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[0091]

## Analysis of HO-1/BVR post translational modifications as potential plasma biomarker of Alzheimer's disease (AD) pathology

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The lack of reliable biomarkers for AD diagnosis represents one of the main difficulties in disease treatment. Blood-related proteins often have been considered potential diagnostic markers for their easy accessibility and way of collection. Several studies showed increased oxidative and nitrosative stress in plasma from AD patients [1, 2]; however, little and controversial knowledge has emerged about the activation of adaptive responses to stress like HO-1/BVR system in blood [3, 4]. Brain studies showed that, despite the increased levels of both HO-1 and BVR as adaptive response to stress, a decrease in the HO-1/BVR system activity occur in hippocampus of subjects with AD and MCI, due to protein oxidative damage [5, 6]. We report in this study increased levels of both HO-1 and BVR in plasma from AD patients coupled with the reduction of bilirubin antioxidant activity, as result of the increased oxidative environment. Moreover, since increased nitrosative stress seems to play the main oxidative role in plasma during AD, we found that proteins alterations were tightly linked to protein nitration, resulting in increased BVR 3NT levels and decreased BVR phosphotyrosine levels and activity. HO-1, however, being less prone to nitrosative damage did not show any PTM alteration. Overall we show that BVR plasma data reflect hippocampal status in AD and is reasonable to use BVR analysis to gain informations about brain oxidative damage and conceivably predict AD onset and development.

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Keywords: Heme oxigenase, biliverdin reductase, Alzheimer's disease, biomarker

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[0095]

## Hormonal and diet modulation of glucose uptake in human blood-brain barrier

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Glucose is recognized as the main energetic substrate for brain, essential to maintain normal its function. The blood-brain barrier (BBB) plays a key role on limiting and regulating glucose access to glial and neuronal cells.
This work's aim was to characterize glucose uptake on a human BBB model, and its modulation by hormones and diet compounds. hCMEC/D3 cell line was used as an hBBB cell model. Cells were deprived of glucose for 2h and compounds were present for 30 min before uptake experiments. Cells were incubated with 50 nM of $^{3}$H-2-deoxy-D-glucose ($^{3}$H-DG) for 1 min, and the internalized glucose was quantified by liquid scintillation counting.
$Ca^{2+}$ and calmodulin seem to play a role on glucose uptake since $Ca^{2+}$ chelation and an inhibitor of calmodulin significantly decreased $^{3}$H-DG uptake. PKC also seems to be involved since chelerythrine decreased and genistein increased $^{3}$H-DG uptake. PKA involvement is also suggested due to an increase of $^{3}$H-DG uptake after incubation with H89.
The effect of several hormones on glucose uptake was tested. Progesterone (50 and 100 μM) and estrone (200 μM) were found to decrease $^{3}$H-DG uptake. Flavonoids are compounds present in our diet that are associated with neuroprotective effects. Different flavonoids and some of their metabolites found in vivo were studied. Catechin and epicatechin did not have any effect, but their metabolites increased $^{3}$H-DG uptake. Quercetin decreased $^{3}$H-DG uptake, but glucuronic acid-conjugated quercetin did not have any effect.
In conclusion: (i) glucose uptake through BBB seems to be regulated by $Ca^{2+}$-dependent pathways and through the involvement of PKC and PKA activities; (ii) glucose uptake through these cells is an hormone-sensitive mechanism; and (iii) consumption of flavonoid-rich diets can interfere with BBB glucose uptake.

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Keywords: Blood-brain barrier, Flavonoids, Glucose, Hormones

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