The role of Hyperbaric Oxygen Therapy in Parkinson's Disease

Dr Nur Ozyilmaz, MD
Integrative Health Specialist & Consultant Paediatrician

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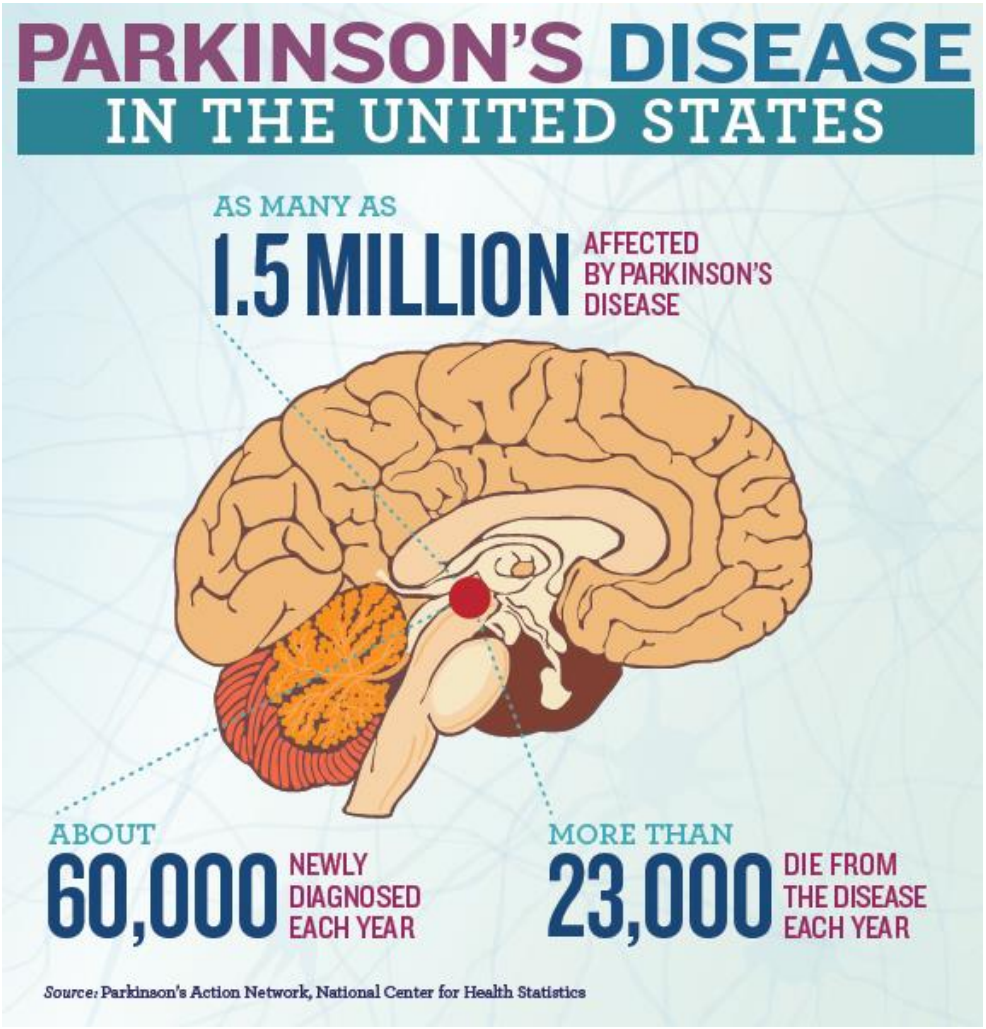
Case I

- 64 years old previously relatively fit and healthy female
- History of chronic constipation, gingivitis, anosmia
- Develops tremor, bradykinesia, voice changes, rigid facial expression, stooped posture, loss of swinging of left arm, small cramped writing, intermittent dystonia on hands and feet
- Diagnosed with **Parkinson's disease!**

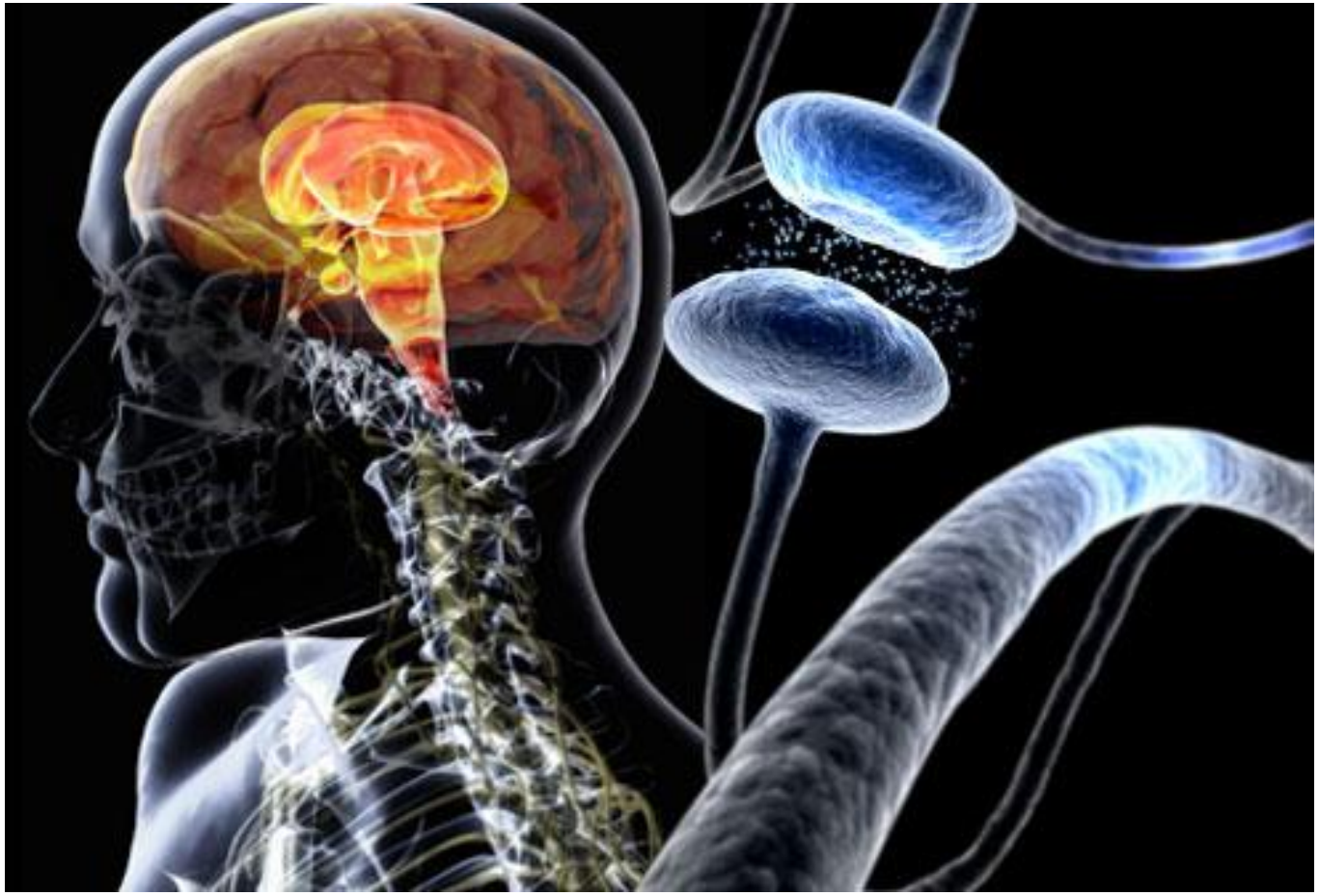
What is Parkinson's Disease?

