

HemeOxygenase-1: Transducer of Sterol Dys-Regulation in Alzheimer Disease

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Abstract

Cholesterol (CH) and oxysterols have been consistently implicated in brain aging, Alzheimer's disease (AD) and other human neurodegenerative conditions, although the mechanisms underlying these relationships remain poorly understood. Heme oxygenase-1 (HO-1) is a highly-inducible stress protein responsible for the catabolism of heme to free iron, carbon monoxide (CO) and biliverdin/bilirubin. HO-1 mRNA and protein levels are augmented in Alzheimer-diseased neural tissues where they may promote pathological iron deposition and oxidative mitochondrial damage characteristic of this disorder. Here, we review evidence derived from cultured rat astroglia, post-mortem human AD brain samples, novel GFAP. HMOX1 transgenic mice and a triple transgenic AD mouse model (3xTg-AD) implicating HO-1 as a pivotal transducer of noxious ambient stimuli into abnormal patterns of brain sterol/oxysterol homeostasis germane to the pathogenesis of AD and other aging-related neurodegenerative disorders.

AD

AD is a progressive, degenerative, dementing disorder and the sixth leading cause of the death in the US [1]. It is estimated that by the year 2050 the number of patients living with AD in the US may rise to 13-16 million while the worldwide prevalence could reach a staggering 1 in 85 or 75-100 million cases [2-5]. Pathological hallmarks of AD include extracellular deposits of β -amyloid (plaques), neurites containing hyperphosphorylated tau (neurofibrillary tangles) and loss of neurons in discrete regions of the basal forebrain, hippocampus and association cortices [6-11]. A largely overlooked pathological feature of AD, originally described over a century ago by Alois Alzheimer, is the accumulation of "adipose inclusions" or "lipoid granules" suggesting aberrant lipid homeostasis in this degenerative state [12]. Although medications (cholinesterase inhibitors) capable of conferring transient symptomatic relief are available for the management of AD, there is currently no disease-modifying intervention which unequivocally slows arrests or reverses the degenerative process.

Brain Sterols/Oxysterols

Cholesterol (CH), its precursors and oxysterols have been consistently implicated in brain aging and neurodegeneration [2,13-15]. The mechanisms underlying this relationship, however, remain ill-defined. In the CNS, sterols including CH subserves numerous biological functions essential for cell survival and homeostasis [16]. Mammalian CNS development is highly dependent on CH [17]; it is therefore not surprising that altered CH homeostasis occurs in a host of neurological conditions [18,19]. Glial CH can be enzymatically (via CH 7 α -, 24- and 25-hydroxylase) or non-enzymatically (via oxidative stress) metabolized to oxysterols. On the one hand, augmented oxysterol concentrations may protect neural tissues by attenuating β -amyloid deposition and by activation of the liver X receptor (LXR). The latter mediates up-regulation of apolipoprotein E (apoE) which, in turn, promotes glial CH efflux that facilitates neuronal membrane repair. However, LXR activation may also inhibit glial 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase and de novo CH biosynthesis. The latter establishes a negative servomechanism that limits the extent of oxysterol production and CH efflux by these cells. Moreover, primary neuronal cultures have been shown to be highly sensitive to 25-OH cytotoxicity, with lesser vulnerability to other common oxysterols such as 7-keto, 22-OH and 7 β -OH [20]. Oxysterols may also promote cytotoxicity in primary astrocytes and apoptosis in microglial cells.

Several critical lines of evidence have implicated sterol (dys) regulation and the formation of oxysterols in the pathogenesis of AD. For example, genetic association studies have linked polymorphisms of APOE, SORL1, CLU and ABCA7 genes, which directly or indirectly impact lipid homeostasis, with the development of AD [21,22]. In addition, dyslipidemia has been identified in several distinct populations as an important midlife risk factor for sporadic AD [23]. Although the mechanisms responsible for this relationship remain poorly understood, investigations conducted in our laboratory suggest that over-expression of heme oxygenase-1 in AD astrocytes may transduce a broad spectrum of noxious stimuli into altered, and potentially deleterious, patterns of brain sterol homeostasis.

