

## Effect of resveratrol on plasmatic molecular indicators of brain tissue response to the hypoperfusion/reperfusion challenge

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It is well-documented that endocannabinoids (eCBs) and congeners show a neuroprotective role in several experimental models of brain injury and that changes in eCB levels in peripheral blood cells may reflect the severity of neurological insult. We have previously shown that the preventive administration of dietary natural compounds may increase the plasmatic levels of palmytoylethanolamide (PEA) and oleoylethanolamide (OEA) following the transient bilateral common carotid artery occlusion (BCCAO)-induced brain tissue challenge (1). Resveratrol (RVT), (3,4', 5-trihidroxystillbene) is a strong natural antioxidant of polyphenolic structure found in grapes and red wine, with many physiological effects, including the prevention of lipid peroxidation in human LDL, inhibition of arachidonic acid metabolism, and platelet activity. RVT has been further shown to protect cerebral tissue and cardiac muscle from tissue damage caused by oxidative stress triggered by reperfusion (2) and has been proposed as a potential neuroprotective agent in treating acute states in focal cerebral ischemia injury (3). In this line, we intend to evaluate whether exogenous administration of RVT prior to induction of BCCAO followed by reperfusion influences the molecular changes occurring in cerebral cortex and plasma, with particular focus on the eCB system. With this aim, cerebral hypoperfusion was produced by a 30 min BCCAO followed by 60 min reperfusion (BCCAO/R). Animals were starved for 12 hours before surgery and 6 hours prior to ischemia RVT (40 mg/kg/0.45 ml of sunflower oil as vehicle) was administered via gavage. Biological samples of plasma, cerebrospinal fluid (CSF), and brain tissue were examined by HPLC, gel zymography, western blot and immunohistochemistry. Data obtained indicate that RVT appears to influence the outcome of BCCAO/R cerebral injury by modulating changes in levels of lipid hydroperoxides, markers of oxidative stress, eCBs and eCB congeners, expression of CB1 and CB2 receptors, peroxisome proliferator-activated receptor (PPAR) alpha, ciclooxigenase-2 (COX-2) protein levels and enzymatic activity of matrix-metalloproteinase-9 (MMP-9). Interestingly, changes in brain of some of these parameters, like lipid hydroperoxides, were also found in plasma. Results obtained suggest that exogenous administration of RVT may modulate the brain tissue compensatory or repair mechanisms triggered by the hypoperfusion/reperfusion and support the possible use of this molecule as treatment to prevent the BCCAO/R-induced brain insult. In addition, the finding that changes in plasma mirrored those found in cerebral tissue, opens to the possibility to test whether RSV exerts its positive activities in humans.

### References

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### Keywords

Frontal cortex; hypoperfusion-reperfusion; endocannabinoids; lipid hydroperoxides; CB receptors; PPAR-alpha; HPLC; western blot; gel zymography; immunohistochemistry.