Parkinson disease (PD) is a chronic progressive neurodegenerative disease of the nervous system characterized by the cardinal features of rigidity, bradykinesia, tremor and postural instability.



Categories

1. **Parkinsonism:** a group of disorders with Basal Ganglia dysfunction
2. **PD or idiopathic Parkinsonism:** The most common form
3. **Secondary Parkinsonism:** Viruses, toxins, drugs, tumors
4. **Parkinsonism plus syndromes:** conditions that mimic PD, symptoms caused by some other neurodegenerative diseases



Etiology

- The mechanisms of PD remain elusive
- Several genes identified including SNCA, PARKIN, DJ-1, PINK-1, and LRRK2 whose mutations are responsible for rare forms of Parkinson's disease.
- oxidative stress, mitochondrial and proteseomal dysfunction and inflammatory system involvement
- ? Autoimmune disease

Signs and symptoms

Tremor

Subtle decrease in dexterity

Decreased arm swing on the first-involved side

Soft voice

Decreased facial expression

Sleep disturbances

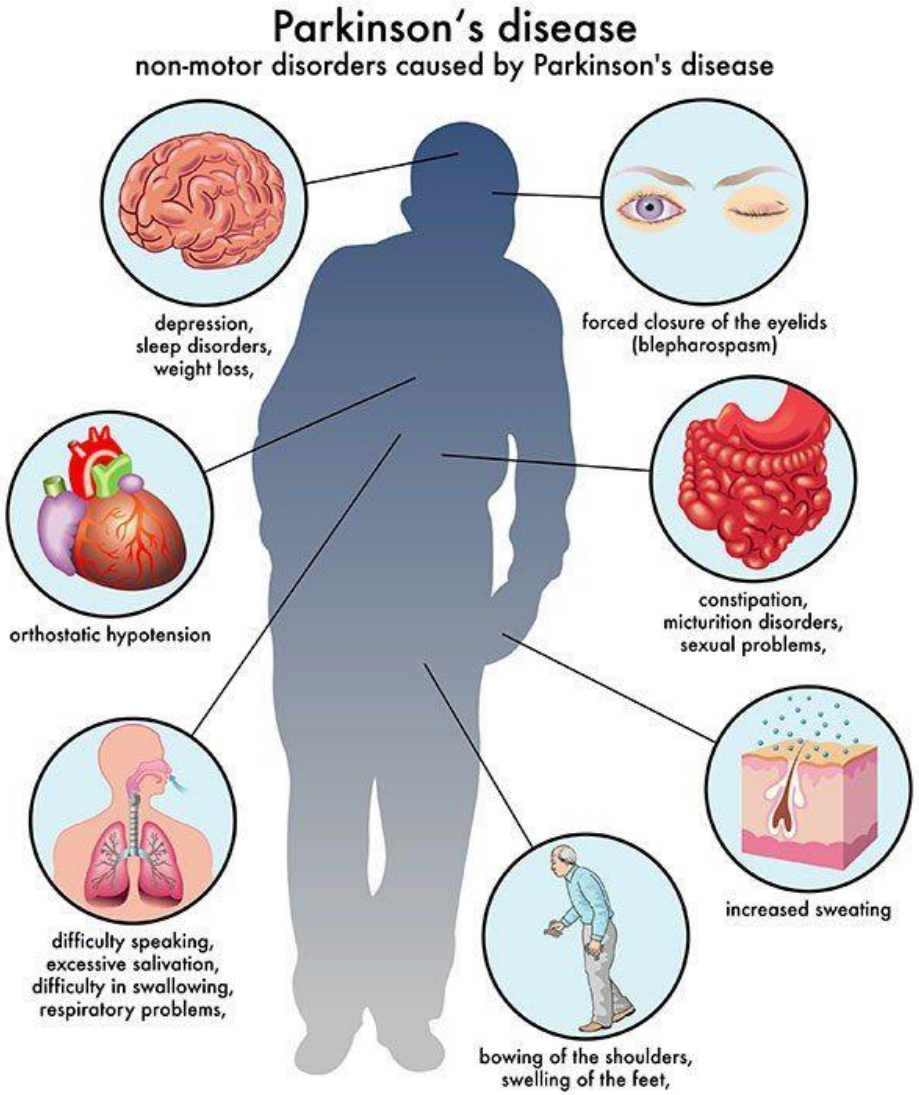
Decreased sense of smell

Symptoms of autonomic dysfunction (eg, constipation, sweating abnormalities, sexual dysfunction, seborrheic dermatitis)

