Selected References on Carbon Monoxide and Parkinsonism/Parkinson’s Disease

This bibliography was compiled by CHE partner Albert Donnay, MHS., a strong proponent of the position that carbon monoxide (CO) is a major risk factor in the development of Parkinson’s disease (PD). He has compiled this list of references in support of this position. At June 2007 CHE Consensus Conference on PD and the Environment, the role of CO in PD was briefly discussed. The scientists present at the Consensus Conference indicated that they did not consider CO a significant risk factor in PD. We will be discussing this difference in scientific views on the September PD work group call.

Please note that this list is for educational purposes only and is not intended to be an exhaustive list. Inclusion of this document herein does not imply endorsement by the Collaborative on Health and the Environment.

REFERENCES ON “PARKINSON AND CARBON MONOXIDE” SINCE 1997
RETRIEVED FROM WWW.PUBMED.GOV ON 2/18/07 (WITH ABSTRACTS IF AVAILABLE)
LISTED IN CHRONOLOGICAL ORDER STARTING WITH MOST RECENT; NOT LISTED ARE 30 OLDER REFERENCES FROM 1950 THROUGH 1997.
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[Role of hemeoxygenase-1 in the neurodegenerative disorders]

[Article in Spanish]

Orozco-Ibarra M, Chirino YI, Pedraza-Chaverri J.

Departamento de Biologia, Facultad de Quimica, Universidad Nacional Autonoma de Mexico, Mexico DF, Mexico.

AIM: To review some evidences about the role of hemeoxygenase-1 (HO-1) in neurodegenerative disorders. DEVELOPMENT: HO is the rate-limiting enzyme that catalyzes the conversion of heme into biliverdin, carbon monoxide, and free iron. They are the inducible HO-1 and the constitutive HO-2. A large body of evidence suggests that HO-1 confers cytoprotection against oxidative stress. Postmortem studies conducted in humans have revealed increase in HO-1 protein in association with Alzheimer disease, Parkinson disease and Huntington disease. It is unknown the meaning of that increase. Nevertheless, there are evidences indicating that the overexpression of HO-1 contributes to the pathological iron deposition suggesting a detrimental role of HO-1. In contrast, there are evidences indicating that the overexpression of HO-1 decreases the neurotoxin-induced cell death in transgenic mice and neuronal cultures suggesting a cytoprotective role of HO-1. CONCLUSION: It is
controversial if the overexpression of HO-1 has a detrimental or cytoprotective role. Therefore, it is necessary to continue the study about the role of the HO-1 in neurodegenerative diseases.


Over-expression of heme oxygenase-1 promotes oxidative mitochondrial damage in rat astroglia.

Song W, Su H, Song S, Paudel HK, Schipper HM.

Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada.

Glial heme oxygenase-1 is over-expressed in the CNS of subjects with Alzheimer disease (AD), Parkinson disease (PD) and multiple sclerosis (MS). Up-regulation of HO-1 in rat astroglia has been shown to facilitate iron sequestration by the mitochondrial compartment. To determine whether HO-1 induction promotes mitochondrial oxidative stress, assays for 8-epiPGF(2alpha) (ELISA), protein carbonyls (ELISA) and 8-OHdG (HPLC-EC) were used to quantify oxidative damage to lipids, proteins, and nucleic acids, respectively, in mitochondrial fractions and whole-cell compartments derived from cultured rat astroglia engineered to over-express human (h) HO-1 by transient transfection. Cell viability was assessed by trypan blue exclusion and the MTT assay, and cell proliferation was determined by [3H] thymidine incorporation and total cell counts. In rat astrocytes, hHO-1 over-expression (x 3 days) resulted in significant oxidative damage to mitochondrial lipids, proteins, and nucleic acids, partial growth arrest, and increased cell death. These effects were attenuated by incubation with 1 microM tin mesoporphyrin, a competitive HO inhibitor, or the iron chelator, deferoxamine. Up-regulation of HO-1 engenders oxidative mitochondrial injury in cultured rat astroglia. Heme-derived ferrous iron and carbon monoxide (CO) may mediate the oxidative modification of mitochondrial lipids, proteins and nucleic acids in these cells. Glial HO-1 hyperactivity may contribute to cellular oxidative stress, pathological iron deposition, and bioenergetic failure characteristic of degenerating and inflamed neural tissues and may constitute a rational target for therapeutic intervention in these conditions. Copyright 2005 Wiley-Liss, Inc.


Heme oxygenase expression in human central nervous system disorders.

Schipper HM.

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Role of heme oxygenase-1 in the regulation of manganese superoxide dismutase gene expression in oxidatively-challenged astroglia.

Frankel D, Mehdinate K, Schipper HM.

Bloomfield Centre for Research in Aging, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Canada.