Heme Oxygenase-1

Heme oxygenase-1 belongs to a family of enzymes widely recognized as dynamic sensors of cellular oxidative stress. HO-1 is a 32 kDa stress protein that mediates the catabolism of heme to biliverdin, free iron, and carbon monoxide (CO). Activating protein-1, activating protein-2, nuclear factor kappa B, heat shock factor and hypoxia inducible factor-1 binding sites, metal response elements (MtRE, CdRE) and antioxidant response elements (ARE) render the mammalian Hmox1 gene highly susceptible to up-regulation by a wide array of pro-oxidant and inflammatory stimuli. The Hmox1 gene is inducible by β -amyloid, hydrogen peroxide and Th1 cytokines and accumulates in CNS tissues affected by AD, Parkinson disease and other neurological conditions [24,25]. The up-regulation of HO-1 may confer cytoprotection by enhancing the breakdown of pro-oxidant heme to the radical scavenging bile pigments, biliverdin and bilirubin [26-29]. Under certain conditions, however, the heme-derived iron and

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Received: September 29, 2014; Accepted: October 17, 2014; Published: October 20, 2014

Citation: Hascalovici J, Schipper HM (2014) HemeOxygenase-1: Transducer of Sterol Dys-Regulation in Alzheimer Disease. J Glycomics Lipidomics 4: 124. doi: 10.4172/2153-0637.1000124

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CO may exacerbate intracellular oxidative stress and substrate damage by provoking free radical generation within mitochondria and other subcellular organelles [30]. Germane to the current discussion, HO-1 promotes mitochondrial iron sequestration, oxidative membrane injury and macroautophagy in rodent astroglia both in vitro and in the intact brain [25,31].

In AD-affected brain regions (temporal cortex, hippocampus, etc.), HO-1 protein is increased several-fold and co-localizes to neurons, astrocytes, neurofibrillary tangles, senile plaques, corpora amylacea and vascular smooth muscle and endothelial cells [32-34]. Potential inducers of HMOX1 in AD brain include reactive oxygen species generated by senescent mitochondria, β -amyloid, pro-inflammatory cytokines (TNF α , IL-1 β) and nitric oxide (NO) released from activated microglia [35], and redox-active transition metals [25,31].

HO-1 as a transducer of sterol dys-regulation

We hypothesized that HO-1 over-expression may impact sterol homeostasis in AD neural tissues by amplifying intracellular oxidative stress within the astrocytic compartment [25]. We determined that HO-1 over-expression in cultured rat astroglia significantly decreases intracellular CH concentrations and increases the levels of several oxysterol species. We identified CO and iron as mediators of the observed net decrease in total CH and increase in oxysterol concentrations [36]. In a subsequent study [37], we observed that HO-1 over-expression (2–3-fold) for 3 days resulted in a 30% rise in CH biosynthesis and a two-fold enhancement of CH efflux. Both effects were abrogated by the competitive HO inhibitor, tin mesoporphyrin. CO, released from exogenous CORM-3, significantly augmented CH biosynthesis; a combination of CO and iron stimulated CH efflux; and heme-derived iron likely fostered oxysterol formation in our model. In addition, co-treatment with LXR antagonists implicated LXR activation

in the modulation of CH homeostasis by heme degradation products (Figure 1). We then proceeded to measure HO-1 protein levels and various sterols/oxysterols (by GC-MS) in post-mortem human brain specimens of persons with sporadic AD, mild cognitive impairment (MCI) and no cognitive impairment (NCI) [38]. In AD and some MCI samples, but not in NCI specimens, HO-1 levels correlated significantly with decreased total CH, increased CH precursors (together suggesting augmented CH efflux) and increased oxysterol concentrations [39], commensurate with our in vitro data. We also explored HO-1/sterol interactions in two in vivo animal models: a novel GFAP.HMOX1 transgenic mouse which conditionally and selectively over-expresses the human HMOX1 gene in astrocytes [40,41]; and an established triple transgenic (3xTg-AD) mouse model of AD [42,43]. Total oxysterols significantly decreased as HO-1 expression increased in GFAP.HMOX1 mice ('antioxidant' HO-1 behavior), whereas total oxysterols increased as HO-1 expression increased in aged 3xTg-AD mice harboring AD-like pathology (a 'pro-oxidant' HO-1 effect). We concluded that in diseased (but not healthy aging) neural tissues, glial HO-1 induction transduces dystrophic stimuli, including many that have been linked to known or suspected AD risk factors [23], into altered patterns of sterol/oxysterol homeostasis. Together, our findings underscore a differential impact of HO-1 on the metabolism of brain sterols/oxysterols contingent on the level of HO-1 expression and the presence or absence of AD-like neuropathology [43].

