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
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LISTED IN CHRONOLOGICAL ORDER STARTING WITH MOST RECENT;NOT LISTED ARE 30 OLDER REFERENCES FROM 1950 THROUGH 1997.
COMPILED BY ALBERT DONNAY, adonnay@jhu.edu
LIST EDITED BY JACKIE HUNT CHRISTENSEN, jackiehc@gmail.com

1. Rev Neurol. 2006 Nov 1-15;43(9):556-62.

[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 deMexico, Mexico DF, Mexico.

AIM: To review some evidences about the role of hemeoxygenase-1 (HO-1) inneurodegenerative disorders. DEVELOPMENT: HO is the rate-limiting enzyme thatcatalyzes the conversion of heme into biliverdin, carbon monoxide, and freeiron. They are the inducible HO-1 and the constitutive HO-2. A large body ofevidence suggests that HO-1 confers cytoprotection against oxidative stress.Postmortem studies conducted in humans have revealed increase in HO-1 protein inassociation with Alzheimer disease, Parkinson disease and Huntington disease. Itis unknown the meaning of that increase. Nevertheless, there are evidencesindicating that the overexpression of HO-1 contributes to the pathological irondeposition suggesting a detrimental role of HO-1. In contrast, there areevidences indicating that the overexpression of HO-1 decreases theneurotoxin-induced cell death in transgenic mice and neuronal culturessuggesting a cytoprotective role of HO-1. CONCLUSION: It is

controversial if theoverexpression of HO-1 has a detrimental or cytoprotective role. Therefore, itis necessary to continue the study about the role of the HO-1 inneurodegenerative diseases.

2: J Cell Physiol. 2006 Mar;206(3):655-63.

Over-expression of heme oxygenase-1 promotes oxidative mitochondrial damage inrat 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 Alzheimerdisease (AD), Parkinson disease (PD) and multiple sclerosis (MS). Up-regulationof HO-1 in rat astroglia has been shown to facilitate iron sequestration by themitochondrial compartment. To determine whether HO-1 induction promotesmitochondrial oxidative stress, assays for 8-epiPGF(2alpha) (ELISA), proteincarbonyls (ELISA) and 8-OHdG (HPLC-EC) were used to quantify oxidative damage tolipids, proteins, and nucleic acids, respectively, in mitochondrial fractionsand whole-cell compartments derived from cultured rat astroglia engineered toover-express human (h) HO-1 by transient transfection. Cell viability wasassessed by trypan blue exclusion and the MTT assay, and cell proliferation wasdetermined by [3H] thymidine incorporation and total cell counts. In ratastrocytes, hHO-1 over-expression (x 3 days) resulted in significant oxidativedamage to mitochondrial lipids, proteins, and nucleic acids, partial growtharrest, and increased cell death. These effects were attenuated by incubationwith 1 microM tin mesoporphyrin, a competitive HO inhibitor, or the ironchelator, deferoxamine. Up-regulation of HO-1 engenders oxidative mitochondrialinjury in cultured rat astroglia. Heme-derived ferrous iron and carbon monoxide(CO) may mediate the oxidative modification of mitochondrial lipids, proteinsand nucleic acids in these cells. Glial HO-1 hyperactivity may contribute tocellular oxidative stress, pathological iron deposition, and bioenergeticfailure characteristic of degenerating and inflamed neural tissues and mayconstitute a rational target for therapeutic intervention in these conditions.

3: Free Radic Biol Med. 2004 Dec 15;37(12):1995-2011.

Heme oxygenase expression in human central nervous system disorders.

Schipper HM.

Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish GeneralHospital, 3755 Cote St. Catherine Road, Montreal QC H3T 1E2, Canada.hyman.schipper@mcgill.ca

