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VIEWPOINT

From sodium intake restriction to nitrate supplementation: Different measures with converging mechanistic pathways?

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Tetrahydrobiopterin

Abstract Endothelial nitric oxide synthase is at the centre of endothelial physiology producing nitric oxide which dilates blood vessels, inhibits platelet aggregation and smooth muscle cell proliferation and reduces adhesion molecule production. The laminar shear stress is a common test used usually as the flow mediated dilatation test (FMD) which is sensitive to saturated fat, sodium and potassium although with the latter ion it is possible potassium has direct effects on ion channels in the smooth muscle cell as well as the endothelial cell. High blood pressure and blood cholesterol both reduce nitric oxide production, the latter probably by increasing caveolin-1 which binds nitric oxide synthase. Saturated fat reduces nitric oxide by elevating LDL cholesterol and caveolin-1 while insulin stimulates nitric oxide synthase activity by serine phosphorylation. Polyphenols from tea, coffee and cocoa and virgin olive oil enhance FMD and eNOS activity is essential for this activity. Wine polyphenols produce mixed results and it is not clear at present that they are beneficial. Blackberries and other polyphenol-rich fruit also enhance FMD.

Dietary nitrate from beetroot and green leafy vegetables is converted to nitrite by salivary microbes and then to nitric oxide and this acts directly on the smooth muscle to lower blood pressure particularly in a low oxygen environment. Dietary nitrate also improves work efficiency and improves flow mediated dilatation.

Introduction

There are many dietary components that have been shown to have an effect on vascular function. In this review we will explore the potential common metabolic pathways that underlie the effects of a very diverse array of components from saturated fat to dietary sodium with NO as the final active mediator for most although endothelial hyperpolarising factor may be important for some.

Endothelial function

Normal vascular relaxation is mediated by a number of endothelial systems including nitric oxide (NO), prostaglandins (PGI2 and PGE2), and a family of endothelium-derived hyperpolarizing factors (EDHF). In response to laminar shear stress, the endothelium continuously releases NO, EDHF, and PGI2 to provide vasodilatation. EDHF is not a single molecule but rather a group of molecules that includes epoxyeicosatrienoic acids, hydrogen peroxide, carbon monoxide, hydrogen sulfide, C-natriuretic peptide, and K+ itself, causes vasodilatation by activation of vascular smooth muscle cell K+ channels, resulting in hyperpolarization.

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Assessment of endothelial function

Endothelial function can be assessed by intra-arterial infusion of acetylcholine which releases calcium via G coupled receptors, phospholipase C and elevation of IP3 or via post ischemic laminar flow mediated dilatation (FMD) which stimulates AKT and PKA to serine phosphorylate eNOS. There are many other suggested mechanisms for eNOS stimulation by laminar flow stress including opening of membrane calcium channels to increase intracellular calcium which binds to calmodulin which then binds to eNOS to aid its movement away from caveolin-1 on the cell membrane. This area has been reviewed extensively [1,2]. Fig. 1 shows the factors influencing eNOS activity.

Nitric oxide synthase (NOS)

This is the most important enzyme in normal endothelial function. Nitric oxide (NO) is synthesized by a family of NO synthases (NOS). There are three NOS isoforms: neuronal (nNOS), endothelial (eNOS), and inducible (iNOS). They have an N-terminal oxygenase domain with heme-, L-arginine-, tetrahydrobiopterin (BH_4)-binding domains, a central calmodulin (CaM)-binding region, and a C-terminal reductase domain with NADPH, FAD, and FMN binding sites [3]. Endothelial NOS which is the main physiologically active isoform in endothelial cells is very actively regulated [4].

NOS converts L arginine to citrulline and this reaction requires oxygen. There are many control points in this reaction including level of both arginine and eNOS cofactors,

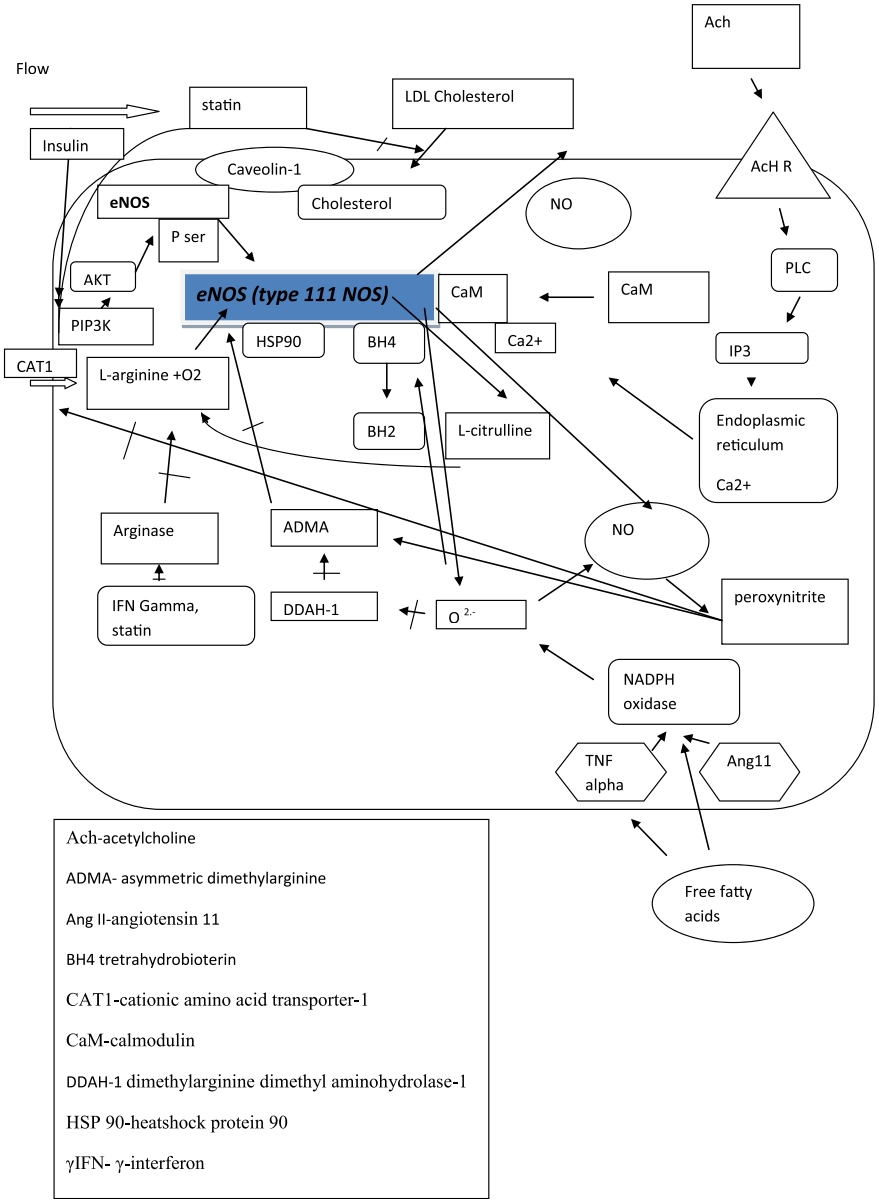

Figure 1 Mechanistic pathways involved in NO production.