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

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In their letter, Kruszelnicka and Surdacki (1) suggested that the liver is likely to be exposed to high concentrations of ingested inorganic nitrate. In vivo, nitrate can be serially reduced to nitrite and then nitric oxide (NO). Lee et al. (2) recently demonstrated that NO promoted a vasodilator-stimulated phosphoprotein (VASP)-mediated switch in hepatic macrophages toward the anti-inflammatory M2 phenotype, reducing inflammation and relieving insulin resistance in the liver of high-fat–fed mice. These observations led Kruszelnicka and Surdacki to speculate that dietary nitrate may increase hepatic NO and subsequent M2 polarization of macrophages with insulin-sensitizing effects.

However, the liver is also a major site of energetic carbohydrate and lipid metabolism, including de novo lipogenesis, lipoprotein synthesis, ketone body production, glycogen storage, and fatty acid β-oxidation. In the liver, NO activates fatty acid β-oxidation to alleviate insulin resistance through a cyclic guanosine monophosphate (cGMP)-VASP–mediated mechanism (3). Therefore, it remains possible that nitrate may, in part, induce insulin sensitization through NO-cGMP signaling and direct manipulation of hepatocyte energy metabolism, especially considering dietary nitrate is also already known to have direct effects on the liver, regulating hepatic erythropoietin production and subsequent systemic physiological effects on hemoglobin and oxygen homeostasis (4).

Furthermore, dietary nitrate has metabolic effects across multiple tissues. As Kruszelnicka and Surdacki mention, we recently demonstrated that dietary nitrate initiates the "browning" response in adipose tissue, upregulating fatty acid oxidation and mitochondrial biogenesis via a nitrate-NO-cGMP–mediated mechanism (5). Given the numerous, well-documented, downstream signaling effects of NO, including vasodilation, mitochondrial biogenesis, upregulation of β-oxidation, and erythropoiesis, it is likely that nitrate will modulate the physiology of multiple tissues. Therefore, identifying the target tissues with the greatest contribution to dietary nitrate's systemic beneficial effects on insulin and glucose homeostasis remains an important question with far-reaching consequences for both the dietary choices of the public and individuals with cardiometabolic disease.

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

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