In the normal mammalian CNS, heme oxygenase-2 (HO-2) is constitutively,abundantly, and fairly ubiquitously expressed, whereas heme oxygenase-1 (HO-1)mRNA and protein are confined to small populations of scattered neurons andneuroglia. Unlike ho-2, the ho-1 gene in neural (and many systemic) tissues isexquisitely sensitive to upregulation by a host of pro-oxidant and other noxiousstimuli. In Alzheimer disease, HO-1 immunoreactivity is significantly augmentedin neurons and astrocytes of the hippocampus and cerebral cortex relative toage-matched, nondemented controls and colocalizes to senile plaques,neurofibrillary tangles, and corpora amylacea. In Parkinson disease, HO-1decorates Lewy bodies of affected dopaminergic neurons and is highlyoverexpressed in astrocytes residing within the substantia nigra. The ho-1 geneis also upregulated in glial cells within multiple sclerosis plaques; in thevicinity of human cerebral infarcts, hemorrhages, and contusions; and in variousother degenerative and nondegenerative human CNS disorders. The products of theheme oxygenase reaction, free ferrous iron, carbon monoxide, andbiliverdin/bilirubin, are all biologically active molecules that may profoundlyinfluence tissue redox homeostasis under a wide range of pathophysiologicalconditions. Evidence adduced from whole animal and in vitro studies indicatesthat enhanced HO-1 activity may either ameliorate or exacerbate neural injury,effects likely contingent upon the specific model employed, the duration andintensity of HO-1 induction, and the chemistry of the local redoxmicroenvironment. HO-1 hyperactivity also promotes mitochondrial sequestrationof nontransferrin iron in oxidatively challenged astroglia and may therebycontribute to the pathological iron deposition and bioenergetic failure amplydocumented in aging and degenerating human neural tissues.

4: Eur Neurol. 2002;48(1):30-3.

Parkinsonism after carbon monoxide poisoning.

Choi IS.

Department of Neurology, Yonsei University College of Medicine, Seoul, Korea.

Of 242 patients with carbon monoxide (CO) poisoning examined between 1986 and1996, parkinsonism was diagnosed in 23 (9.5%). There were 11 men and 12 women.The age at onset ranged from 16 to 69 (mean 45.8) years, with the peak incidenceduring the 6th decade. The latency before the appearance of parkinsonism variedfrom 2 to 26 (median 4) weeks, but parkinsonism developed within 1 month afteran acute insult in the majority of the patients. All showed encephalopathy withmildly to severely impaired cognitive functions during or immediately afterdelayed CO sequelae. The common symptoms were gait disturbance, impairedmentality, urinary incontinence, and mutism. The most frequent signs wereshort-step gait, hypokinesia, masked face, increased muscle tone (rigidity),glabella sign, grasp reflex, and retropulsion. Intentional tremor wasoccasionally found, but resting tremor could not be seen. There was nocorrelation between the neuroimaging findings and the development ofparkinsonism. Levodopa and anticholinergic drugs were not effective. Of 16patients followed up for 1 year, 13 (81.3%) recovered spontaneously within 6months. In

conclusion, parkinsonism after CO poisoning is not rare and usuallyappears as a part of delayed CO encephalopathy. Any drug is not effective, butthe prognosis is good. Copyright 2002 S. Karger AG, Basel

5: J Cell Physiol. 2000 Oct;185(1):80-6.

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

Frankel D, Mehindate K, Schipper HM.

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

Manganese superoxide dismutase (MnSOD) is an antioxidant enzyme that reducessuperoxide anion to hydrogen peroxide in cell mitochondria. MnSOD isoverexpressed in normal aging brain and in various central nervous systemdisorders; however, the mechanisms mediating the upregulation of MnSOD underthese conditions remain poorly understood. We previously reported thatcysteamine (CSH) and other pro-oxidants rapidly induce the heme oxygenase-1(HO-1) gene in cultured rat astroglia followed by late upregulation of MnSOD inthese cells. In the present study, we demonstrate that antecedent upregulationof HO-1 is necessary and sufficient for subsequent induction of the MnSOD genein neonatal rat astroglia challenged with CSH or dopamine, and in astroglialcultures transiently transfected with full-length human HO-1 cDNA. Treatmentwith potent antioxidants attenuates MnSOD expression in HO-1-transfectedastroglia, strongly suggesting that intracellular oxidative stress signals MnSODgene induction in these cells. Activation of this HO-1-MnSOD axis may play animportant role in the pathogenesis of Alzheimer disease, Parkinson disease andother free radical-related neurodegenerative disorders. In these conditions,compensatory upregulation of MnSOD may protect mitochondria from oxidativedamage accruing from heme-derived free iron and carbon monoxide liberated by theactivity of HO-1.

