New study shows how spikes in nitrite can have

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A new study provides insight into how a short burst in nitrite can exert lasting beneficial effects on the heart, protecting it from stress and assaults such as heart attacks. In this study, just published in *Circulation Research*, researchers at Boston University School of Medicine have demonstrated for the first time that short elevations in circulating levels of this simple anion are sufficient to have a lasting impact on the heart by modulating its oxidation status and its protein machinery.

Nitrite, an oxidation product of the ubiquitous short-lived cell signaling molecule, nitric oxide (NO), was until recently thought to be biologically inert at the relatively low levels found in the body. Traces of nitrite are present in our diet and significant amounts are continuously produced from nitrate, another oxidation product of NO and a constituent of green, leafy vegetables. The suspicion that high levels of nitrite and nitrate may cause cancer, as well as concerns about their risk to compromise the ability of red blood cells to deliver oxygen to tissues, have led to strict regulations aimed at limiting our exposure to these substances through drinking water and food products.

In the past few years, however, multiple research groups have shown that low concentrations of nitrite exert numerous beneficial effects, ranging from anti-bacterial activities to increases in local blood flow, and that they can somehow protect tissues from damage when oxygen is suddenly cut off and then rapidly restored, as occurs during heart attacks and strokes.

To study the molecular underpinnings of this protective effect of nitrite, the researchers at Boston University School of Medicine used a rat model in which they administered nitrite only once, causing a short spike in circulating levels, as a way to simulate the types of naturally occurring increases in nitrite that follow exercise or consumption of a meal rich in nitrate.

The researchers used a systems-biology approach in which changes in multiple biological and biochemical systems (e.g., the composition of a large number of proteins, the concentration of several small molecule metabolites, and functional outcomes) are simultaneously monitored and then integrated to produce one final picture in order to provide a broader view of the impact of this treatment on the heart. They tested their theory that following these changes over time and at different doses of nitrite might help to explain the protective effects of nitrite on the heart.

"What we found was that a single brief nitrite treatment elicited persisting changes in the heart's oxidation status together with lasting alterations to numerous proteins involved in the heart's energy metabolism, redox regulation, and signaling," said David H. Perlman, a post-doctoral research associate in the Cardiovascular Proteomics Center at Boston University School of Medicine, and lead author of the study. "These alterations were particularly striking because they persisted at least 24 hours after the actual nitrite levels had returned back to normal, and they were correlated strongly with the improvements in heart function observed at the same time."

He noted that this type of protection, called 'cardiac preconditioning', is a recently discovered phenomenon shown to be caused by numerous pharmacological agents.

"The proteins we have implicated include some key proteins, such as mitochondrial aldehyde dehydrogenase, that have been shown by others

to be critical to cardiac protection afforded by other agents and triggers," added Perlman. "This is exciting because it ties nitrite-triggered cardioprotection into the broader preconditioning field. Our study complements and extends other work, and identifies new players of potential importance for protection of the heart."

Perlman explained that nitrite levels in our bodies change under a number of circumstances, such as when we run up a flight of stairs or eat a big serving of salad.

"For years, the resulting bursts in nitrite were considered to be of little if any physiological relevance. Now we have good reason to believe that even small spikes in nitrite concentration can alter protein function in the heart in ways that afford protection," noted Perlman.

"We are intrigued by the breadth and magnitude of the proteomic changes in heart mitochondria elicited by a single, short-lasting elevation in nitrite concentration and believe that our findings will have broad implications for mitochondrial signalling and cardiac energetics," commented Martin Feelisch, senior author of the study. "It looks as though nitrite is triggering an ancient program aimed at fine-tuning mitochondrial function. Although the present study focussed on the heart, our observations may extend to other tissues and translate into relevant changes in muscle function elsewhere. If true, this may help explain, for example, the training effects of very short periods of exercise, which are known to be associated with elevations in circulating nitrite concentrations."

Interestingly, only low and high doses of nitrite, but not those in-between, were found to be protective. Although further studies will be needed to fully delineate the mechanisms of nitrite-induced cardioprotection, this study informs ongoing basic and translational studies by highlighting the importance of the dose-effect relationship for

nitrite and the broad array of downstream targets possibly involved in its cardioprotective efficacy, the researchers concluded.

Source: Boston University