Manganese superoxide dismutase (MnSOD) is an antioxidant enzyme that reduces superoxide anion to hydrogen peroxide in cell mitochondria. MnSOD is overexpressed in normal aging brain and in various central nervous system disorders; however, the mechanisms mediating the upregulation of MnSOD under these conditions remain poorly understood. We previously reported that cysteamine (CSH) and other pro-oxidants rapidly induce the heme oxygenase-1 (HO-1) gene in cultured rat astroglia followed by late upregulation of MnSOD in these cells. In the present study, we demonstrate that antecedent upregulation of HO-1 is necessary and sufficient for subsequent induction of the MnSOD gene in neonatal rat astroglia challenged with CSH or dopamine, and in astroglial cultures transiently transfected with full-length human HO-1 cDNA. Treatment with potent antioxidants attenuates MnSOD expression in HO-1-transfected astroglia, strongly suggesting that intracellular oxidative stress signals MnSOD gene induction in these cells. Activation of this HO-1-MnSOD axis may play an important role in the pathogenesis of Alzheimer disease, Parkinson disease and other free radical-related neurodegenerative disorders. In these conditions, compensatory upregulation of MnSOD may protect mitochondria from oxidative damage accruing from heme-derived free iron and carbon monoxide liberated by the activity of HO-1. Copyright 2000 Wiley-Liss, Inc.


Heme oxygenase-1: role in brain aging and neurodegeneration.

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The brain lesion responsible for parkinsonism after carbon monoxide poisoning.

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Department of Neurology, Yonsei University College of Medicine, CPO Box 8044, Seoul, Korea.

BACKGROUND: Parkinsonism is a common neurological sequela of carbon monoxide (CO) poisoning, but its pathophysiological mechanism has yet to be clarified. OBJECTIVES: To describe a married couple who were both affected by CO poisoning, but only 1 of whom developed CO-induced parkinsonism, and to discuss the possible underlying pathophysiological mechanism of CO-induced parkinsonism by comparing the neuroimaging findings of these patients. DESIGN AND SETTING: Case report from a clinical neurology department. PATIENTS: A married couple experienced CO poisoning simultaneously. One month later, only the husband gradually developed delayed sequelae, including parkinsonism and intellectual impairment. On detailed neurological examination, the husband showed mild but definite rigidity and bradykinesia, while no parkinsonian signs were observed in the wife. Neuropsychological examination revealed impaired memory and attention in both patients, but they were more severe in the husband than in the wife. Magnetic resonance imaging scans of the patients' brains disclosed diffuse high-intensity white matter signals in both patients and bilateral pallidal necrosis in the wife. Dopamine transporter imaging showed that the degree of dopamine neuronal loss was comparable between these patients. Magnetic resonance spectroscopy revealed more severe white matter damage in the husband than in the wife. Thirteen months later, neurological and neuropsychological examination showed complete recovery from parkinsonism as well as intellectual impairment. Follow-up magnetic resonance spectroscopy also suggested remarkable improvements in white matter damage. CONCLUSION: These results
support the role of whitematter damage in producing parkinsonism after CO poisoning and highlight the possible usefulness of magnetic resonance spectroscopy in predicting delayed sequelae in patients after CO poisoning. Arch Neurol. 2000;57:1214-1218


P450 and heme oxygenase enzymes in the basal ganglia and their roles in Parkinson's disease.

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Environmental risk factors in Parkinson's disease.

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Glial HO-1 expression, iron deposition and oxidative stress in neurodegenerative diseases.

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The mechanisms responsible for the pathological deposition of brain iron in Parkinson's disease, Alzheimer's disease and other human neurodegenerative disorders remain poorly understood. In rat primary astrocyte cultures, we demonstrated that dopamine, cysteamine, H(2)O(2) and menadione rapidly induce heme oxygenase-1 (HO-1) expression (mRNA and protein) followed by sequestration of non-transferrin-derived (55)Fe by the mitochondrial compartment. The effects of dopamine on HO-1 expression were inhibited by ascorbate implicating a free radical mechanism of action. Dopamine-induced mitochondrial iron trapping was abrogated by administration of the heme oxygenase inhibitors, tin mesoporphyrin (SnMP) or dexamethasone (DEX) indicating that HO-1 upregulation is necessary for subsequent mitochondrial iron deposition in these cells. Overexpression of the human HO-1 gene in cultured rat astroglia by transient transfection also stimulated mitochondrial (55)Fe deposition, an effect that was again preventible by SnMP or DEX administration. We hypothesize that free ferrous iron and carbon monoxide generated by HO-1-mediated heme degradation promote mitochondrial membrane injury and the deposition of redox-active iron within this organelle. We have shown that the percentages of GFAP-positive astrocytes that co-
express HO-1 in Parkinson-affected substantia nigra and Alzheimer-diseased hippocampus are significantly increased relative to age-matched controls. Stress-induced up-regulation of HO-1 in astroglia may be responsible for the abnormal patterns of brain iron deposition and mitochondrial insufficiency documented in various human neurodegenerative disorders.


Neural heme oxygenase-1 expression in idiopathic Parkinson's disease.