6: Exp Gerontol. 2000 Sep;35(6-7):821-30.

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

Schipper HM.

Bloomfield Centre for Research in Aging, Lady Davis Institute for MedicalResearch, Sir Mortimer B. Davis Jewish General Hospital, McGill University,Que., H3T 1E2, Montreal, Canada. czhs@musica.mcgill.ca

The mechanisms responsible for excessive iron deposition and mitochondrialinsufficiency in the aging and degenerating nervous system remain poorlyunderstood. Heme oxygenase-1 (HO-1) is a 32kDa stress protein that degrades

hemeto biliverdin, free iron and carbon monoxide. Our laboratory has shown thatcysteamine, dopamine, beta-amyloid, IL-1beta and TNF-alpha up-regulate HO-1followed by mitochondrial sequestration of non-transferrin-derived 55Fe incultured rat astroglia. In these cells and in rat astroglia transfected with thehuman HO-1 gene, mitochondrial iron trapping is abrogated by the HO-1inhibitors, tin-mesoporphyrin and dexamethasone. We determined that HO-1immunoreactivity is enhanced greatly in neurons and astrocytes of thehippocampus and cerebral cortex of Alzheimer subjects and co-localizes to senileplaques and neurofibrillary tangles (NFT). HO-1 staining is also augmented inastrocytes and decorates neuronal Lewy bodies in the Parkinson nigra.Collectively, our findings suggest that HO-1 over-expression contributes to thepathological iron deposition and mitochondrial damage documented in theseaging-related neurodegenerative disorders. We recently observed that,paradoxically, HO-1 mRNA levels are markedly suppressed in peripherallymphocytes of patients with early sporadic Alzheimer disease and may thusprovide a useful biological marker of this condition.

7: Arch Neurol. 2000 Aug;57(8):1214-8.

The brain lesion responsible for parkinsonism after carbon monoxide poisoning.

Sohn YH, Jeong Y, Kim HS, Im JH, Kim JS.

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 thepossible underlying pathophysiological mechanism of CO-induced parkinsonism bycomparing the neuroimaging findings of these patients. DESIGN AND SETTING: Casereport from a clinical neurology department. PATIENTS: A married coupleexperienced CO poisoning simultaneously. One month later, only the husbandgradually developed delayed sequelae, including parkinsonism and intellectualimpairment. On detailed neurological examination, the husband showed mild butdefinite rigidity and bradykinesia, while no parkinsonian signs were observed inthe wife. Neuropsychological examination revealed impaired memory and attentionin both patients, but they were more severe in the husband than in the wife.Magnetic resonance imaging scans of the patients' brains disclosed diffusehigh-intensity white matter signals in both patients and bilateral pallidalnecrosis in the wife. Dopamine transporter imaging showed that the degree ofdopamine neuronal loss was comparable between these patients. Magnetic resonancespectroscopy revealed more severe white matter damage in the husband than in thewife. Thirteen months later, neurological and neuropsychological examinationsshowed complete recovery from parkinsonism as well as intellectual impairment.Follow-up magnetic resonance spectroscopy also suggested remarkable improvementsin white matter damage. CONCLUSION: These results

support the role of whitematter damage in producing parkinsonism after CO poisoning and highlight thepossible usefulness of magnetic resonance spectroscopy in predicting delayedsequelae in patients after CO poisoning. Arch Neurol. 2000;57:1214-1218

8: Adv Neurol. 1999;80:271-86.

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

Riedl AG, Watts PM, Brown CT, Jenner P.

Neurodegenerative Disease Research Centre, King's College, London, UnitedKingdom.

9: Mov Disord. 1999 Nov;14(6):928-39.

Environmental risk factors in Parkinson's disease.

Kuopio AM, Marttila RJ, Helenius H, Rinne UK.

Department of Neurology, University of Turku, Finland.