A general feeling of weakness, malaise

Depression or anhedonia

Slowness in thinking



Diagnosis

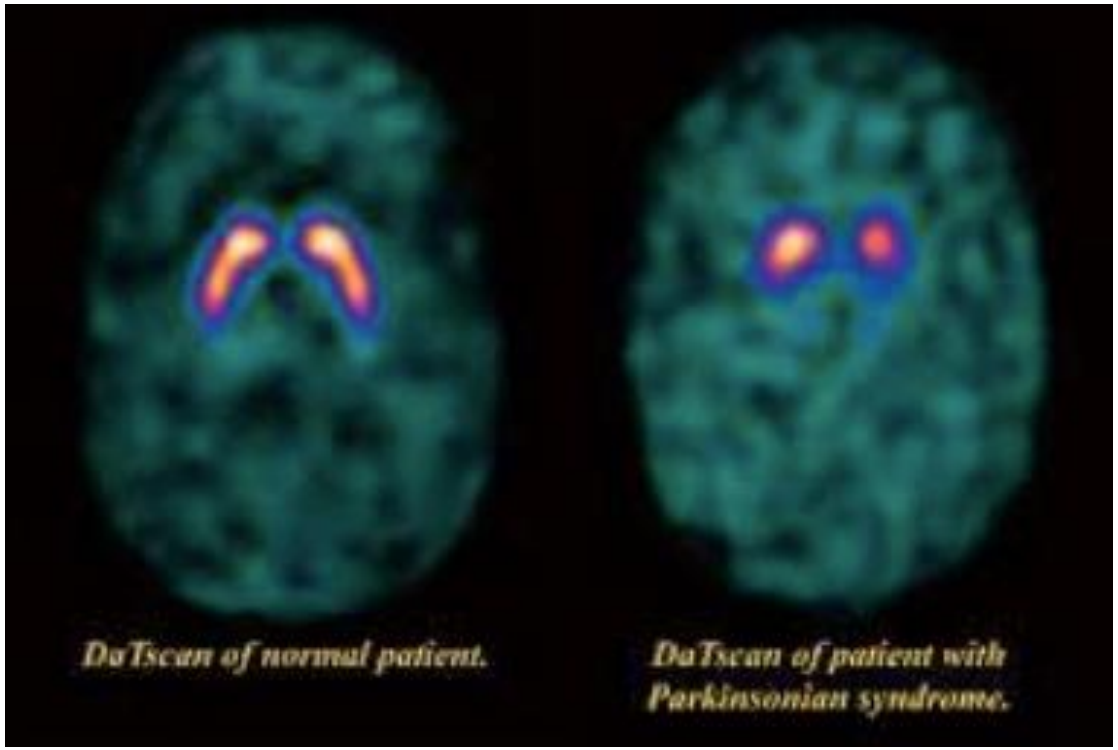
PD is a clinical diagnosis

No laboratory biomarkers exist for the condition

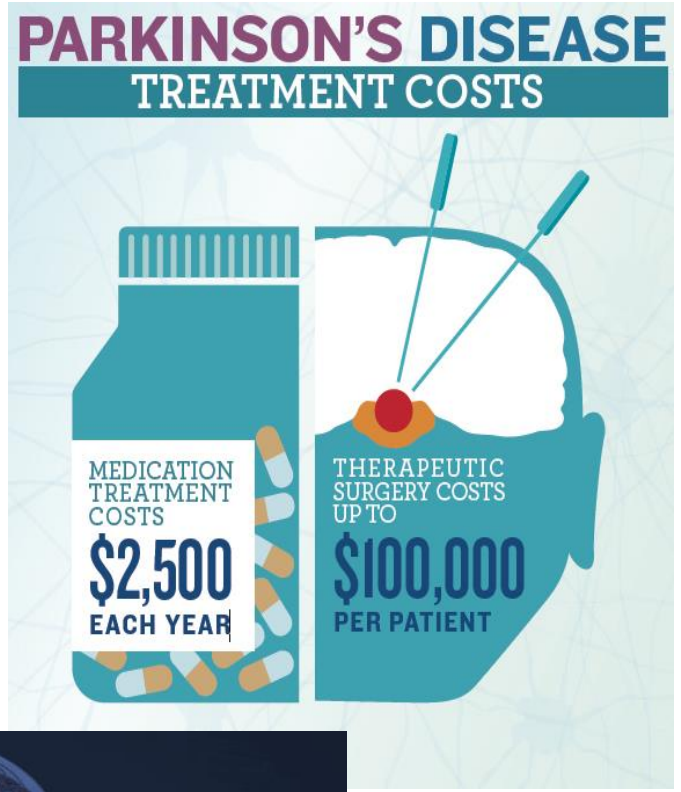
Findings on routine (MRI) and (CT) scan are unremarkable

MRI is useful to exclude strokes, tumors, multi-infarct state, hydrocephalus, and the lesions of Wilson disease.

PET and DaT scans



Treatment



Symptomatic drug therapy

Levodopa/carbidopa: The gold standard of symptomatic treatment

Monoamine oxidase (MAO)–B inhibitors

Other dopamine agonists (eg, ropinirole, pramipexole)

Anticholinergic agents (eg, trihexyphenidyl, benztropine)

Treatment for non-motor symptoms

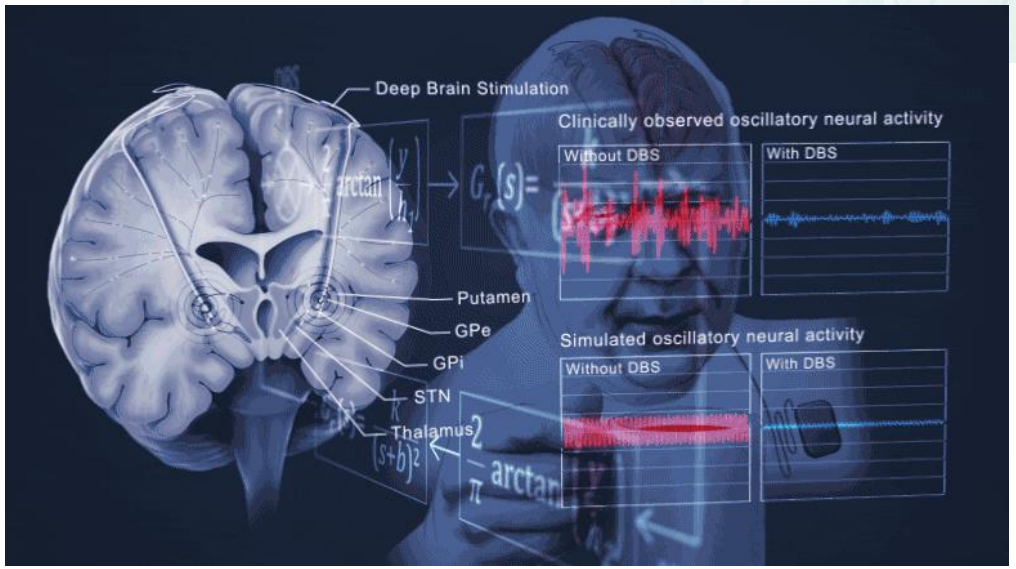
Sildenafil citrate (Viagra): For erectile dysfunction

Polyethylene glycol: For constipation

Modafinil: For excessive daytime somnolence

Methylphenidate: For fatigue (potential for abuse and addiction)

Deep brain stimulation



Continuing Case I

Investigations

- FBC, U&E, LFT, Bone Profile, CRP: Normal
- MRI: Normal
- Stool comprehensive test: Candida overgrowth, low beneficial bacteria
- Urine organic and amino acids: high benzoic acid, arabinase, Citramalic Acid, Phenylacetic Acid (PAA), α-Hydroxyisobutyric Acid, Pyroglutamic Acid
- Toxicity: PCB, pesticides, mercury, aluminum

Treatment

- Nutrition: LCHF/ altered with ketogenic diet
- Exercise
- Optimizing gut flora
- Treating candida overgrowth
- Detoxification
- Optimizing methylation pathway
- Supplements (glutathione precursors, antioxidants, anti-inflammatories)
- Low dose naltrexone
- Bioresonance & PEMFR
- Non-laser light therapy
- HBOT x 40 sessions

