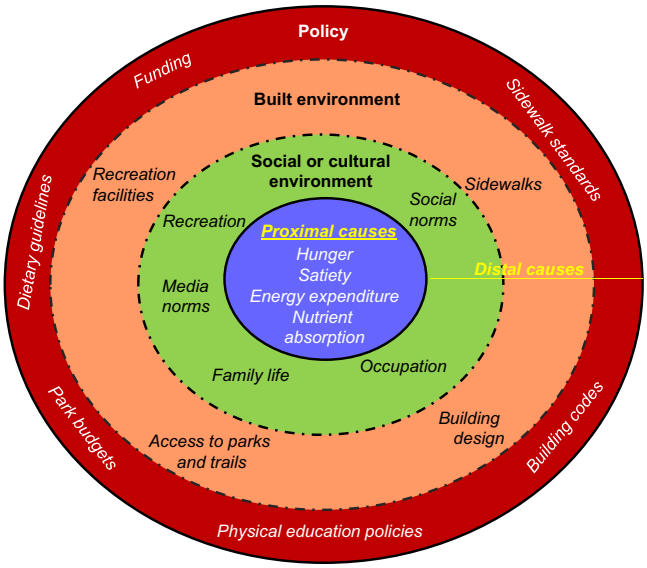

Fig. 1. Distal and proximal causes of obesity. Graphical illustration of the common causes of, or factors that contribute to, obesity: influencing factors distal to the disease, such as policy as well as structural and chemical "obesogens" of the built and social (cultural) environment, may contribute to the prevalence of obesity. Funding for obesity research, dietary guidelines, physical education policies, and sidewalk standards are examples of potential influences related to *policy,* which is most distal to the actual disease. The *built environment,* which comprises places created or modified by people—i.e., where individuals work, their transportation systems, and life outside their homes—is another cause distal to obesity. The *social or cultural environment* includes those family or cultural influences that affect behavioral activity, occupation (which may involve shift work), and social and media norms, all of which could affect eating habits and physical activity. Lastly, direct mechanisms that control hunger, satiety, energy expenditure, and nutrient absorption are *proximal causes* of obesity. These proximal causes, which are regulated by nitric oxide, could be more tangible targets for treating obesity and diabetes compared with distal influences and causes.