Vital Reaction

Clinical Studies Collection

❖ Brain-related studies – molecular hydrogen's effect on:

➢ Parkinson's Disease:

- Pilot study of H_2 therapy in Parkinson's disease: A randomized double-blind placebo-controlled trial
- Molecular hydrogen is protective against 6-hydroxydopamine-induced nigrostriatal degeneration in a rat model of Parkinson's disease
- Hydrogen in Drinking Water Reduces Dopaminergic Neuronal Loss in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine Mouse Model of Parkinson's Disease
- Drinking hydrogen water and intermittent hydrogen gas exposure, but not lactulose or continuous hydrogen gas exposure, prevent 6-hydorxydopamine-induced Parkinson's disease in rats

➢ Mental Health:

- Molecular hydrogen: an overview of its neurobiological effects and therapeutic potential for bipolar disorder and schizophrenia
- Molecular hydrogen increases resilience to stress in mice

➢ Traumatic Brain Injury:

- Molecular hydrogen in drinking water protects against neurodegenerative changes induced by traumatic brain injury
- Hydrogen-rich saline protects against oxidative damage and cognitive deficits after mild traumatic brain injury
- Beneficial effects of hydrogen gas in a rat model of traumatic brain injury via reducing oxidative stress
- Inhalation of hydrogen gas attenuates brain injury in mice with cecal ligation and puncture via inhibiting neuroinflammation, oxidative stress and neuronal apoptosis
- Protective effects of hydrogen on fetal brain injury during maternal hypoxia

➢ Neuroprotective Findings:

- Hydrogen is Neuroprotective and Preserves Cerebrovascular Reactivity in Asphyxiated Newborn Pigs
- Hydrogen is neuroprotective against surgically induced brain injury
- Neuroprotective effects of hydrogen gas on brain in three types of stress models: A ^{31}P-NMR and ESR study
- Oral 'hydrogen water' induces neuroprotective ghrelin secretion in mice
- Consumption of molecular hydrogen prevents the stress-induced impairments in hippocampus-dependent learning tasks during chronic physical restraint in mice
- Delayed neurovascular dysfunction is alleviated by hydrogen in asphyxiated newborn pigs
- Hydrogen-rich saline is cerebroprotective in a rat model of deep hypothermic circulatory arrest

- Neuroprotective effect of hydrogen-rich saline in acute carbon monoxide poisoning
- Hydrogen rich saline reduces immune-mediated brain injury in rats with acute carbon monoxide poisoning

- **Alzheimer's Disease:**
  - Drinking Hydrogen Water Ameliorated Cognitive Impairment in Senescence-Accelerated Mice
  - Hydrogen-rich saline reduces oxidative stress and inflammation by inhibit of JNK and NF-κB activation in a rat model of amyloid-beta-induced Alzheimer's disease
  - Consumption of hydrogen water prevents age-dependent memory impairment accompanying neurodegeneration in Alzheimer's model mice

- **Stroke:**
  - Hydrogen-rich water protects against ischemic brain injury in rats by regulating calcium buffering proteins
  - Hydrogen supplemented air inhalation reduces changes of prooxidant enzyme and gap junction protein levels after transient global cerebral ischemia in the rat hippocampus
  - Hydrogen-rich saline improves memory function in a rat model of amyloid-beta-induced Alzheimer's disease by reduction of oxidative stress
  - Maternal molecular hydrogen administration ameliorates rat fetal hippocampal damage caused by in utero ischemia-reperfusion
  - Hydrogen improves neurological function through attenuation of blood–brain barrier disruption in spontaneously hypertensive stroke-prone rats

- **Hemorrhage:**
  - Beneficial effect of hydrogen-rich saline on cerebral vasospasm after experimental subarachnoid hemorrhage in rats
  - Neuroprotective Effect of Hydrogen-Rich Saline against Neurologic Damage and Apoptosis in Early Brain Injury following Subarachnoid Hemorrhage: Possible Role of the Akt/GSK3β Signaling Pathway
  - Hydrogen inhalation is neuroprotective and improves functional outcomes in mice after intracerebral hemorrhage

- **General title but brain benefits included:**
  - Molecular Hydrogen and its Potential Application in Therapy of Brain Disorders
  - Molecular hydrogen: An inert gas turns clinically effective
  - Electrochemically Reduced Water Protects Neural Cells from Oxidative Damage
  - Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine
  - A review of experimental studies of hydrogen as a new therapeutic agent in emergency and critical care medicine
  - Recent Progress Toward Hydrogen Medicine: Potential of Molecular Hydrogen for Preventive and Therapeutic Applications
  - Improved brain MRI indices in the acute brain stem infarct sites treated with hydroxyl radical scavengers, Edaravone and hydrogen, as compared to Edaravone alone. A non-controlled study
  - The evolution of molecular hydrogen: a noteworthy potential therapy with clinical significance

❖ Heart-related studies – molecular hydrogen's effect on:

➢ Cardiac Arrest:

