Role of the mitochondria on the paradoxical effect of red wine polyphenols on angiogenesis

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Résumé en anglais	Red wine polyphenol (RWPC) extracts has been reported to possess vasoprotective properties that involve nitric oxide (NO) release from endothelial cells via a redox-sensitive pathway. Besides, the molecular target of RWPC to release NO has been recently revealed and it involves the activation of the estrogen receptor alpha (ERα). Paradoxical effects of RWPC have been shown with regard to angiogenesis. Indeed in a rat model of postischemic neovascularization, low- dose is pro- whereas high dose is anti- angiogenic. NO and ERα are key regulators of mitochondrial function. Furthermore, angiogenesis is a highly energetic process associated with mitochondrial biogenesis. However, whether RWPC induces changes in mitochondrial function has never been addressed and it is the aim of this study. The effects of RWPC at low concentration (10- 4 g/l, LCP) and high concentration (10- 2 g/l, HCP) after 48 hours time exposure were investigated on human endothelial cells. Mitochondrial respiration, expression of biogenesis factors and DNA content was assessed using oxygraphy and qRT- PCR, respectively. In vitro capillary formation using Matrigel® was performed. The mechanism involved with respect to ER using the ER- antagonist fulvestrant was studied. The involvement of both NADPH oxidase and NO synthase was addressed using apocynin and L- NA respectively. LCP, but not HCP, increased mitochondrial respiration. The effect of LCP was associated with an increase of both expression of several mitochondrial biogenesis factors (NRF- 1, NRF- 2, ERRα, Tfam, PolG) and mitochondrial DNA content whereas HCP had no effect on these parameters. All the effects of LCP on mitochondrial respiration are prevented by fulvestrant, apocynin and L- NA. LCP also promoted in vitro capillary elongation that was prevented by fulvestrant, apocynin and L- NA. Finally, the inhibition of mitochondrial protein synthesis using chloramphenicol suppressed the pro- angiogenic property of LCP. The present study highlights the implication of the axis ER, NADPH oxidase and NOS pathways on both increase mitochondrial function and capillary elongation in response to RWPC at low concentration. They explain the paradoxical effect of RWPC depending on the concentration with respect to angiogenesis, mitochondria being key targets for its pro- angiogenic properties.
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