Concluding remarks and future perspective

We adduced evidence implicating glial HO-1 expression as a likely transducer of altered sterol homeostasis in human AD and across several experimental models of neurodegeneration. Our data indicate that HO-1 over-expression and the heme catabolic products, CO and Fe significantly impact CNS sterol homeostasis by influencing brain regulatory mechanisms governing sterol biosynthesis,

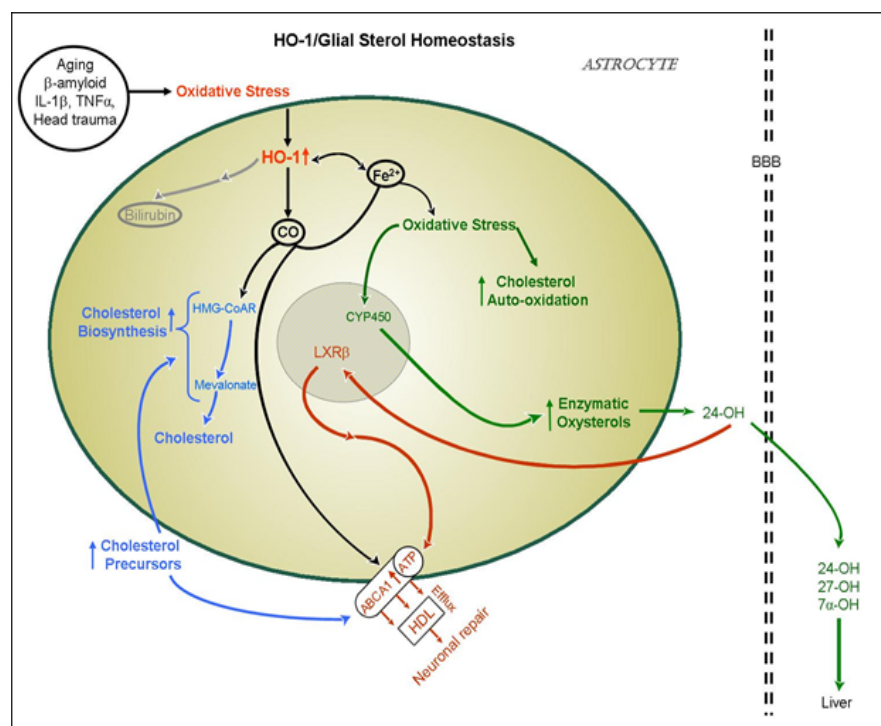


Figure 1: A model depicting the impact of HO-1 over-expression on astroglial sterol homeostasis. Republished from Hascalovici et al. J Neurochem (2009) 108, 72-81 with permission.

efflux and oxidation. Further investigations along these lines should disclose whether aberrant HO-1/sterol dynamics akin to those described here constitute a ubiquitous pathway of pathological brain aging and degeneration and, hence, a robust target for therapeutic intervention. Several metalloporphyrin inhibitors of hemeoxygenase activity are already in clinical use for the management of neonatal hyperbilirubinemia (jaundice) and certain adult liver conditions and could be adapted for the treatment of CNS disorders. Recently, novel imidazole-based inhibitors that are relatively selective for the HO-1 isoform and display favorable blood-brain barrier penetration were shown to ameliorate cognitive dysfunction in the APPs_{we/PS1^{ΔE9}} mouse model of AD [43]. It will be important to ascertain whether this salutary effect on behavior is due, in whole or in part, to normalization of brain sterol/oxysterol homeostasis in these animals.

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