- Delayed Inhalation of Hydrogen Improves Myocardial dysfunction in a Porcine Model of Cardiac Arrest and Cardiopulmonary Resuscitation
- Hydrogen Inhalation is Superior to Mild Hypothermia in Improving Cardiac Function and Neurological Outcome in an Asphyxial Cardiac Arrest Model of Rats
- H_2 Gas Improves Functional Outcome After Cardiac Arrest to an Extent Comparable to Therapeutic Hypothermia in a Rat Model

➢ Myocardial Ischemia/Reperfusion:

- Anti-inflammatory effect of hydrogen-rich saline in a rat model of regional myocardial ischemia and reperfusion
- Effects of saturated hydrogen peroxide on Akt/GSK3β signaling pathway and cardiac function in myocardial cells of rats with myocardial ischemia reperfusion injury
- Pharmacological Postconditioning with Lactic Acid and Hydrogen Rich Saline Alleviates Myocardial Reperfusion Injury in Rats
- Inhalation of hydrogen gas reduces infarct size in the rat model of myocardial ischemia–reperfusion injury
- Anti-inflammatory effect of hydrogen-rich saline in a rat model of regional myocardial ischemia and reperfusion
- Amelioration of rat cardiac cold ischemia/reperfusion injury with inhaled hydrogen or carbon monoxide, or both
- Hydrogen-Rich Saline Protects Myocardium Against Ischemia/Reperfusion Injury in Rats
- Inhaled Hydrogen Gas Therapy for Prevention of Lung Transplant-Induced Ischemia/Reperfusion Injury in Rats

➢ Miscellaneous areas of focus:

- Hydrogen Gas Inhalation Improves Survival in Rats With Lethal Hemorrhagic Shock Resuscitated With Saline
- Hydrogen-Rich Saline Attenuates Lipopolysaccharide-Induced Heart Dysfunction by Restoring Fatty Acid Oxidation in Rats by Mitigating C-Jun N-Terminal Kinase Activation Hydrogen-rich water protects against ischemic brain injury in rats by regulating calcium buffering proteins
- Hydrogen-rich saline attenuates vascular smooth muscle cell proliferation and neointimal hyperplasia by inhibiting reactive oxygen species production and inactivating the Ras-ERK1/2-MEK1/2 and Akt pathways
- Chronic hydrogen-rich saline treatment reduces oxidative stress and attenuates left ventricular hypertrophy in spontaneous hypertensive rats
- The Effect of Hydrogen Gas on a Mouse Bilateral Common Carotid Artery Occlusion
- Beneficial effect of hydrogen-rich saline on cerebral vasospasm after experimental subarachnoid hemorrhage in rats
- Oral intake of hydrogen-rich water inhibits intimal hyperplasia in arterialized vein grafts
- Inhalation of hydrogen gas attenuates left ventricular remodeling induced by intermittent hypoxia
- Hydrogen-rich saline prevents neointima formation after carotid balloon injury by suppressing ROS and the TNF-α/NF-κB pathway

- The Potential Cardioprotective Effects of Hydrogen in Irradiated Mice
- Consumption of hydrogen water prevents atherosclerosis in apolipoprotein E knockout mice
- Consumption of Molecular Hydrogen Prevents the Stress-Induced Impairments in Hippocampus-Dependent Learning Tasks during Chronic Physical Restraint in Mice
- Hydrogen inhalation ameliorates ventilator-induced lung injury
- Hydrogen is Neuroprotective and Preserves Cerebrovascular Reactivity in Asphyxiated Newborn Pigs

❖ Effects of peroxynitrite and hydroxyl radical on the brain:

- **Hippocampus & Hydroxyl Radical:**
  - Role of oxidative stress in Alzheimer's disease
  - Involvement of free radicals in dementia of the Alzheimer type: a hypothesis
  - Oxidative Stress and the Pathogenesis of Alzheimer's disease
  - Oxidative Damage Is the Earliest Event in Alzheimer Disease
  - Oxidative stress and the amyloid beta peptide in Alzheimer's disease

- **Hippocampus & Peroxynitrite:**
  - Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid β-peptide
  - Peroxynitrite induces Alzheimer-like tau modifications and accumulation in rat brain and its underlying mechanisms
  - Evidence of neuronal oxidative damage in Alzheimer's disease -

- **Basal ganglia / substantia nigra & Hydroxyl Radical:**
  - Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia
  - Transition Metals, Ferritin, Glutathione, and Ascorbic Acid in Parkinsonian Brains
  - Is Parkinson's disease a progressive siderosis of substantia nigra resulting in iron and melanin induced neurodegeneration?
  - Oxidative stress and the pathogenesis of Parkinson's disease
  - Parkinson's Disease Is Associated with Oxidative Damage to Cytoplasmic DNA and RNA in Substantia Nigra Neurons

- **Basal ganglia / substantia nigra & Peroxynitrite:**
  - Oxidative DNA Damage in the Parkinsonian Brain: An Apparent Selective Increase in 8-Hydroxyguanine Levels in Substantia Nigra
  - Increased nitrotyrosine immunoreactivity in substantia nigra neurons in MPTP treated baboons is blocked by inhibition of neuronal nitric oxide synthase
  - Protein Nitration in Parkinson's disease
  - Oxidative Stress in Huntington's disease

