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COMMENTARY

Oxidative Stress and Obesity: The Chicken or the Egg?

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Over the past 30 years much research has focused on elucidating mechanisms linked to progression of obesity and its cardiovascular comorbidities. As the central dogma regarding the pathophysiology of obesity unfolds, it is evident that the expansion of visceral adipose tissue caused by overconsumption of nutrients plays a central role. As visceral fat stores expand, adipocytes generate increasing levels of reactive oxygen species (ROS) that incite increased expression and secretion of inflammatory adipokines (1–3). Oxidative stress leads to insulin resistance within adipose tissue as well as in peripheral tissues. Insulin resistance is one of the hallmarks of obesity and accounts for many of its comorbidities, including hypertension (4).

Accumulation of oxidative stress in adipose tissue is one of the early events in the development of metabolic syndrome in obesity (5). On the other hand, weight loss by calorie restriction and/or exercise can ameliorate the state of oxidative stress (6). Nonetheless, a cause and effect relationship between oxidative stress and obesity is not well understood. NADPH oxidase is a major contributor to oxidative stress in many tissues, including adipose tissue and the vasculature (5,7,8). Conversely, factors causing oxidative stress, such as angiotensin II, that induce insulin resistance do not necessarily induce body weight gain (9). Therefore, whether oxidative stress, per se, leads to weight gain is an important gap in our understanding of the pathophysiology of obesity.

In this issue, Youn et al. (10) propose that oxidative stress contributes to obesity rather than the other way around, as has been the conventional thinking (a chicken-and-egg scenario). The most significant finding of their study is the first demonstration that ROS of vascular origin play an important causal role in the development of obesity. They hypothesize that ROS generated in vascular smooth muscle cells (VSMCs) by NADPH oxidase induce obesity. In this elegant study, they used both knock-in and knockout mouse models designed to enhance or abrogate NADPH oxidase–mediated oxidative stress. NADPH oxidase plays a major role in generating ROS in VSMCs (7,8). These multisubunit oxidases consist of one of the catalytic NOX proteins (NOX1 or NOX4 in the vasculature) and p22phox, the latter acting to stabilize NOX expression and serving as a docking station for the remaining cytoplasmic subunits of the oxidase complex (Fig. 1). To address their hypothesis, the authors used a transgenic mouse ($tg^{sm/p22phox}$) model that overexpresses p22phox in VSMCs. In a previous report by this group, they validated specific p22phox overexpression in VSMCs and demonstrated concomitant increases in NOX1 expression and H_2O_2 generation (11). Despite the elevated level of oxidative stress, they detected no abnormalities in endothelium-dependent vasodilation in aortic explants nor did they observe increases in systolic blood pressure. They attributed the preservation of vascular function to a compensatory response that counters the deleterious effects of oxidative stress and is characterized by an H_2O_2-induced increase in the expression of endothelial nitric oxide synthase protein with subsequent generation of nitric oxide (NO), in concert with an increase in extracellular superoxide dismutase expression (Fig. 1).

Youn et al. (10) report that 6-month-old $tg^{sm/p22phox}$ mice fed a high-fat diet (HFD) for 6 weeks developed markedly exaggerated obesity compared with HFD-fed wild-type (WT) mice. Specifically, HFD-fed $tg^{sm/p22phox}$ mice gained 50% more weight than their WT counterparts. HFD feeding also augmented body fat accumulation, leptin levels, and glucose intolerance in $tg^{sm/p22phox}$ mice, components of the metabolic syndrome, compared with WT mice (Fig. 1). Importantly, weight gain was not due to increased calories consumed by the $tg^{sm/p22phox}$ mice. It should be noted that given a sufficiently long exposure to an HFD, say 4–6 months depending on the diet formulation, WT mice develop metabolic syndrome

