Letter by Carlström and Lundberg Regarding Article, “SIRT3-AMP–Activated Protein Kinase Activation by Nitrite and Metformin Improves Hyperglycemia and Normalizes Pulmonary Hypertension Associated With Heart Failure With Preserved Ejection Fraction”

To the Editor:
We read with interest the article by Lai and coworkers1 published in Circulation about the favorable cardiovascular and metabolic effects of inorganic nitrite and metformin in patients with pulmonary hypertension in heart failure with preserved ejection fraction. Accumulating studies have demonstrated the therapeutic effects of stimulating the nitrate–nitrite–nitric oxide (NO) pathway in renal, cardiovascular, and metabolic disorders. However, the underlying mechanisms are still being debated.

Patients with metabolic syndrome are generally considered to have a higher risk of developing pulmonary hypertension in heart failure with preserved ejection fraction. In this study, Lai et al use a novel animal model of combined metabolic syndrome and pulmonary hypertension in heart failure with preserved ejection fraction and demonstrate that long-term treatment with inorganic nitrate combined with nitrite for 12 weeks reduces pulmonary pressures and vascular remodeling and improves glycemic control. The findings of glucose lowering and improved glucose tolerance in metabolic syndrome are in agreement with a previous study using dietary nitrate supplementation in aged mice lacking endothelial NO synthase.2

In the present study, Lai et al conclude that activation of sirtuin-3 (SIRT3) and AMP-activated protein kinase in skeletal muscle is crucial for the observed effects associated with nitrate and nitrite treatment. The concept of improved AMP-activated protein kinase signaling by the nitrate-nitrite-NO pathway supports recent studies in rat vascular smooth muscle cells and isolated rat hearts3 and in mouse liver in a model of the metabolic syndrome.4

The authors argue that activation of SIRT3 is independent of NO formation and instead propose that reactive oxygen species are required for the nitrite-mediated effects (Figure 4F). However, we do not fully agree with the authors’ conclusion. Lai et al use a combination of peg-catalase and peg–superoxide dismutase and suggest that this antioxidant treatment abolished the favorable effect of nitrite (10 µmol/L) in human skeletal muscles cells exposed to palmitic acid, glucose, and insulin. However, from Figures 4F and 5A, it seems clear that antioxidant treatment alone restored SIRT3 expression during treatment with palmitic acid, glucose, and insulin, which leaves no room for further improvement with nitrite. In our opinion, this could rather suggest that the effect of inorganic nitrite on SIRT3 and AMP-activated protein kinase activation is due to attenuation of oxidative stress, which is in agreement with recently published studies.4,5 Moreover, the authors used a combination of nitrate and nitrite treatment. It would be interesting to find out whether dietary nitrate alone is sufficient to achieve activation of SIRT3.

In summary, the work by Lai et al sheds new light on the underlying mechanisms of nitrate-nitrite–mediated therapeutic effects in cardiovascular and metabolic disease. Although additional studies are warranted, these findings could possibly open a new door to therapeutic applications in patients with metabolic syndrome and increased cardiovascular risk.
DISCLOSURES
None.

AFFILIATION
From Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden.

REFERENCES


Letter by Carlström and Lundberg Regarding Article, "SIRT3-AMP-Activated Protein Kinase Activation by Nitrite and Metformin Improves Hyperglycemia and Normalizes Pulmonary Hypertension Associated With Heart Failure With Preserved Ejection Fraction"

Mattias Carlström and Jon O. Lundberg

_Circulation_. 2016;134:e77-e78
doi: 10.1161/CIRCULATIONAHA.116.021905
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/134/6/e77