Effect of flavonoids on endotelial dysfunction in L-NAME Hypertensive rats: role of oxidative stress and nitric oxide

MD. Paredes, AB. Meseguer, PA. Romecín, MM. Molina, JE. Millán, NM Atucha, J. Castillo, J. Garcia-Estañ, MC. Ortiz-Ruiz

1 Dept. Fisiología, Fac Medicina, UMU. madopaca@um.es
2 Trasplante Hematopoyético/Terapia Celular, IMIB-HUVA, Campus Salud, El Palmar. clara@um.es

ABSTRACT

Introduction: Hypertension is an important health problem given its high prevalence and its role as a critical cardiovascular risk factor. Epidemiological studies have shown an inverse association between flavonoid-rich diet consumption and the risk of hypertension and cardiovascular disease. In this study, we evaluated the effects of several flavonoid extracts on N(G)-nitro-L-arginine methyl ester (L-NAME) induced hypertension in rats.

Material and methods: Adult male rats, were divided into seven groups (n=4-6): (1) Control, (2) L-NAME (10 mg/Kg/day); and L-NAME plus (3) Apigenin (1,44 mg/Kg/day), (4) Lemon Extract (LBC, 2,84 mg/Kg/day), (5) Grapefruit+Bitter Orange Extract (GBC, 9,28 mg/Kg/day), (6) Cocoa Extract (COE, 2,52 mg/Kg/day) and (7) Diosmin (7,16 mg/Kg/day), a pharmaceutical flavonoid control.

After 6 weeks of treatment we obtain urine samples, and we measured mean arterial pressure (MAP) and obtained plasma and kidney samples. We also extracted the thoracic aorta to evaluate the endothelium-dependent response to acetylcholine (ACh).

Results: L-NAME increased MAP (40%) and flavonoids treatment induced a significant reduction in MAP in all the groups (LBC, -68%; COE, -46%; Apigenin, -32%; GBC, -14%; Diosmin, -11%). This effect was accompanied by a partial or full prevention of most of the effects induced by L-NAME. The maximal Ach-induced relaxation was enhanced by all the flavonoids: COE, 39%; LBC, 31%; Apigenin, 25%; GBC, 4%; Diosmin, 2%, which was associated with a significant increased of its NO-dependent component, increased natriuresis, decreased levels of oxidative stress (OS), increased levels of nitric oxide (NO), and a decreased in proteinuria.

Discussion: Flavonoids markedly attenuated the development of L-NAME-induced hypertension and ameliorated the maximal Ach-induced relaxation. We think that certain flavonoids chemical structures could be crucial for this improvement. Thus, a 5,7-meta-dihydroxy substitution on A-ring and 2,3-double bond and 4-keto group of the C-ring in Apigenin are related to anti-inflammatory activity. Moreover, 3',4'-ortho-dihydroxy on B-ring (Cocoa Extract, LBC), 3-hydroxy on C-ring (COE), and 2,3-double bond on C-ring in combination with the 4-oxo group (Apigenin, Diosmin) appear to be important for an angiotensin-converting enzyme inhibitor (ACEI) and antioxidant activities. Additionally, a 5,7-meta-dihydroxy substitution in the 4-oxoflavonoids (all except COE) have protective effect against LDL oxidation. Finally, hydroxylation substitution on B and C rings but not the A-ring is essential for the antioxidant effects of flavonoids.

Conclusions: The consumption of flavonoids has antihypertensive effects in L-NAME treated rats. This effect may be mediated by decreasing OS levels and increasing NO levels, the anti-inflammatory modulation and ACEI activity, which contributes to the endothelial and renal function recovery.