Unified Parkinson's Disease Rating Scale	At the time of diagnosis in 2012	2018
I. Mentation, Behavior and Mood		
• Intellectual Impairment	Moderate memory loss	None
• Thought Disorder	Vivid dreams	None
• Depression	Sustained depression with vegetative symptoms (insomnia, poor appetite, loss of interest)	None
• Motivation/Initiative	Less assertive than usual	Normal
II. Activities of Daily Living		
• Speech	Normal	Normal
• Salivation	Normal	Normal
• Swallowing	Normal	Normal
• Handwriting	Moderately slow & small mostly legible	Normal
• Cutting Food & Handling utensils	Can cut most foods with some difficulty	Normal
• Dressing	Needs assistance with buttoning &sleeves	Normal
• Hygiene	Normal	Normal
• Falling	Rare falling	None
• Freezing when Walking	Occasional freezing	None
• Walking	Mild difficulty, no swing left arm	Normal
• Tremor	Moderate; bothersome to patient	Left leg-only when anxious
• Sensory Complaints	Frequent painful sensations	Occasional

Unified Parkinson's Disease Rating Scale	At the time of diagnosis in 2012	2018
III. Motor Examination		
Speech	Monotone but understandable	Normal
Facial Expression	Masked face, loss of facial express	Normal
Tremor at Rest	Moderate in amplitude & present most of the time	Only left leg when anxious
Action or Postural Tremor of Hands	Slight; present with action	None
Rigidity	Marked, FROM full range of achieved	Absent
Finger Taps	Moderately impaired	Normal
Leg Agility	Moderately impaired	Normal
Arising from Chair	Frequently unable to arise without help	Normal
Posture	Moderately stooped posture	Mostly normal
Gait	Short steps with shuffles	Normal
Postural Stability	Impaired	Normal
Bradykinesia	Moderate slowness, small amplitude of movement	Minimal slowness

Unified Parkinson's Disease Rating Scale	At the time of diagnosis in 2012	2018
Dyskinesia	Daily	None
Early Morning Dystonia	Daily	None
Insomnia	Severe	Resolved

In summary:

6 years after diagnosis of PD

- Not on any PD medication
- Disease not progressing
- Significant improvement with complete resolution of majority of the symptoms

Case II

53 years old male, CEO

- *1. Parkinsonism (2005) / 40 years old*
- *2. Reduced uptake in the left putamen and minimally reduced uptake in the left caudate and right putamen (DAT scan December 2005)*
- *3. Right hip replacement (July 2009)*
- *4. Bilateral STN stimulators inserted (November 2012)*
- *5. Medtronic ACTIVA PC box replacement (August 2017)*

Present complaints: Painful dyskinesia, dystonia, left leg tremor, walking with extreme difficulty, insomnia

Medications: Stalevo 125mg qds and *Amantadine* 100mg

Case II, Progress

Before HBOT	After 20 sessions of HBOT with no other intervention
Upper body dyskinesia	30% improvement
Left leg tremor	50% improvement
walking with extreme difficulty & only short distance	30% improvement
Severe rigidity, full range of motion achieved with difficulty	50% improvement
Freezing when walking	50% improvement
Poor quality interrupted sleep	Sleeps well

• Numerous in vivo and in vitro studies confirms that HBOT induces neurogenesis

- Wang XL. et al. [Hyperbaric oxygen promotes the migration and differentiation of endogenous neural stem cells in neonatal rats with hypoxic-ischemic brain damage] Zhongguo Dang Dai Er Ke Za Zhi. 2009;11(9):749–52. [PubMed]
- Zhang XY. et al. The role of beta-catenin signaling pathway on proliferation of rats neural stem cells after hyperbaric oxygen therapy in vitro. Cell Mol Neurobiol. 2011;31(1):101–9. doi: 10.1007/s10571-010-9559-z. [PubMed]
- Milosevic J. et al. Non-hypoxic stabilization of hypoxia-inducible factor alpha (HIF-alpha): relevance in neural progenitor/stem cells. Neurotox Res. 2009;15(4):367–80. doi: 10.1007/s12640-009-9043-z. [PubMed] [Cross Ref]
- Godman CA. et al. Hyperbaric oxygen treatment induces antioxidant gene expression. Ann N Y Acad Sci. 2010;1197:178–83. doi: 10.1111/j.1749-6632.2009.05393.x. [PubMed]
- Yang YJ. et al. Hyperbaric oxygen induces endogenous neural stem cells to proliferate and differentiate in hypoxic-ischemic brain damage in neonatal rats. Undersea Hyperb Med. 2008;35(2):113–29. [PubMed]
- Zhang T. et al. Hyperbaric oxygen therapy improves neurogenesis and brain blood supply in piriform cortex in rats with vascular dementia. Brain Inj. 2010;24(11):1350–7. doi: 10.3109/02699052.2010.504525. [PubMed]
- Gunther A. et al. Reduced infarct volume and differential effects on glial cell activation after hyperbaric oxygen treatment in rat permanent focal cerebral ischaemia. Eur J Neurosci. 2005;21(11):3189–94. doi: 10.1111/j.1460-9568.2005.04151.x. [PubMed]

Potential mechanisms of HBOT and HIF-1α.

Med Gas Res. 2011; 1: 14.
Published online 2011 Jun 27. doi: 10.1186/2045-9912-1-14

PMCID: PMC3231808
PMID: 22146131

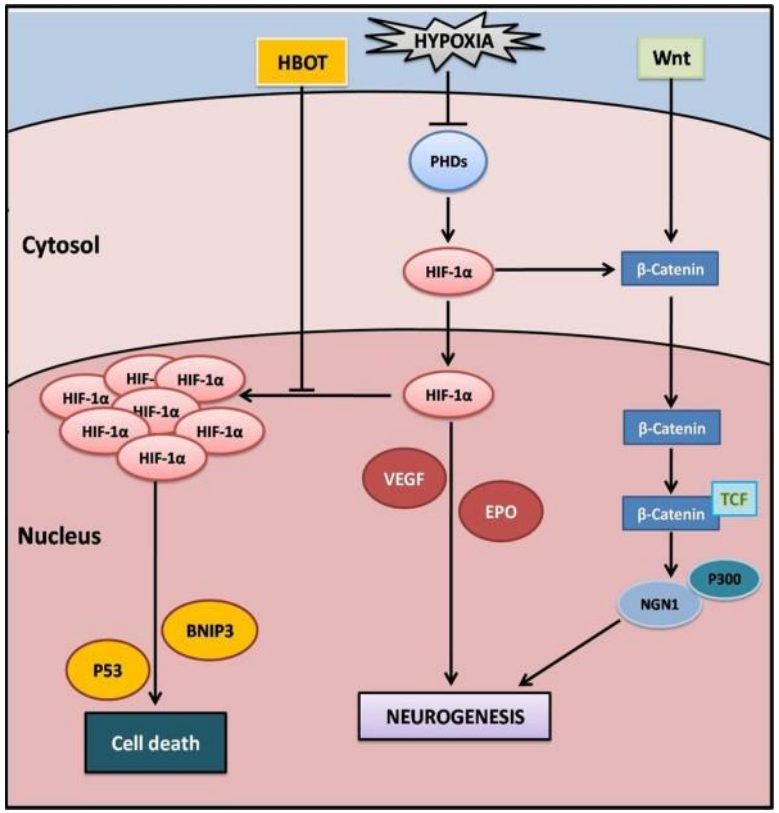
Hyperbaric oxygen therapy promotes neurogenesis: where do we stand?