Schipper HM, Liberman A, Stopa EG.

Bloomfield Centre for Research in Aging, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Quebec, Canada.

Heme oxygenase-1 is a cellular stress protein expressed in brain and other tissues in response to oxidative challenge and other noxious stimuli. In the present study, immunohistochemistry was used to assess HO-1 expression in various postmortem human brain specimens derived from PD and control subjects. In the substantia nigra of both PD and control specimens, moderate HO-1 immunoreactivity was consistently observed in neuromelanin-containing (dopaminergic) neurons. Lewy bodies in PD nigra neurons exhibited intense HO-1 immunostaining in their peripheries. In both PD and control specimens, neuronal HO-1 staining was faint or nondetectable in the other brain regions surveyed. The fraction of GFAP-positive astroglia expressing HO-1 in PD substantia nigra (77.1 +/- 12.3) was significantly greater than that observed in the substantia nigra of control subjects (18.7 +/- 7.1; P = 0.0015). In the other regions examined, percentages of GFAP-positive astroglia coexpressing HO-1 were relatively low and did not differ significantly (P > 0.05) between control and PD specimens. Upregulation of HO-1 in the substantia nigra of PD subjects supports the view that the affected tissue is experiencing chronic oxidative stress. In addition, excessive cellular levels of heme-derived free iron and carbon monoxide resulting from HO-1 overactivity may contribute to the pathogenesis of PD.


[Atlas of cranial and spinal MRI--magnetic resonance imaging in carbon monoxide poisoning and Parkinsonian syndrome]

[Article in Japanese]

Ikeda K, Sasaki S, Ichijo S, Matsuoka Y, Irimajiri S.

REFERENCES ON “PARKINSON AND CARBON MONOXIDE” SINCE 1990

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The mechanisms responsible for the pathological deposition of brain iron in Parkinson's disease, Alzheimer's disease and other human neurodegenerative disorders remain poorly understood. In rat primary astrocyte cultures, we demonstrated that dopamine, cysteamine, H(2)O(2) and menadione rapidly induce heme oxygenase-1 (HO-1) expression (mRNA and protein) followed by sequestration of non-transferrin-derived (55)Fe by the mitochondrial compartment. The effects of dopamine on HO-1 expression were inhibited by ascorbate implicating a free radical mechanism of action. Dopamine-induced mitochondrial iron trapping was abrogated by administration of the heme oxygenase inhibitors, tin mesoporphyrin (SnMP) or dexamethasone (DEX) indicating that HO-1 upregulation is necessary for subsequent mitochondrial iron deposition in these cells. Overexpression of the human HO-1 gene in cultured rat astroglia by transient transfection also stimulated mitochondrial (55)Fe deposition, an effect that was again preventible by SnMP or DEX administration. We hypothesize that free ferrous iron and carbon monoxide generated by HO-1-mediated heme degradation promote mitochondrial membrane injury and the deposition of redox-active iron within this organelle. We have shown that the percentages of GFAP-positive astrocytes that co-express HO-1 in Parkinson-affected substantia nigra and Alzheimer-diseased hippocampus are significantly increased relative to age-matched controls. Stress-induced regulation of HO-1 in astroglia may be responsible for the abnormal patterns of brain iron deposition and mitochondrial insufficiency documented in various human neurodegenerative disorders.


Neural heme oxygenase-1 expression in idiopathic Parkinson's disease.

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Heme oxygenase-1 is a cellular stress protein expressed in brain and other tissues in response to oxidative challenge and other noxious stimuli. In the present study, immunohistochemistry was used to assess HO-1 expression in various postmortem human brain specimens derived from PD and control subjects. In the substantia nigra of both PD and control specimens, moderate HO-1 immunoreactivity was consistently observed in neuromelanin-containing (dopaminergic) neurons. Lewy bodies in PD nigra neurons exhibited intense HO-1 immunostaining in their peripheries. In both PD and control specimens, neuronal HO-1 staining was faint or nondetectable in the other brain regions surveyed. The fraction of GFAP-positive astroglia expressing HO-1 in PD substantia nigra (77.1 +/- 12.3) was significantly greater than that observed in the substantia nigra of control subjects (18.7 +/- 7.1; P = 0.0015). In the other regions examined, percentages of GFAP-positive astroglia coexpressing HO-1 were relatively low and did not differ significantly (P > 0.05) between control and PD specimens. Upregulation of HO-1 in the substantia nigra of PD subjects supports the view that the affected tissue is experiencing chronic oxidative stress. In addition, excessive cellular levels of heme-derived free iron and carbon monoxide resulting from HO-1 overactivity may contribute to the pathogenesis of PD.


[Atlas of cranial and spinal MRI--magnetic resonance imaging in carbon monoxide poisoning and Parkinsonian syndrome]

[Article in Japanese]

Ikeda K, Sasaki S, Ichijo S, Matsuoka Y, Irimajiri S.