Invited Commentary

Polyphenol studies: time for a physiological tea party?

(First published online 22 August 2011)

Endothelial dysfunction is a common complication of atherosclerosis, when impaired vasorelaxation due to reduced endothelial-derived NO (EDNO) bioactivity results in altered endothelial function. There are several reasons why EDNO bioactivity decreases, but these can be synthesised into two major phenomena taking place in dysfunctional arteries: (1) reduced EDNO production by endothelial cells and (2) accelerated EDNO inactivation once it is produced and starts diffusing.

Exacerbated by senescence and mostly induced by inflammation and oxidative stress, a reduced production of EDNO follows enhanced ceramide levels in endothelial cells\(^1\). This results in altered endothelial NO synthase (eNOS) phosphorylation patterns and, in turn, reduced vasomotor function. The intracellular mechanisms responsible have been largely clarified and, indeed (pharmacological or nutritional) strategies aimed at restoring proper redox status rest on solid scientific ground. In particular, eNOS synthetic activity is dependent on maintaining tetrahydrobipterin (BH\(_4\)) in a highly reduced state. With a proper BH\(_4\):bipterin ratio eNOS readily produces NO; however, when the BH\(_4\):redox ratio declines, the internal electron transport chain of eNOS becomes uncoupled, which actually generates superoxide instead of NO. Thus, eNOS needs a properly reduced intracellular milieu; otherwise, it might further exacerbate oxidative stress and endothelial dysfunction rather than producing EDNO. This is why provision of antioxidant compounds has been suggested as a valuable tool to improve vasomotion. Indeed, there is now considerable evidence of beneficial effects of vitamin C supplementation on endothelial function and blood pressure\(^2\), although the effects of vitamin E are still equivocal\(^3\).

The other cause of endothelial dysfunction is enhanced inactivation of EDNO. Though – from a quantitative viewpoint – the exact contribution of EDNO inactivation is as yet to be ascertained, several biochemical and kinetic studies have addressed this issue. Indeed, superoxide anion readily reacts with EDNO, at a rate (6-7\(\times\)10\(^7\)molL\(^{-1}\)) that is about three times faster than that between superoxide and superoxide dismutase (SOD); as a result, EDNO can outcompete SOD and act as a stronger ‘antioxidant’ than the latter. The reaction between EDNO and superoxide, however, forms peroxinitrite, in turn creating more damage. In brief, the conversion of EDNO to deleterious reactive nitrogen species limits EDNO bioavailability and contributes to the altered vessel function.

In this issue of the BJN, Gómez-Guzmán et al\(^4\) report on the mixed effects of epicatechin in an animal model of endothelial dysfunction and associated hypertension. This investigation follows along the research lines that started with Duffy et al\(^5\). Indeed, the role of tea flavonoids – in particular epigallocatechin gallate – in maintaining proper vasomotion is being clarified. Though usually labelled as antioxidants, polyphenols exert multiple biological activities, some of which might bear important consequences on vascular reactivity. As an example, they are anti-inflammatory agents and, thus, lessen the production of cyclo-oxygenase (COX)- and lipoxygenase-derived hydroperoxides. Direct hydroxylation of eNOS also contributes to enhanced EDNO production. Finally, several enzymes depend on the so-called peroxide tone; by maintaining a proper intracellular environment, e.g. by keeping BH\(_4\) in a reduced state, polyphenols facilitate eNOS activity and decrease COX activation\(^6\).

Of note, the salubrious cardiovascular effects of \((-\)\)-epicatechin reported by Gómez-Guzmán et al. did not translate into ameliorated blood pressure and only mildly prevented endothelial dysfunction as induced by L-NAME (l-NG-nitroarginine methyl ester (l-NAME) (which prevents EDNO from being synthesised). While these data apparently contrast with the widespread notion that flavonoids and, in particular, catechins improve vascular health and blood pressure, some aspects of this and previous investigations are worth underscoring. Gómez-Guzmán et al. used ‘physiological’ doses of \((-\)\)-epicatechin, i.e. amounts that approximate human consumption. Other data have been obtained with higher doses of flavonoids, hence shifting the focus from nutrition to pharmacology. Also, several \textit{in vitro} data are still being collected after the addition of non-physiological concentrations of flavonoids and other polyphenols, which are subjected to extensive first-pass metabolism and reach the target organ in minute amounts\(^7\). In brief, most \textit{in vitro} data available to date do not necessarily translate into \textit{in vivo} situations. Can we distil the large number of publications on polyphenols and vascular reactivity to provide science-based advice to endothelial dysfunction and hypertensive subjects? One of the factors to consider and compute here is this: the one important difference between food items and
medicines is that the former contain substances to which we have been exposed throughout our lifetime. In other words, while insufficient intakes of micronutrients result in overt illness such as scurvy, anaemia or pellagra, i.e. alterations in the ‘gross’ functioning of the body, sub-optimal consumptions have more subtle and undetectable effects that do not translate into immediate clinically recognisable alterations of physiology. Yet, such ‘fine’ alterations might bear important long-term consequences and play major roles in the development of degenerative disorders, including CVD, cancer and neurodegeneration. In summary, while everyone looks and hopes for remarkable short-term effects of food and food components, we should better focus on the mild yet important long-term effects that a proper diet has on human physiology. Indeed, most studies of micronutrients, including polyphenols, are being conducted on healthy people, hence lessening the possibility of seeing alterations in relevant biomarkers. Within this frame, regular consumption of tea and other polyphenol-rich foods is associated with long-term positive effects on vascular health, because of enhanced eNOS activation, reduced cellular free-radical production and other as yet unexplored mechanisms\(^{(8,9)}\). Conversely, the use of pharmaceutical preparations based on single molecules is promising, but needs further investigation. In this respect, one final caveat – as mentioned by the authors – is that of potential liver damage associated with the intake of green tea extracts. Indeed, France is prohibiting the marketing of hydroalcoholic green tea extracts and there is animal evidence of altered liver enzymes subsequent to treatment.

In conclusion, despite the lay public’s perception, the effects of tea and other foods and beverages on endothelial function have not been clearly elucidated. Research is proceeding in the right direction, though, and through careful and physiologically relevant experiments we will eventually be able to provide evidence-based advice.

References


Francesco Visioli
Laboratory of Functional Foods
IMDEA-Food
Madrid
Spain
email francesco.visioli@imdea.org