



Resveratrol Directly Binds to Mitochondrial Complex I and Increases Oxidative Stress in Brain Mitochondria of Aged Mice

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Resveratrol is often described as a promising therapeutic molecule for numerous diseases, especially in metabolic and neurodegenerative disorders. While the mechanism of action is still debated, an increasing literature reports that resveratrol regulates the mitochondrial respiratory chain function. In a recent study we have identified mitochondrial complex I as a direct target of this molecule. Nevertheless, the mechanisms and consequences of such an interaction still require further investigation. In this study, we identified *in silico* by docking study a binding site for resveratrol at the nucleotide pocket of complex I. *In vitro*, using solubilized complex I, we demonstrated a competition between NAD⁺ and resveratrol. At low doses (<5 μM), resveratrol stimulated complex I activity, whereas at high dose (50 μM) it rather decreased it. *In vivo*, in brain mitochondria from resveratrol treated young mice, we showed that complex I activity was increased, whereas the respiration rate was not improved. Moreover, in old mice with low antioxidant defenses, we demonstrated that complex I activation by resveratrol led to oxidative stress. These results bring new insights into the mechanism of action of resveratrol on mitochondria and highlight the importance of the balance between pro- and antioxidant effects of resveratrol depending on its dose and age. These parameters should be taken into account when clinical trials using resveratrol or analogues have to be designed.

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