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Comment on Lee et al. Diabetes 2015;64:2836–2846. Comment on Roberts et al. Diabetes 2015;64:471–484

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Lee et al. (1) elegantly demonstrated a novel mechanism of favorable metabolic effects of endothelial nitric oxide (NO) that stimulated the polarization of hepatic resident macrophages (Browicz-Kupffer cells) toward an anti-inflammatory M2 phenotype, suppressed M1-type proinflammatory activation, and protected against high-fat diet–induced hepatic inflammation and insulin resistance. M2 polarization also can be advantageous in adipose tissue macrophages because hypoxia-inducible factor-2α, expressed mainly in M2-like adipose tissue macrophages, ameliorates adipose tissue inflammation and insulin resistance in obesity (2).

The dietary ingestion of inorganic nitrate, previously considered a stable NO metabolite or a potentially toxic food constituent, was recently shown to exert beneficial metabolic effects in rodents—white adipose tissue browning, enhanced mitochondrial biogenesis, increased oxygen consumption and fatty acid β-oxidation in adipocytes, lower visceral fat accumulation, and improved glucose homeostasis—via the NO synthases–independent nitrate-nitrite-NO pathway (3,4). Some of these effects were linked to nitrate/nitrite reduction by xanthine oxidoreductase in adipocytes and potentiated under low-oxygen conditions (4), corresponding to hypoxia observed in obese white adipose tissue.

Because about 75% of the hepatic blood supply originates from the portal vein, the liver is presumably exposed to especially high postprandial nitrate concentrations. Accordingly, NO generation from nitrate/nitrite might be pronounced in the liver with the consequent enhancement of M2 polarization of Browicz-Kupffer cells, thus counteracting hepatic inflammation and insulin resistance, as described for NO formed by endothelial NO synthase (1). Furthermore, another potential hepatic target of nitrate-derived NO could be the insulin-degrading enzyme (governing insulin clearance from the portal circulation), whose activity decreases upon S-nitrosylation (5).

Of note, the alternative pathway of NO formation (from nitrate/nitrite) may be of particular importance in subjects with cardiovascular risk factors associated with endothelial NO synthase uncoupling, i.e., generation of superoxide instead of NO (6). Hence, as the intake of nitrate reported in the experimental studies (3,4) is achievable with vegetable-rich diets, the proposed hypothetical mechanisms can contribute to a reduced risk of type 2 diabetes with a higher consumption of green leafy vegetables (7), a major source of dietary nitrate.

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

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