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# Vitamin nicotinamide riboside protects mice from diabetes complications

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A naturally occurring vitamin, nicotinamide riboside (NR), can lower blood sugar levels, reduce fatty liver, and prevent peripheral nerve damage in mouse models of prediabetes and type 2 diabetes (T2D), according to a new study by researchers at the University of Iowa and the Iowa City VA Health Care System.

The findings provide a scientific rationale for conducting human trials to test the effects of NR on metabolic disorders including prediabetes and T2D, as well as obesity, fatty liver disease, and neuropathies.

NR is a vitamin precursor of NAD+, an important cellular metabolite that is required for cells to convert fuel into energy, but which declines with age. NR is currently attracting a great deal of attention for its potential role in improving metabolic health and promoting healthy aging.

"There is a real fascination right now in the world of personalized nutrition, biotechnology, and pharmaceutical research to find strategies to boost NAD+ levels. NR has emerged as the lead molecule to elevate NAD+ metabolites," says Charles Brenner, PhD, professor and Roy J. Carver Chair of Biochemistry at the University of Iowa Carver College of Medicine and lead author of the new study.

In 2004, Brenner, then at Dartmouth, discovered NR as an unanticipated vitamin precursor of NAD+. In the new study, published May 27 in the journal *Scientific Reports*, Brenner, together with Randy Kardon, MD,

PhD, and Mark Yorek, PhD, who are jointly affiliated with University of Iowa Health Care and the Iowa City VA Health System, and Samuel Trammell, PhD, who was a graduate student in Brenner's UI lab, tested the effects of NR supplementation on mouse models of prediabetes and type 2 diabetes.

The team studied six groups of mice: control mice on a normal chow diet with or without NR supplementation, prediabetic mice on a high-fat diet with or without NR supplementation, and T2D mice on a high-fat diet with or without NR supplement. The mice receiving NR were fed the supplement for the last eight weeks of the 21-week experiment.

As had been shown in previous studies, NR greatly protected the prediabetic and T2D mice from weight gain due to the high-fat diet. But the new study also showed that NR had other beneficial effects on whole body metabolism in the prediabetic and T2D mice. It protected high-fat fed mice from hepatic steatosis - the build-up of fat globules in the liver - which was severe in the prediabetic and T2D mice that did not receive NR. NR also reduced liver damage in the mice on high-fat diets, and greatly improved blood sugar levels in the prediabetic and T2D mice.

NR also protected against peripheral nerve damage, or neuropathy, a common, serious complication of prediabetes and T2D. Peripheral nerves control touch and pain sensing in the limbs, fingers, and toes. Damage to these nerves can be painful, and can progress to a loss of sensation that allows injuries to go unnoticed. According to the National Institute of Diabetes and Digestive and Kidney Diseases, about 60 to 70 percent of people with diabetes have some form of neuropathy. Peripheral neuropathy is a leading cause of diabetic foot ulcers and limb amputation in people with T2D.

In Brenner's study, prediabetic and T2D mice experienced damage to their sensory nerves while the diabetic mice also experienced motor

neuron deficits. NR protected the prediabetic and diabetic mice against neuropathy and maintained their normal sensitivity to heat.

"We have successfully addressed mouse models of prediabetes and type 2 diabetes with the naturally occurring vitamin NR," says Brenner, who also is co-director of the Obesity Research and Education Initiative, professor of internal medicine, and a member of the Fraternal Order of Eagles Diabetes Research Center at the UI. "What we have seen to date in mice justifies clinical testing of NR in overweight adults and adults with diabetes."

## New tools for NR research

The study showed that a non-invasive test measuring nerve density in the mouse corneas was a sensitive and accurate biomarker of neuropathy. This test, known as corneal confocal microscopy, is already used on people in the clinic and could, therefore, be a useful tool for researchers to track the neuroprotective effects of NR in human trials.

Brenner's team also has developed technology that allows researchers to accurately measure levels of all the NAD+ metabolites in tissues or body fluids. In the new study, this technology was, for the first time, applied to a disease model and revealed that prediabetes and T2D produced unexpected deficits in NAD+ metabolites in the liver, which were partially restored by the NR supplement.

"NAD+ metabolomics shows that NAD+ itself goes down in prediabetes and T2D, but it is not depressed as strikingly as two other metabolites: NADP+ and NADPH," Brenner explains. "When we supplement with NR, the NAD+ bounces back but the NADP+ and NADPH levels don't fully recover, suggesting that the disease process specifically targets these metabolites, which are required for natural resistance to reactive oxygen species (ROS). These results are consistent with research

showing that the development of insulin-insensitivity is related to ROS damage and that NR boosts the body's natural anti-oxidant defenses."

This study was funded by grants from the Fraternal Order of Eagles Diabetes Research Center at the UI, the Roy J. Carver Charitable Trust, the National Institutes of Health, and the Department of Veterans Affairs.

Brenner invented intellectual property related to uses of NR, which has been licensed and developed by ChromaDex Corp. (NASDAQ:CDXC), the company that manufactures and distributes NR and provided the NR for this study. Brenner has also received a research grant from and serves on the scientific advisory board of ChromaDex, Inc. He is co-founder and Chief Scientific Adviser of Healthspan Research, LLC, which sells NR supplements.

**More information:** Samuel A.J. Trammell et al, Nicotinamide Riboside Opposes Type 2 Diabetes and Neuropathy in Mice, *Scientific Reports* (2016). DOI: 10.1038/srep26933

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