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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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We thank Kruszelnicka and Surdacki (1) for their insightful comments on our recent article (2), which suggested a favorable metabolic effect of endothelial nitric oxide (NO) that stimulates the polarization of hepatic resident macrophages toward an anti-inflammatory M2 phenotype. Kruszelnicka and Surdacki ask whether the nitrate-nitrite pathway exerts beneficial metabolic effects in the liver. This is an excellent question not only for nitrates as potential therapies but also for other strategies, which might increase NO bioavailability and thus attenuate the effects of obesity on hepatic insulin signaling.

Attempts have been made to identify common underlying molecular mechanisms linking metabolic and cardiovascular disease in humans, and one candidate is a defect in the endogenous synthesis and/or reduced bioavailability of NO. Therefore, strategies to improve NO bioavailability may attenuate or reverse the metabolic effects of obesity. Pharmacologic options to increase NO bioavailability include NO donors, the use of the phosphodiesterase-5 inhibitor sildenafil, or the use of sodium nitrite/nitrate. In support of this idea, animal data and observations from clinical studies suggest improvement in fasting glucose levels in type 2 diabetes following treatment with sildenafil (3).

Sodium nitrite and sodium nitrate were generally believed to be inert oxidation products of NO metabolism; however, recent work has demonstrated a reverse pathway where nitrates/nitrites can be reduced back to NO. Nitrites/nitrates reduce cellular injury during ischemic reperfusion injury, and it has been suggested that nitrites/nitrates could represent an endogenous source of NO, especially during periods of hypoxia. Thus, clinical interest in nitrites has been primarily in the treatment of ischemic reperfusion injury, such as stroke, myocardial infarction, or cardiac arrest (4).

The beneficial metabolic effects of nitrate/nitrite have recently been reported (5), and whether these effects are mediated indirectly through effects on adipose tissue or directly on hepatic tissues remains to be investigated. Unpublished work from our laboratory suggests that daily supplementation of drinking water with sodium nitrite for 2 weeks is sufficient to increase hepatic NO content as measured by electron spin resonance spectroscopy. Investigations are under way to determine whether nitrite supplementation can improve hepatic insulin sensitivity during high-fat feeding.

Target nitrate/nitrite levels can be achieved clinically by higher consumption of green leafy vegetables, which have also been linked to a lower risk of type 2 diabetes. This proposed hypothesis by Kruszelnicka and Surdacki (1) may provide a mechanistic link between a diet rich in vegetables and a reduction in type 2 diabetes risk and warrants continued investigation into the potential beneficial role of the nitrate-nitrite-NO pathway on liver metabolism.

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

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