We studied the environmental risk factors of Parkinson's disease (PD) inFinland, particularly those related to rural environment, in a prevalencematerial in 1992. The population numbered 196,864 people, including urban andrural areas. In this community-based study, we used a case-control method withpersonal investigation of the case subjects (n = 123) and matched controlsubjects (n = 246). Analyses were carried out by conditional logistic regressionmodel. Case subjects had far fewer domestic animals at home during theirlifetime, including cows, sheep, pigs, and chickens. The difference was evenmore obvious in those under the age of 20 years, including also cats and horses,but diminished after 20 years. The number of different animal species wassmaller with case subjects as was the duration of animal contacts. Case subjectsfound their work physically heavier and exercised more. The mean age at onset inever-smoking men was significantly higher than in never-smoking men. No specialreason for non-smoking increased, and a physical reason decreased the risk ofPD. Area of birth or living, farming and other occupations, types of drinkingwater, pesticide and herbicide use, head injuries, use of alcohol, education,and carbon monoxide poisonings were similar among case subjects and controlsubjects. In conclusion, domestic animals, or something that is connected withthe animals, may have a protecting effect against PD. Alternatively, theobserved negative associations of domestic animals at home and subsequent PD mayonly be a marker of other environmental conditions or lifestyles.

10: Eur Neurol. 1999;42(3):141-4.

Delayed movement disorders after carbon monoxide poisoning.

Choi IS, Cheon HY.

Department of Neurology, Yonsei University College of Medicine, Seoul, Korea.

Of 242 patients with carbon monoxide (CO) poisoning examined between 1986 and1996, delayed movement disorders were diagnosed in 32 (13. 2%). There were 15men and 17 women. Ages at insult ranged from 9 to 69 years (mean 45.3 years). Ofthe 32 patients with delayed movement disorders, 23 (71.9%) had parkinsonism, 5dystonia, 3 chorea and 1 myoclonus. All were associated with delayed COencephalopathy. The median latency between CO poisoning and the onset ofmovement disorders was 4 weeks for parkinsonism, 51 weeks for dystonia, 4 weeksfor chorea and 8 weeks for myoclonus. The latency of dystonia onset after COpoisoning was longer than that of other types of movement disorders. The CTfindings in delayed movement disorders after CO poisoning were variable, andthere was no correlation between the sites of imaging and the development ofmovement disorders. Abnormal dyskinesias disappeared within 8 weeks, andpatients recovered from parkinsonism within 6 months. In conclusion, delayedmovement disorders after CO poisoning are not rare, and usually appear as a partof delayed CO encephalopathy. The prognosis is good.

11: Neurotox Res. 1999 Sep;1(1):57-70.

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

Schipper HM.

Bloomfield Centre for Research in Aging, Lady Davis Institute for MedicalResearch, Montreal, Quebec, Canada. czhs@musica.mcgill.ca

The mechanisms responsible for the pathological deposition of brain iron inParkinson's disease, Alzheimer's disease and other human neurodegenerativedisorders remain poorly understood. In rat primary astrocyte cultures, wedemonstrated that dopamine, cysteamine, H(2)O(2) and menadione rapidly induceheme oxygenase-1 (HO-1) expression (mRNA and protein) followed by sequestrationof non-transferrin-derived (55)Fe by the mitochondrial compartment. The effectsof dopamine on HO-1 expression were inhibited by ascorbate implicating a freeradical mechanism of action. Dopamine-induced mitochondrial iron trapping wasabrogated by administration of the heme oxygenase inhibitors, tin mesoporphyrin(SnMP) or dexamethasone (DEX) indicating that HO-1 upregulation is necessary forsubsequent mitochondrial iron deposition in these cells. Overexpression of thehuman HO-1 gene in cultured rat astroglia by transient transfection alsostimulated mitochondrial (55)Fe deposition, an effect that was again preventibleby SnMP or DEX administration. We hypothesize that free ferrous iron and carbonmonoxide generated by HO-1-mediated heme degradation promote mitochondrialmembrane injury and the deposition of redox-active iron within this organelle.We have shown that the percentages of GFAP-positive astrocytes that co-

expressHO-1 in Parkinson-affected substantia nigra and Alzheimer-diseased hippocampusare significantly increased relative to age-matched controls. Stress-inducedup-regulation of HO-1 in astroglia may be responsible for the abnormal patternsof brain iron deposition and mitochondrial insufficiency documented in varioushuman neurodegenerative disorders.

12: Exp Neurol. 1998 Mar;150(1):60-8.