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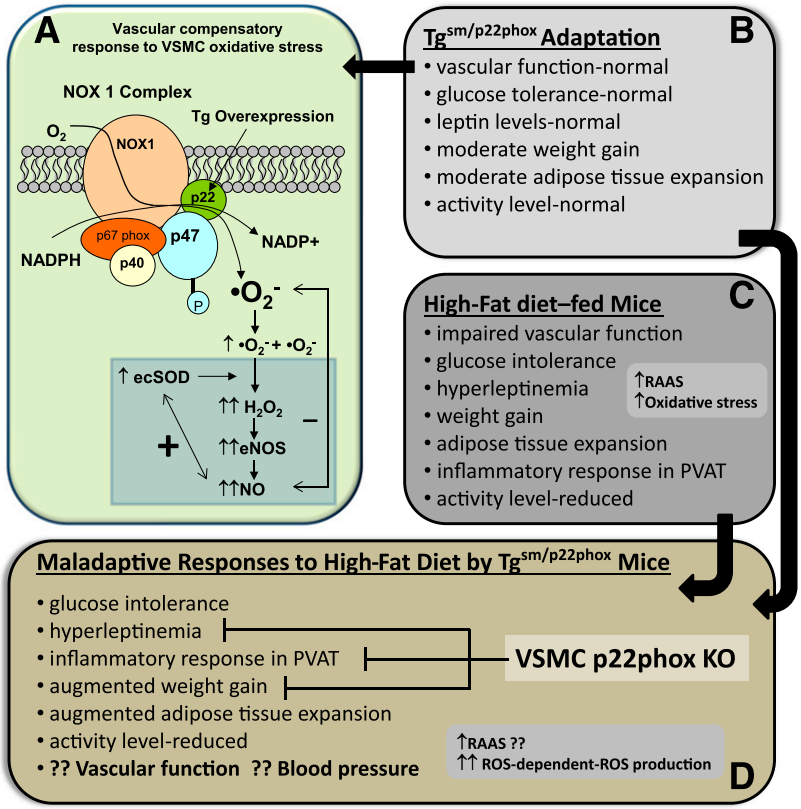

Figure 1—Oxidative stress of vascular origin induces obesity. *Panels A* and *B* depict excessive superoxide generation by the NADPH oxidase complex in VSMCs of $tg^{sm/p22phox}$ mice under baseline conditions and the compensatory vascular and metabolic responses that contribute to preservation of vascular function as reported previously by the authors (11). WT mice fed a Western diet high in fat for several months exhibit a number of abnormalities typically observed in metabolic syndrome (*C*). The consequences of feeding $tg^{sm/p22phox}$ mice an HFD for 6 weeks are similar to those observed with long-term HFD feeding (*D*). ecSOD, extracellular superoxide dismutase; eNOS, endothelial nitric oxide synthase; KO, knockout; PVAT, perivascular fat; RAAS, renin-angiotensin-aldosterone system.

(Fig. 1). Thus, $tg^{sm/p22phox}$ mice exhibit a relatively rapid induction of obesity, which the authors ascribe to the early and marked increase in leptin levels that are likely induced by the combination of elevated vascular ROS and an HFD environment. The authors also suggest the possibility that ROS of vascular origin diffuse into nearby skeletal muscle cells, inciting a feed-forward scenario to induce mitochondrial ROS formation (ROS-induced ROS). As such, vascular ROS may induce skeletal muscle dysfunction, leading to reduced activity and energy expenditure that would promote obesity. Their results were further supported by studies on knockout mice that are deficient in vascular ROS production ($p22phox^{loxp/loxp}$/$tg^{smmhc/cre}$ mice). In these mice, HFD feeding did not induce weight gain or leptin resistance. Moreover, knockout mice fed an HFD exhibited decreased T-cell infiltration into perivascular fat, suggesting that vascular ROS could incite an inflammatory response that contributes to the development of obesity.

The idea that ROS of vascular origin are a cause rather than a consequence of obesity is very appealing, nonetheless several questions remain unanswered. First, in Fig. 3 of their article, it is evident that 6-month-old $tg^{sm/p22phox}$ mice are approximately 15–20% heavier than WT mice under baseline conditions. Despite being overweight, $tg^{sm/p22phox}$ mice do not exhibit the suite of abnormalities observed in HFD-fed $tg^{sm/p22phox}$ mice (Fig. 1). Perhaps this could be interpreted as evidence that vascular ROS by itself promotes a condition of overweight independent of hyperleptinemia, glucose intolerance, and inflammation. Second, the authors did not address whether the adaptive mechanisms related to NO signaling (Fig. 1*A*) encountered in $tg^{sm/p22phox}$ mice fed a normal diet (11) are abrogated in HFD-fed mice. In this regard, it might be predicted that there will be a loss of vasoprotection in concert with augmented obesity and a dysregulated inflammatory response, and this would eventually lead to vascular dysfunction and hypertension. These issues may help to answer the role of NO and immune function in oxidative stress–mediated vascular dysfunction, as these mice are targeted for vascular-mediated oxidative stress. Third, it would also be interesting to know whether oxidative stress–mediated responses to factors contributing to hyperleptinemia, insulin resistance, reduced activity, and inflammation, such as renin-angiotensin-aldosterone system activation, could also be potentiated in $tg^{sm/p22phox}$

mice. It is hoped that future extensions of the study by Youn et al. (10) will provide further mechanistic insight into the pathophysiology of obesity and the role of vascular oxidative stress in mediating vascular dysfunction in obesity.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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