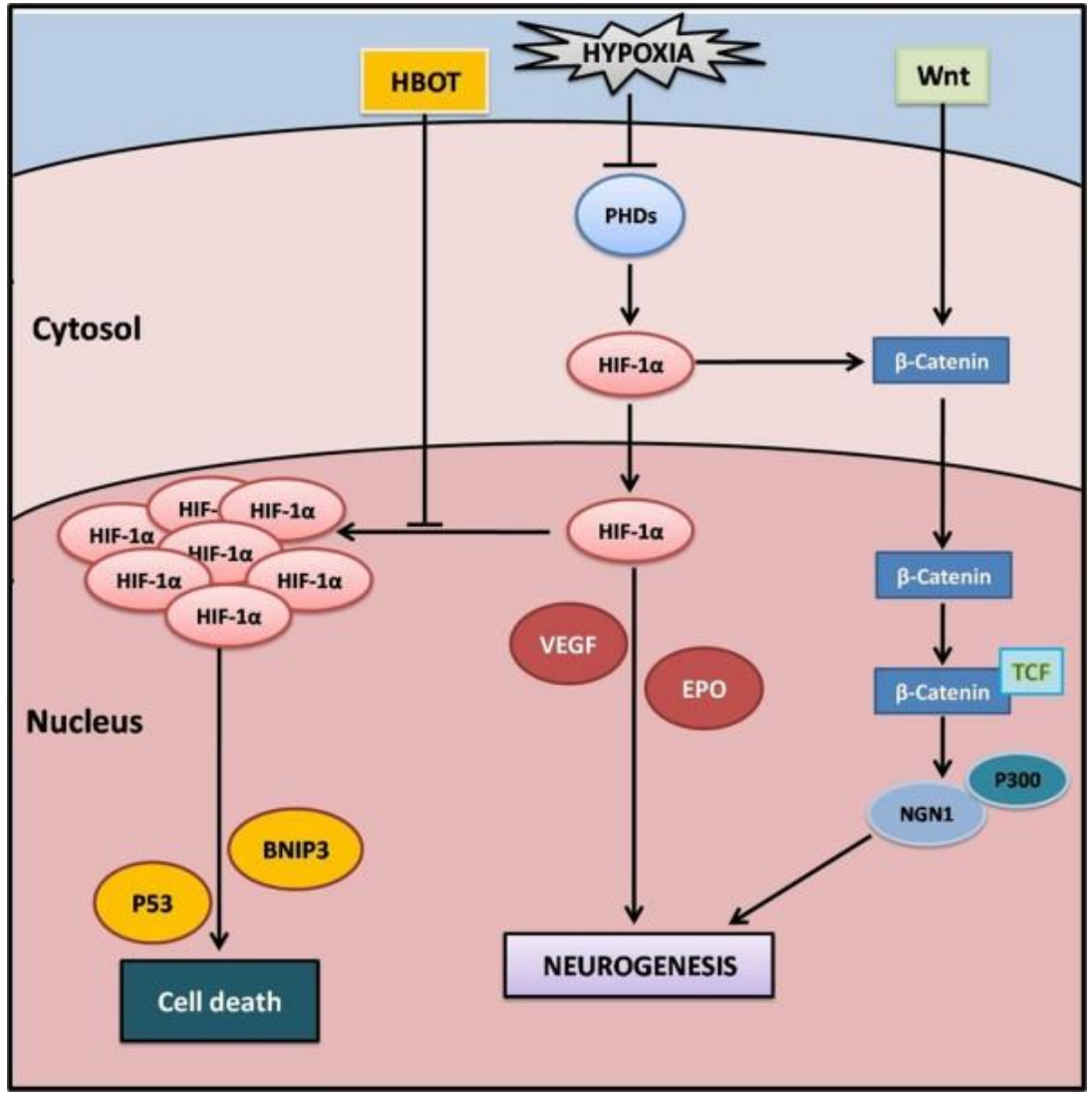
Jun Mu,[1,2] Paul R Krafft,[1] and John H Zhang[1,2,3]

Abstract

Go to:

Neurogenesis in adults, initiated by injury to the central nervous system (CNS) presents an autologous repair mechanism. It has been suggested that hyperbaric oxygen therapy (HBOT) enhances neurogenesis which accordingly may improve functional outcome after CNS injury. In this present article we aim to review experimental as well as clinical studies on the subject of HBOT and neurogenesis. We demonstrate hypothetical mechanism of HBOT on cellular transcription factors including hypoxia-inducible factors (HIFs) and cAMP response element binding (CREB). We furthermore reveal the discrepancy between experimental findings and clinical trials in regards of HBOT. Further translational preclinical studies followed by improved clinical trials are needed to elucidate potential benefits of HBOT.




HBOT
HYPOXIA
Wnt
PHDs
Cytosol
HIF-1α
β-Catenin
HIF-1α
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HIF-1α
HIF-1α
HIF-1α
HIF-1α
HIF-1α
β-Catenin
VEGF
EPO
TCF
β-Catenin
Nucleus
P300
NGN1
BNIP3
P53
NEUROGENESIS
Cell death

Curr Neuropharmacol. 2018 Jan 10. doi: 10.2174/1570159X16666180110130253. [Epub ahead of print]

"Understanding the Role of Hypoxia inducible factor during neurodegeneration for new therapeutics opportunities".

Merelli A[1], Rodriguez JCG[2], Folch J[3], Regueiro MR[4], Camins A[5], Lazarowski A[6].

Author information

Abstract

Neurodegeneration (NDG) is linked with the progressive loss of neural function with intellectual and/or motor impairment. Several diseases affecting older individuals, including Alzheimer's disease, Amyotrophic Lateral Sclerosis, Huntington's disease, Parkinson's disease, stroke, Multiple Sclerosis and many others, are the most relevant disorders associated with NDG. Since other pathologies such as refractory epilepsy, brain infections, or hereditary diseases such as "neurodegeneration with brain iron accumulation", also lead to chronic brain inflammation with loss of neural cells, NDG can be said to affect all ages. Owing to an energy and/or oxygen supply imbalance, different signaling mechanisms including MAPK/PI3K-Akt signaling pathways, glutamatergic synapse formation, and/or translocation of phosphatidylserine, might activate some central executing mechanism common to all these pathologies and also related to oxidative stress. Hypoxia inducible factor 1-□ (HIF-1□) plays a twofold role through gene activation, in the sense that this factor has to "choose" whether to protect or to kill the affected cells. Most of the afore-mentioned processes follow a protracted course and are accompanied by progressive iron accumulation in the brain. We hypothesize that the neuroprotective effects of iron chelators are acting against the generation of free radicals derived from iron, and also induce sufficient -but not excessive- activation of HIF-1□, so that only the hypoxia-rescue genes will be activated. In this regard, the expression of the erythropoietin receptor in hypoxic/inflammatory neurons could be the cellular "sign" to act upon by the nasal administration of pharmacological doses of Neuro-EPO, inducing not only neuroprotection, but eventually, neurorepair as well.

