NEW HOT PAPERS - 2009

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Jon O. Lundberg talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Pharmacology & Toxicology.

Article Title: The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics
Authors: Lundberg, JO;Weitzberg, E;Gladwin, MT
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(addresses have been truncated)

SW: Why do you think your paper is highly cited?

We are working in a young and exciting field which has many active groups. The topic is of interest to a quite extensive group of scientists, including biochemists, pharmacologists, physiologists, and toxicologists, as well as clinically active researchers.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

The paper summarizes the latest development in this rapidly emerging field and we discuss the major new discoveries made over the past several years.

SW: Would you summarize the significance of your paper in layman's terms?

We and others have discovered and started to characterize a previously unknown pathway for the generation of nitric oxide (NO) in mammals. NO is a key messenger in mammalian biology and this free radical gas is classically generated by specific enzymes—the NO synthases. These enzymes use L-arginine and oxygen to generate NO, which has a key role in vasoregulation, neurotransmission, immunity, and more. The bioactivity of NO is acutely terminated by its rapid oxidation to nitrite (NO2-) and nitrate (NO3-).

These inorganic anions have generally been considered to be completely inert. However, it has now become clear that various pathways exist for the reduction of nitrate and nitrite back to bioactive NO again. Interestingly, this pathway is greatly accelerated under hypoxic conditions, when the oxygen-dependent NO synthase is malfunctioning. The physiological and therapeutical implications of the nitrate-nitrite-NO pathway are just now being revealed. As an example, nitrite mediates vasodilation

via NO formation, and it protects against ischemia-reperfusion injury in animal models.

In humans, inorganic nitrate decreases blood pressure via NO generation. This latter finding is very interesting from a nutritional point of view, since nitrate is abundant in our diet (mainly in green leafy vegetables).

"From the recent research discussed in our article, it is now clear that dietary nitrate is not necessarily a threat to human health."

SW: How did you become involved in this research, and were there any problems along the way?

Our group and Ben Benjamin's group at Aberdeen University first described NO-synthase-independent NO generation from nitrate and nitrite in 1994. A year later, Jay Zweier's group at the Davis Heart and Lung Research Institute in Columbus, Ohio, demonstrated nitrite reduction to NO in the ischemic heart. The field was quite slow initially, likely because the NO synthase pathway took all the focus at that time. Also, many researchers would simply not believe that nitrate and nitrite can be biologically active.

The dogma was that they are inert oxidation products of NO metabolism. The field really took off during the years 2000-2003 when work by Mark Gladwin of the Pulmonary and Vascular Medicine Branch, NHLBI, in Bethesda, MD, along with ours at Karolinska, showed that low concentrations of nitrite could elicit vasodilation, and then again in 2004-2005 when Amrita Ahluwalia at the William Harvey Research Institute in London and Gladwin's group went on to demonstrate the cytoprotective effects of nitrite.

SW: Where do you see your research leading in the future?

We hope to be able to convincingly show that the nitrate-nitrite-NO pathway is an important complement to the L-arginine/NOS pathway for the generation of bioactive nitrogen oxides within our bodies. In particular, we need to better explore the physiological importance of this pathway and how it is regulated, which is not a trivial task since there are no specific pharmacological inhibitors available. In addition, it will be of great interest to explore the therapeutic opportunities for nitrate and nitrite in diseases such as hypertension, atherosclerosis, and ischemia-reperfusion injury.

SW: Do you foresee any social or political implications for your research?

Nitrate and nitrite are found in our diet and, for over 50 years, they have been linked to diseases in humans, most notably gastric cancer. Although the link between nitrate in food and cancer has never been proven, the fear of nitrate and nitrite is still widespread. This is reflected in the strict regulation of nitrate levels in food and drinking water. From the recent research discussed in our article, it is now clear that dietary nitrate is not necessarily a threat to human health. In fact, we are hoping that it will eventually be considered an essential nutrient.

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