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 MedicalResearch, Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Quebec,Canada.

Heme oxygenase-1 is a cellular stress protein expressed in brain and othertissues in response to oxidative challenge and other noxious stimuli. In thepresent study, immunohistochemistry was used to assess HO-1 expression invarious postmortem human brain specimens derived from PD and control subjects.In the substantia nigra of both PD and control specimens, moderate HO-1immunoreactivity was consistently observed in neuromelanin-containing(dopaminergic) neurons. Lewy bodies in PD nigra neurons exhibited intense HO-1immunostaining in their peripheries. In both PD and control specimens, neuronalHO-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 substantianigra of control subjects (18.7 +/- 7.1; P = 0.0015). In the other regionsexamined, percentages of GFAP-positive astroglia coexpressing HO-1 wererelatively low and did not differ significantly (P > 0.05) between control andPD specimens. Upregulation of HO-1 in the substantia nigra of PD subjectssupports the view that the affected tissue is experiencing chronic oxidativestress. In addition, excessive cellular levels of heme-derived free iron andcarbon monoxide resulting from HO-1 overactivity may contribute to thepathogenesis of PD.

13: No To Shinkei. 1998 Jan;50(1):86-7.

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

[Article in Japanese]

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

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

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6: Exp Gerontol. 2000 Sep;35(6-7):821-30.

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7: Arch Neurol. 2000 Aug;57(8):1214-8.

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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 thepossible underlying pathophysiological mechanism of CO-induced parkinsonism bycomparing the neuroimaging findings of these patients. DESIGN AND SETTING: Casereport from a clinical neurology department. PATIENTS: A married coupleexperienced CO poisoning simultaneously. One month later, only the husbandgradually developed delayed sequelae, including parkinsonism and intellectualimpairment. On detailed neurological examination, the husband showed mild butdefinite rigidity and bradykinesia, while no parkinsonian signs were observed inthe wife. Neuropsychological examination revealed impaired memory and attentionin both patients, but they were more severe in the husband than in the wife.Magnetic resonance imaging scans of the patients' brains disclosed diffusehigh-intensity white matter signals in both patients and bilateral pallidalnecrosis in the wife. Dopamine transporter imaging showed that the degree ofdopamine neuronal loss was comparable between these patients. Magnetic resonancespectroscopy revealed more severe white matter damage in the husband than in thewife. Thirteen months later, neurological and neuropsychological examinationsshowed complete recovery from parkinsonism as well as intellectual impairment.Follow-up magnetic resonance spectroscopy also suggested remarkable improvementsin white matter damage. CONCLUSION: These results support the role of whitematter damage in producing parkinsonism after CO poisoning and highlight thepossible usefulness of magnetic resonance spectroscopy in predicting delayedsequelae in patients after CO poisoning. Arch Neurol. 2000;57:1214-1218

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Neurodegenerative Disease Research Centre, King's College, London, UnitedKingdom.

9: Mov Disord. 1999 Nov;14(6):928-39.

Environmental risk factors in Parkinson's disease.

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We studied the environmental risk factors of Parkinson's disease (PD) inFinland, particularly those related to rural environment, in a prevalencematerial in 1992. The population numbered 196,864 people, including urban andrural areas. In this community-based study, we used a case-control method withpersonal investigation of the case subjects (n = 123) and matched controlsubjects (n = 246). Analyses were carried out by conditional logistic regressionmodel. Case subjects had far fewer domestic animals at home during theirlifetime, including cows, sheep, pigs, and chickens. The difference was evenmore obvious in those under the age of 20 years, including also cats and horses,but diminished after 20 years. The number of different animal species wassmaller with case subjects as was the duration of animal contacts. Case subjectsfound their work physically heavier and exercised more. The mean age at onset inever-smoking men was significantly higher than in never-smoking men. No specialreason for non-smoking increased, and a physical reason decreased the risk ofPD. Area of birth or living, farming and other occupations, types of drinkingwater, pesticide and herbicide use, head injuries, use of alcohol, education,and carbon monoxide poisonings were similar among case subjects and controlsubjects. In conclusion, domestic animals, or something that is connected withthe animals, may have a protecting effect against PD. Alternatively, theobserved negative associations of domestic animals at home and subsequent PD mayonly be a marker of other environmental conditions or lifestyles.

