Karolinska Institutet

Institutionen för fysiologi och farmakologi

DIETARY INORGANIC NITRATE:

ROLE IN EXERCISE PHYSIOLOGY, CARDIOVASCULAR AND METABOLIC REGULATION

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Aulan Farmakologen, Nanna Svartz väg 2, Solna

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ABSTRACT

Nitric oxide (NO) is a ubiquitous signaling molecule with a vast number of tasks in the body, including regulation of cardiovascular and metabolic function. A decreased bioavailability of NO is a central event in disorders such as hypertension and metabolic syndrome. NO is also important in the regulation of blood flow and metabolism during exercise. The production of NO has previously been thought to be under the exclusive control of the nitric oxide synthases (NOS) but this view is now being seriously challenged. Recent lines of research suggest the existence of an NO-synthase independent pathway in which the supposedly inert NO oxidation products nitrate (NO_3^-) and nitrite (NO_2^-) can be reduced back to NO in blood and tissues. An important additional source of nitrate is our everyday diet and certain vegetables are particularly rich in this anion. In this thesis the possibility that dietary derived nitrate is metabolized in vivo to form reactive nitrogen oxides with NO-like bioactivity has been explored.

It is shown that nitrate in amounts easily achieved via the diet, increases the systemic levels of nitrite and reduces blood pressure in healthy humans. Moreover, nitrate reduces whole body oxygen cost during submaximal and maximal exercise; a surprising effect involving improvement in mitochondrial efficiency and reduced expression of specific mitochondrial proteins regulating proton conductance. Alterations in the mitochondrial affinity for oxygen can explain this reduction in both submaximal and maximal oxygen consumption and predicts basal metabolic rate in humans. Finally, in mice lacking endothelial NO synthase, dietary supplementation with nitrate could reverse several features of the metabolic syndrome that develop in these animals. These studies demonstrate that dietary nitrate can fuel a nitrate-nitrite-NO pathway with important implications for cardiovascular and metabolic functions in health and disease.