The heme oxygenase/biliverdin reductase system in subjects with Down syndrome and later transition to Alzheimer's disease

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Down syndrome (DS) is a genetic disorder characterized by the anomalous presence of three copies of chromosome 21 (instead of two). It is regarded as the most common chromosomal cause of mental retardation. Pathologically, the dementia that develops in DS individuals is similar in many respects to that of Alzheimer disease (AD); Abeta (soluble, insoluble and oligomers) and hyperphosphorylated tau were detected in post-mortem samples of frontal cortex from DS subjects. As a consequence of Abeta and tau production, significant oxidative stress-induced damage was found in this brain area, as demonstrated by the overall increase of lipid- and protein- oxidation markers. One of the mechanisms through which neural cells counteract free radical generation and oxidative stress is the enhancement of the cell adaptive response. The heme oxygenase/biliverdin reductase (HO/BVR) system plays a main role in the cell stress response by the fact that the inducible isoform HO-1, a redox-sensitive enzyme, reduces levels of pro-oxidant heme and generates biliverdin which is then transformed to bilirubin (BR), a molecule with strong antioxidant activity. Both HO-1 overexpression and increased concentrations of BR have in fact been demonstrated in the brain, cerebrospinal fluid, plasma and lymphocytes of patients with AD. The above mentioned lines of evidence prompted us to evaluate whether or not the pro-oxidant status found in DS brain, is responsible for the activation of the HO-1/BVR system. Differently from AD subjects, HO-1 did not show any overexpression in the frontal cortex of DS individuals and this finding was paralleled by the concomitant increase in total Bach1 levels, this latter being a transcription factor which binds the ARE sequence in the promoter region and blocks HO-1 gene transcription. Conversely, HO-1 overexpression and reduced Bach1 levels were detected in the frontal cortex of DS subjects who developed AD later in the age, thus suggesting a role for the activation of HO-1 in the transition from 'healthy' to 'demented' DS. Indeed, HO-1 activation was also shown in the frontal cortex of age-matched controls proposing the involvement of age in HO-1 up-regulation. No significant changes were found in the constitutive HO-2 protein levels in both DS and DS/AD frontal cortices. Interestingly, a marked increase in nitrosative post-translational modification on BVR structure was found which implies a reduction in the BVR activity. These data lend support to the hypothesis of an early increase of oxidative stress in DS frontal cortex which, together with a dysregulation of the HO-1/BVR system and reduced cell stress response, contribute to the later transition to dementia of alzheimerian type in these subjects.