J Neurochem. 2010 Oct;115(1):209-19. doi: 10.1111/j.1471-4159.2010.06917.x. Epub 2010 Aug 19.

HIF prolyl hydroxylase inhibition increases cell viability and potentiates dopamine release in dopaminergic cells.

Johansen JL[1], Sager TN, Lotharius J, Witten L, Mørk A, Egebjerg J, Thirstrup K.

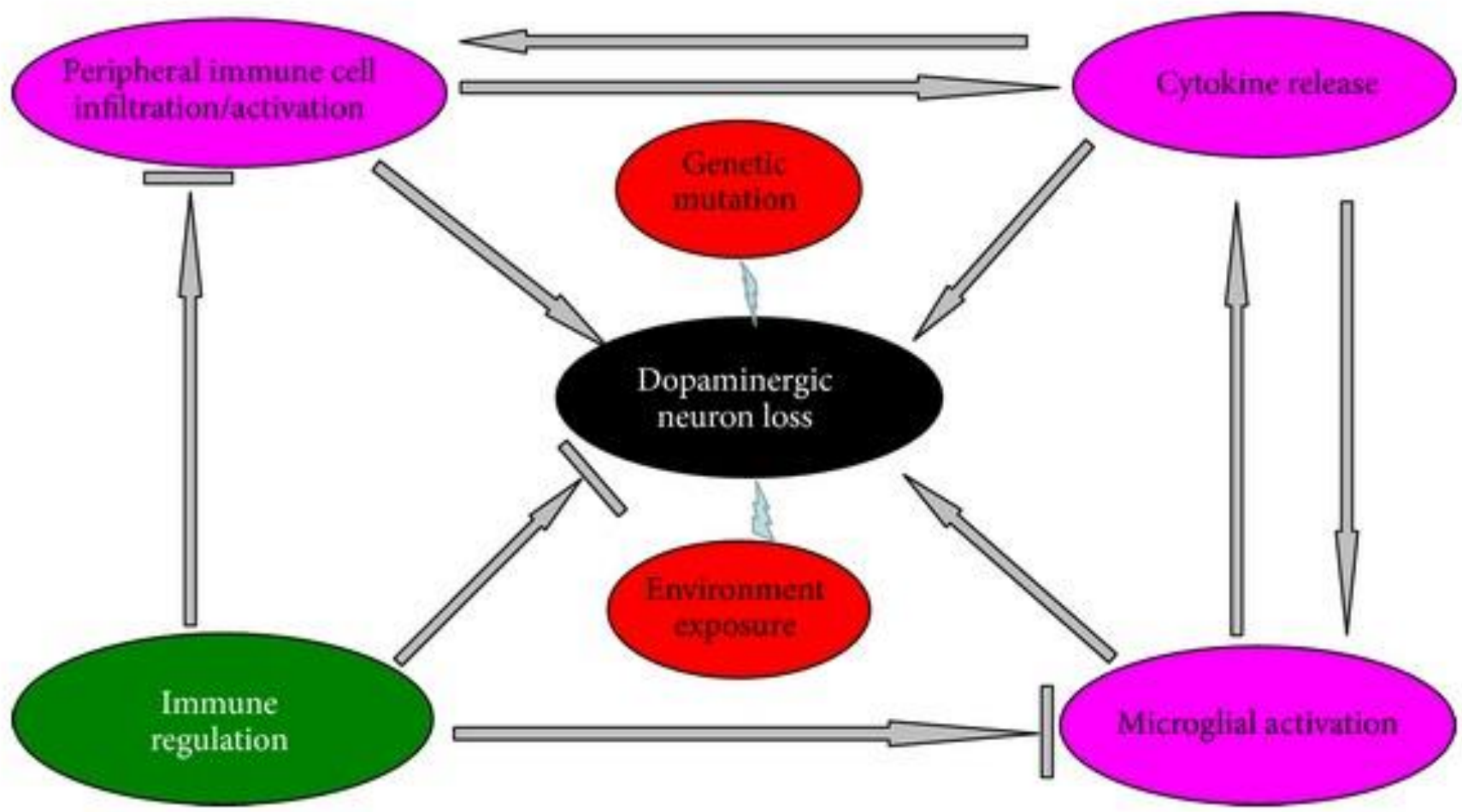
Author information

Abstract

Hypoxia-inducible factor (HIF) controls the expression of genes that adapts the cellular condition to accommodate oxidative stress. The potential beneficial effect of HIF up-regulation in ischemia has recently gained interest substantiated by the known HIF-regulation of erythropoietin and other hypoxia accommodating genes. So far the perspectives for HIF up-regulation has been focused on anemia and ischemia related diseases but little information is available about the relevance of HIF biology for neurodegenerative disease like Parkinson's disease. We therefore sought out to characterize the effect of HIF-up-regulation on survival and dopamine homeostasis in dopaminergic cells. We used a low molecular weight HIF prolyl hydroxylase (HPH) inhibitor and lentiviral based shRNA knockdown of HPH subtypes as molecular tools to increase HIF protein level and downstream HIF-regulated genes. We show that HIF induction results in protection against oxidative stress in cellular models based on PC12 cells and LUHMES cells. In addition, HPH inhibition elevates tyrosine hydroxylase expression and activity, which causes increased dopamine synthesis and release in both PC12 cells and a primary rat ventral mesencephalic cell culture. All together these findings suggest that prolyl hydroxylases may represent novel targets for therapeutic intervention in disorders characterized by dopamine homeostasis dysregulation like Parkinson's disease.

Biomed Res Int. 2014;2014:308654. doi: 10.1155/2014/308654. Epub 2014 Jun 24.

Evidence of inflammatory system involvement in Parkinson's disease



Inflammatory factors involved in Parkinson's disease

Cytokines and other soluble molecules	IL-1, IL-2, IL-4, IL-6, IL-10, TNF-, IFN-, TGF-, IL-6, MMP-3, IL-17, and IL-18
Pattern recognition receptors (PRRs)	TLRs (TLR-1, -2, -3, and -7), NLRs, and complements
Immune cells	Microglia, monocyte, NK cell, T-cell, and B cell

Zh Nevropatol Psikhiatr Im S S Korsakova. 1989;89(10):38-40.

