Resveratrol induces a mitochondrial complex I-dependent increase in NADH oxidation responsible for sirtuin activation in liver cells

Titre	Resveratrol induces a mitochondrial complex I-dependent increase in NADH oxidation responsible for sirtuin activation in liver cells
Type de publication	Article de revue
Auteur	Desquiret-Dumas, Valérie [1], Guegen, Naig [2], Leman, Géraldine [3], Baron, Stephanie [4], Nivet-Antoine, Valerie [5], Chupin, Stéphanie [6], Chevrollier, Arnaud [7], Vessieres, Emilie [8], Ayer, Audrey [9], Ferré, Marc [10], Bonneau, Dominique [11], Henrion, Daniel [12], Reynier, Pascal [13], Procaccio, Vincent [14]
Editeur	American Society for Biochemistry and Molecular Biology
Type	Article scientifique dans une revue à comité de lecture
Année	2013
Langue	Anglais
Date	2013
Numéro	51
Pagination	36662 - 75
Volume	288
Titre de la revue	The Journal of biological chemistry
ISSN	1083-351X
Mots-clés	Animals [15], Electron Transport Complex I/metabolism [16], Enzyme Activation [17], Hep G2 Cells [18], Hepatocytes/drug effects/metabolism [19], Humans [20], Mice [21], Mice, Inbred C57BL [22], Mitochondria, Liver/drug effects/metabolism [23], NAD/metabolism [24], Oxidation-Reduction [25], Sirtuin 3/metabolism [26], Stilbenes/pharmacology [27]
Résumé en anglais	Resveratrol (RSV) has been shown to be involved in the regulation of energetic metabolism, generating increasing interest in therapeutic use. SIRT1 has been described as the main target of RSV. However, recent reports have challenged the hypothesis of its direct activation by RSV, and the signaling pathways remain elusive. Here, the effects of RSV on mitochondrial metabolism are detailed both in vivo and in vitro using murine and cellular models and isolated enzymes. We demonstrate that low RSV doses (1-5 muM) directly stimulate NADH dehydrogenases and, more specifically, mitochondrial complex I activity (EC50 approximately 1 muM). In HepG2 cells, this complex I activation increases the mitochondrial NAD(+)/NADH ratio. This higher NAD(+) level initiates a SIRT3-dependent increase in the mitochondrial substrate supply pathways (i.e. the tricarboxylic acid cycle and fatty acid oxidation). This effect is also seen in liver mitochondria of RSV-fed animals (50 mg/kg/day). We conclude that the increase in NADH oxidation by complex I is a crucial event for SIRT3 activation by RSV. Our results open up new perspectives in the understanding of the RSV signaling pathway and highlight the critical importance of RSV doses used for future clinical trials.

URL de la notice	http://okina.univ-angers.fr/publications/ua8395 [28]
DOI	10.1074/jbc.M113.466490 [29]
Lien vers le document	http://dx.doi.org/10.1074/jbc.M113.466490 [29]
Titre abrégé	J Biol Chem

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