- **Parietal / Temporal lobe & Hydroxyl Radical:**
  - Imbalances of trace elements related to oxidative damage in Alzheimer's disease brain Mitochondrial involvement and oxidative stress in temporal lobe epilepsy
  - Mitochondria, oxidative stress, and temporal lobe epilepsy

- **Pituitary gland and Hydroxyl Radical:**
  - Inflammation and Oxidative Stress Are Elevated in the Brain, Blood, and Adrenal Glands during the Progression of Post-Traumatic Stress Disorder in a Predator Exposure Animal Model
  - Nitric oxide synthase in the human pituitary gland
  - Nitric oxide controls the hypothalamic-pituitary response to cytokines
  - Pituitary Adenoma Nitroproteomics: Current Status and Perspectives

- **Cerebral Cortex and Peroxynitrite:**
  - Role of NO production in NMDA receptor-mediated neurotransmitter release in cerebral cortex
  - Widespread Peroxynitrite-Mediated Damage in Alzheimer's Disease
  - Augmentation of Nitric Oxide, Superoxide, and Peroxynitrite Production During Cerebral Ischemia and Reperfusion in the Rat

- **General:**
  - Nitric oxide, superoxide and peroxynitrite: Putative mediators of NMDA-induced cell death in cerebellar granule cells
  - Fluctuation of serum NO_x concentration at stroke onset in a rat spontaneous stroke model (M-SHRSP): Peroxynitrite formation in brain lesions
  - Peroxynitrite-Mediated Protein Nitration and Lipid Peroxidation in a Mouse Model of Traumatic Brain Injury
  - Dynamics of Nitric Oxide and Peroxynitrite During Global Brain Ischemia/Reperfusion in Rat Hippocampus: NO-sensor Measurement and Modeling Study

❖ Effect of peroxynitrite and hydroxyl radical on the heart:

➢ Peroxynitrite-related studies:

- Cardiomyocyte overexpression of iNOS in mice results in peroxynitrite generation, heart block, and sudden death
- Peroxynitrite induces both vasodilatation and impaired vascular relaxation in the isolated perfused rat heart
- Peroxynitrite Is a Major Contributor to Cytokine-Induced Myocardial Contractile Failure
- Peroxynitrite induced nitration and inactivation of myofibrillar creatine kinase in experimental heart failure
- Peroxynitrite aggravates myocardial reperfusion injury in the isolated perfused rat heart
- Role of Oxidative-Nitrosative Stress and Downstream Pathways in Various Forms of Cardiomyopathy and Heart Failure
- Inhibition of Mitochondrial Electron Transport by Peroxynitrite
- Aconitase is readily inactivated by peroxynitrite, but not by its precursor, nitric oxide.
- Apoptotic cascade initiated by angiotensin II in neonatal cardiomyocytes: role of DNA damage
- Peroxynitrite is a major trigger of cardiomyocyte apoptosis in vitro and in vivo
- Peroxynitrite Causes Endoplasmic Reticulum Stress and Apoptosis in Human Vascular Endothelium
- Peroxynitrite-induced cardiac myocyte injury
- Attenuation of vascular relaxation after development of tachyphylaxis to peroxynitrite in vivo
- Peroxynitrite-mediated attenuation of alpha- and beta-adrenoceptor agonist-induced vascular responses in vivo.
- Elevation in arterial blood pressure following the development of tachyphylaxis to peroxynitrite
- Cardiac Nerves Affect Myocardial Stunning Through Reactive Oxygen and Nitric Oxide Mechanisms

➢ Hydroxyl radical-related studies:

- Hydroxyl Radical Inhibits Sarcoplasmic Reticulum Ca^{2+}-ATPase Function by Direct Attack on the ATP Binding Site
- Detection of hydroxyl radical in the mitochondria of ischemic-reperfused myocardium by trapping with salicylate
- Prevention of hydroxyl radical formation: a critical concept for improving cardioplegia. Protective effects of deferoxamine.
- Hydroxyl radical generation, levels of tumor necrosis factor-alpha, and progression to heart failure after acute myocardial infarction

- High-performance liquid chromatographic detection of hydroxylated benzoic acids as an indirect measure of hydroxyl radical in heart: its possible link with the myocardial reperusion injury
- Hydroxyl radical generation during exercise increases mitochondrial protein oxidation and levels of urinary dityrosine
- Hydroxyl Radical Generation During Mitochondrial Electron-Transfer and the Formation of 8-Hydroxydesoxyguanosine in Mitochondrial-DNA
- Use of aromatic hydroxylation of phenylalanine to measure production of hydroxyl radicals after myocardial ischemia in vivo. Direct evidence for a pathogenetic role of the hydroxyl radical in myocardial stunning.
- Detection of hydroxyl radicals in the post-ischemic reperfused heart using salicylate as a trapping agent