[Hyperbaric oxygenation in the complex treatment of Parkinson disease].

[Article in Russian]

Neretin Vla, Lobov MA, Kotov SV, Cheskidova GF, Molchanova GS.

Abstract

Hyperbaric oxygenation (HBO) was used for the treatment of 64 patients suffering from parkinsonism of different etiology. HBO sessions were provided daily, 8-12 per course, the treatment pressure amounted to 1.3-2 atm exposure to 40-60 minutes. The beneficial effect was marked in 55 patients. The results of the treatment turned out better in vascular parkinsonism, in patients under 65 years, with a disease standing of 1-5 years. The akineticorigid syndrome regressed to a greater degree, whereas in trembling hyperkinesis, HBO turned out to be less potent.

Medicine (Baltimore). 2018 Mar;97(9):e0029. doi: 10.1097/MD.0000000000010029.

Hyperbaric oxygen treatment for Parkinson's disease with severe depression and anxiety: A case report.

Xu JJ[1], Yang ST, Sha Y, Ge YY, Wang JM.

Med Gas Res. 2011; 1: 14.
Published online 2011 Jun 27. doi: 10.1186/2045-9912-1-14
PMCID: PMC3231808
PMID: 22146131

Hyperbaric oxygen therapy promotes neurogenesis: where do we stand?

Jun Mu,[1,2] Paul R Krafft,[1] and John H Zhang[1,2,3]

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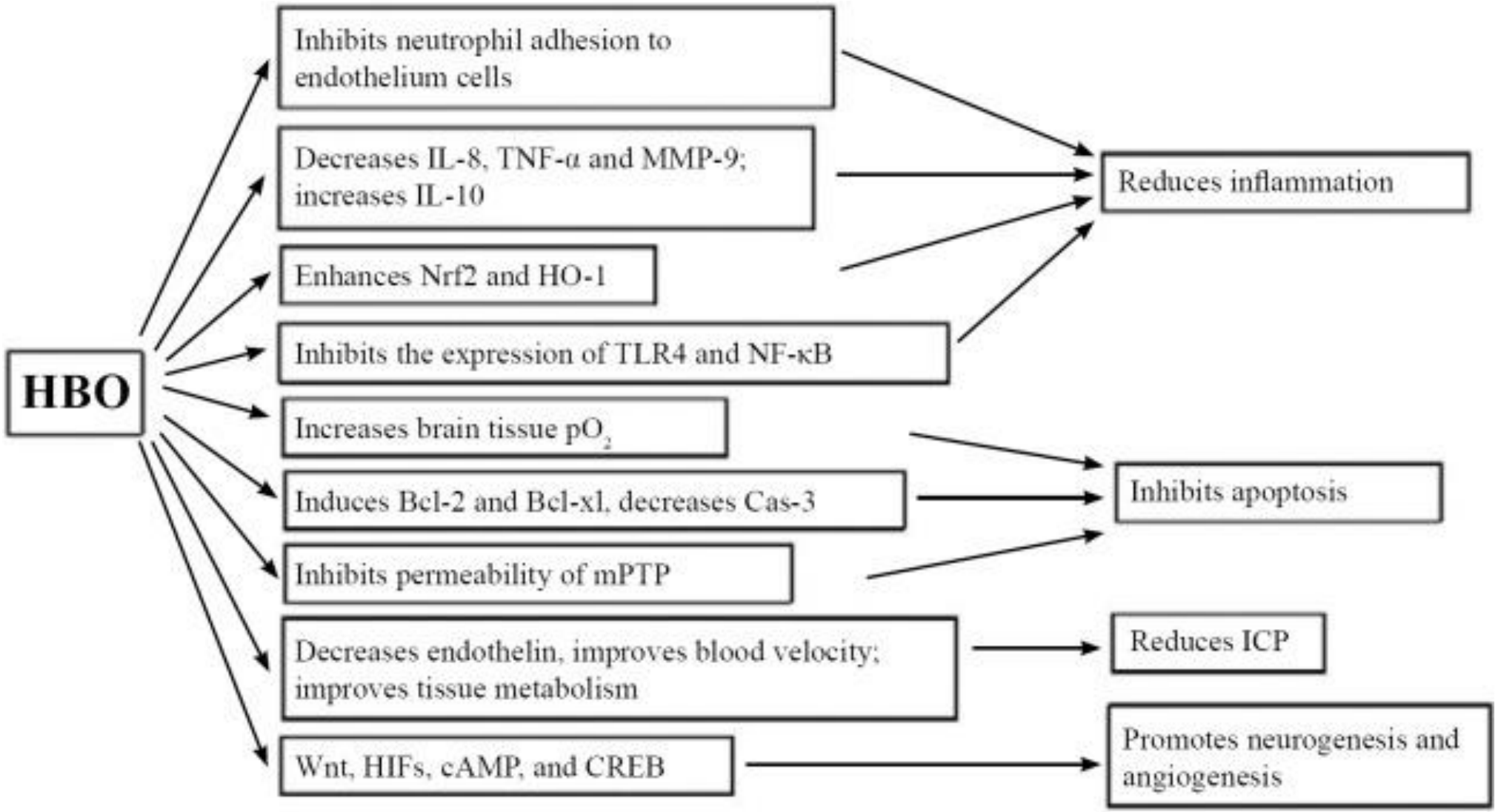
Neurosci Res. 2018 Jul;132:58-62. doi: 10.1016/j.neures.2017.11.008. Epub 2017 Nov 28.

Mild hyperbaric oxygen inhibits the decrease of dopaminergic neurons in the substantia nigra of mice with MPTP-induced Parkinson's disease.

Kusuda Y[1], Takemura A[1], Nakano M[2], Ishihara A[3].

Potential benefit of HBOT



Gut-Brain Axis

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See 1 citation found by title matching your search:

PLoS One. 2011;6(12):e28032. doi: 10.1371/journal.pone.0028032. Epub 2011 Dec 1.

Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson's disease.

Forsyth CB[1], Shannon KM, Kordower JH, Voigt RM, Shaikh M, Jaglin JA, Estes JD, Dodiya HB, Keshavarzian A.

Gut microbiota are related to Parkinson's disease and clinical phenotype.

Scheperjans F[1], Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, Haapaniemi E, Kaakkola S, Eerola-Rautio J, Pohja M, Kinnunen E, Murros K, Auvinen P.

Eur J Pharmacol. 2017 Dec 15;817:86-95. doi: 10.1016/j.ejphar.2017.05.042. Epub 2017 May 23.

The gut-brain axis in Parkinson's disease: Possibilities for food-based therapies.

Perez-Pardo P[1], Kliest T[1], Dodiya HB[2], Broersen LM[3], Garssen J[3], Keshavarzian A[4], Kraneveld AD[5].

