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Estrogen receptor alpha as a key target of red wine polyphenols action on the endothelium

Submitted by Emmanuel Lemoine on Wed, 12/11/2013 - 17:07

Titre	Estrogen receptor alpha as a key target of red wine polyphenols action on the endothelium
Type de publication	Article de revue
Auteur	Chalopin, Matthieu [1], Tesse, Angela [2], Martinez, Maria Carmen [3], Rognan, Didier [4], Arnal, Jean-François [5], Andriantsitohaina, Ramaroson [6]
Editeur	Public Library of Science
Type	Article scientifique dans une revue à comité de lecture
Année	2010
Langue	Anglais
Date	2010
Numéro	1
Volume	5
Titre de la revue	PloS one
ISSN	1932-6203
Mots-clés	Animals [7], Endothelium, Vascular [8], Estrogen [9], Flavonoids [10], Mice [11], Mice, Knockout [12], Models, Molecular [13], Nitric [14], Phenols [15], Polyphenols [16], Wine [17]

Résumé en anglais	BACKGROUND: A greater reduction in cardiovascular risk and vascular protection associated with diet rich in polyphenols are generally accepted; however, the molecular targets for polyphenols effects remain unknown. Meanwhile evidences in the literature have enlightened, not only structural similarities between estrogens and polyphenols known as phytoestrogens, but also in their vascular effects. We hypothesized that alpha isoform of estrogen receptor (ERalpha) could be involved in the transduction of the vascular benefits of polyphenols.METHODOLOGY/PRINCIPAL FINDINGS: Here, we used ERalpha deficient mice to show that endothelium-dependent vasorelaxation induced either by red wine polyphenol extract, Provinols, or delphinidin, an anthocyanin that possesses similar pharmacological profile, is mediated by ERalpha. Indeed, Provinols, delphinidin and ERalpha agonists, 17-beta-estradiol and PPT, are able to induce endothelial vasodilatation in aorta from ERalpha Wild-Type but not from Knock-Out mice, by activation of nitric oxide (NO) pathway in endothelial cells. Besides, silencing the effects of ERalpha completely prevented the effects of Provinols and delphinidin to activate NO pathway (Src, ERK 1/2, eNOS, caveolin-1) leading to NO production. Furthermore, direct interaction between delphinidin and ERalpha activator site is demonstrated using both binding assay and docking. Most interestingly, the ability of short term oral administration of Provinols to decrease response to serotonin and to enhance sensitivity of the endothelium-dependent relaxation to acetylcholine, associated with concomitant increased NO production and decreased superoxide anions, was completely blunted in ERalpha deficient mice. CONCLUSIONS/SIGNIFICANCE: This study provides evidence that red wine polyphenols, especially delphinidin, exert their endothelial benefits via ERalpha activation. It is a major breakthrough bringing new insights of the potential therapeutic of polyphenols against cardiovascular pathologies.
URL de la notice	http://okina.univ-angers.fr/publications/ua247 [18]
DOI	10.1371/journal.pone.0008554 [19]
Lien vers le document	http://dx.doi.org/10.1371/journal.pone.0008554 [19]

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[19] http://dx.doi.org/10.1371/journal.pone.0008554

Publié sur *Okina* (http://okina.univ-angers.fr)