10: Eur Neurol. 1999;42(3):141-4.

Delayed movement disorders after carbon monoxide poisoning.

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Of 242 patients with carbon monoxide (CO) poisoning examined between 1986 and1996, delayed movement disorders were diagnosed in 32 (13. 2%). There were 15men and 17 women. Ages at insult ranged from 9 to 69 years (mean 45.3 years). Ofthe 32 patients with delayed movement disorders, 23 (71.9%) had parkinsonism, 5dystonia, 3 chorea and 1 myoclonus. All were associated with delayed COencephalopathy. The median latency between CO poisoning and the onset ofmovement disorders was 4 weeks for parkinsonism, 51 weeks for dystonia, 4 weeksfor chorea and 8 weeks for myoclonus. The latency of dystonia onset after COpoisoning was longer than that of other types of movement disorders. The CTfindings in delayed movement disorders after CO poisoning were variable, andthere was no correlation between the sites of imaging and the development ofmovement disorders. Abnormal dyskinesias disappeared within 8 weeks, andpatients recovered

from parkinsonism within 6 months. In conclusion, delayedmovement disorders after CO poisoning are not rare, and usually appear as a partof delayed CO encephalopathy. The prognosis is good.

11: Neurotox Res. 1999 Sep;1(1):57-70.

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

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The mechanisms responsible for the pathological deposition of brain iron inParkinson's disease, Alzheimer's disease and other human neurodegenerativedisorders remain poorly understood. In rat primary astrocyte cultures, wedemonstrated that dopamine, cysteamine, H(2)O(2) and menadione rapidly induceheme oxygenase-1 (HO-1) expression (mRNA and protein) followed by sequestrationof non-transferrin-derived (55)Fe by the mitochondrial compartment. The effectsof dopamine on HO-1 expression were inhibited by ascorbate implicating a freeradical mechanism of action. Dopamine-induced mitochondrial iron trapping wasabrogated by administration of the heme oxygenase inhibitors, tin mesoporphyrin(SnMP) or dexamethasone (DEX) indicating that HO-1 upregulation is necessary forsubsequent mitochondrial iron deposition in these cells. Overexpression of thehuman HO-1 gene in cultured rat astroglia by transient transfection alsostimulated mitochondrial (55)Fe deposition, an effect that was again preventibleby SnMP or DEX administration. We hypothesize that free ferrous iron and carbonmonoxide generated by HO-1-mediated heme degradation promote mitochondrialmembrane injury and the deposition of redox-active iron within this organelle.We have shown that the percentages of GFAP-positive astrocytes that co-expressHO-1 in Parkinson-affected substantia nigra and Alzheimer-diseased hippocampusare significantly increased relative to age-matched controls. Stress-inducedup-regulation of HO-1 in astroglia may be responsible for the abnormal patternsof brain iron deposition and mitochondrial insufficiency documented in varioushuman neurodegenerative disorders.

12: Exp Neurol. 1998 Mar;150(1):60-8.

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 othertissues in response to oxidative challenge and other noxious stimuli. In thepresent study, immunohistochemistry was used to assess HO-1 expression invarious postmortem human brain specimens derived from PD and control subjects.In the substantia nigra of both PD and control specimens, moderate HO-1immunoreactivity was consistently observed in neuromelanin-containing(dopaminergic) neurons. Lewy bodies in PD nigra neurons exhibited intense HO-1immunostaining in their peripheries. In both PD and control specimens, neuronalHO-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 substantianigra of control subjects (18.7 +/- 7.1; P = 0.0015). In the other regionsexamined, percentages of GFAP-positive astroglia coexpressing HO-1 wererelatively low and did not differ significantly (P > 0.05) between control andPD specimens. Upregulation of HO-1 in the substantia nigra of PD subjectssupports the view that the affected tissue is experiencing chronic oxidativestress. In addition, excessive cellular levels of heme-derived free iron andcarbon monoxide resulting from HO-1 overactivity may contribute to thepathogenesis of PD.

13: No To Shinkei. 1998 Jan;50(1):86-7.

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

[Article in Japanese]

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