Mov Disord. 2015 Apr;30(4):494-8. doi: 10.1002/mds.25979. Epub 2014 Aug 7.

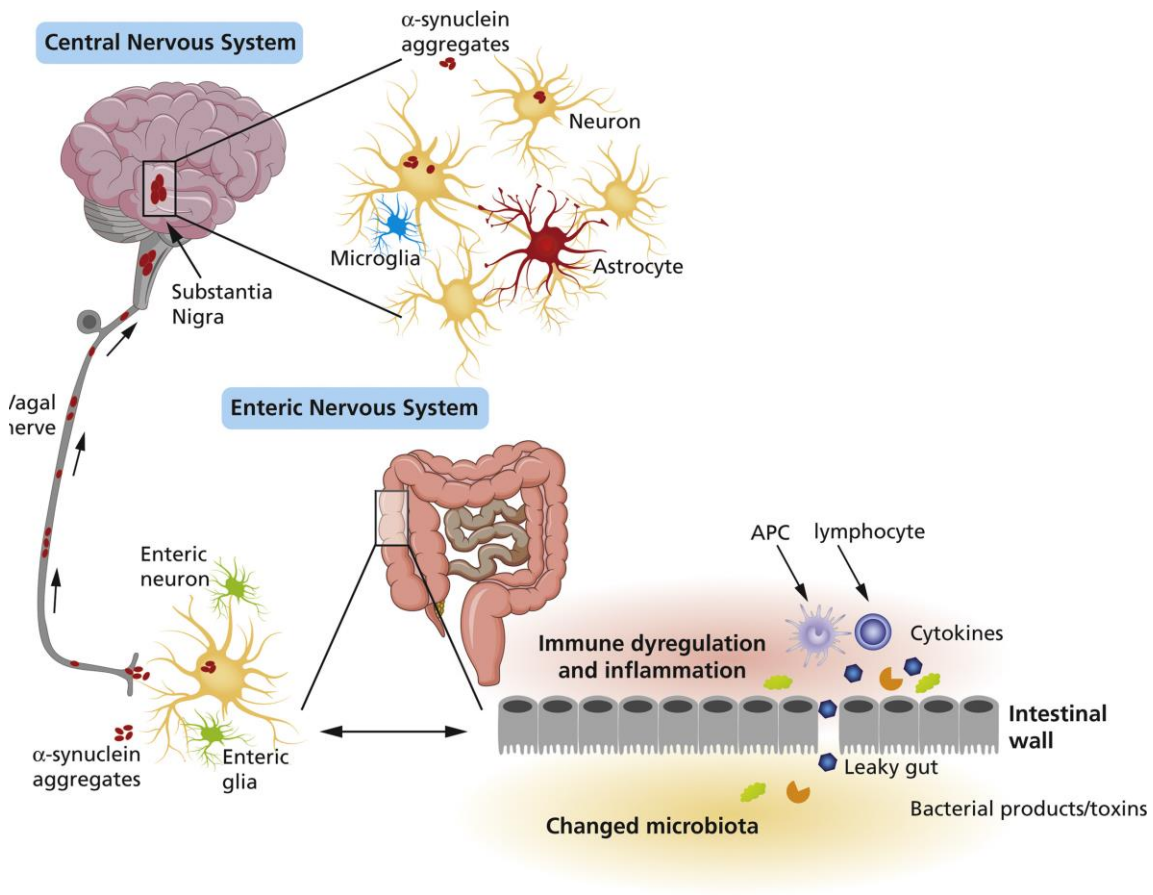
Enteric glial cells: new players in Parkinson's disease?

Clairembault T[1], Leclair-Visonneau L, Neunlist M, Derkinderen P.

J Parkinsons Dis. 2018 Jun 23. doi: 10.3233/JPD-181327. [Epub ahead of print]

Stomaching the Possibility of a Pathogenic Role for Helicobacter pylori in Parkinson's Disease.

McGee DJ, Lu XH, Disbrow EA.



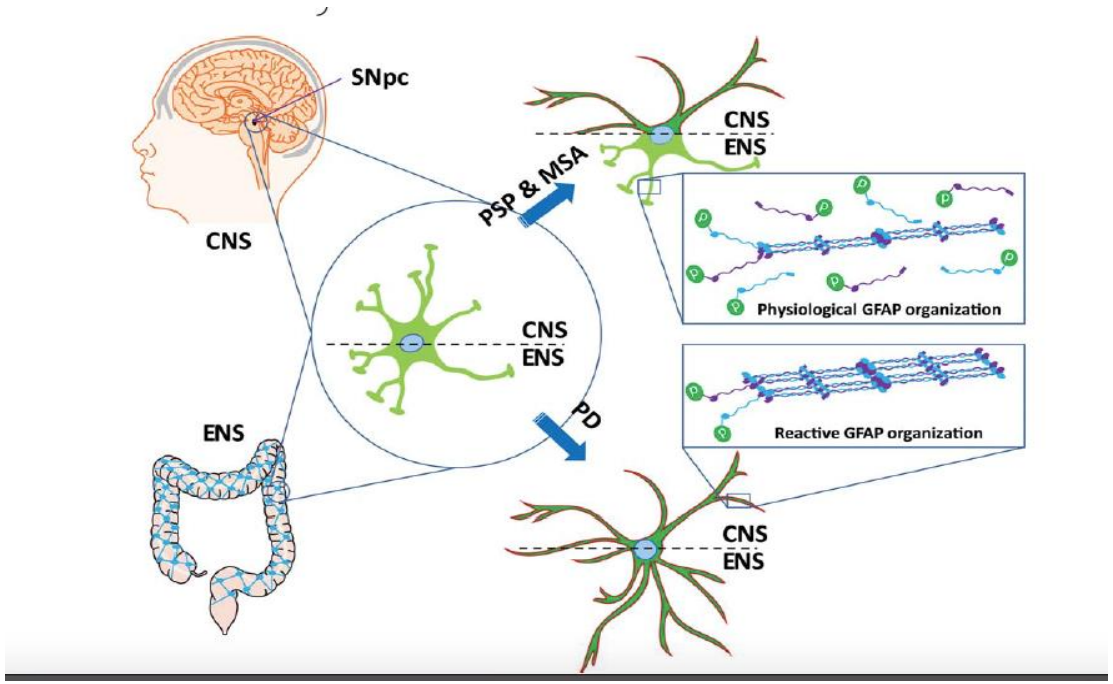
Enteric Glial Cells: New Players in Parkinson's Disease?

Thomas Clairembault, BSc,[1,2,3] Laurène Leclair-Visonneau, MD,[1,2,4] Michel Neunlist, PhD,[1,2,3] and Pascal Derkinderen, MD, PhD[1,2,4*]

- Lewy pathology has been described in neurons of the enteric nervous system in nearly all Parkinson's disease (PD) patients at autopsy

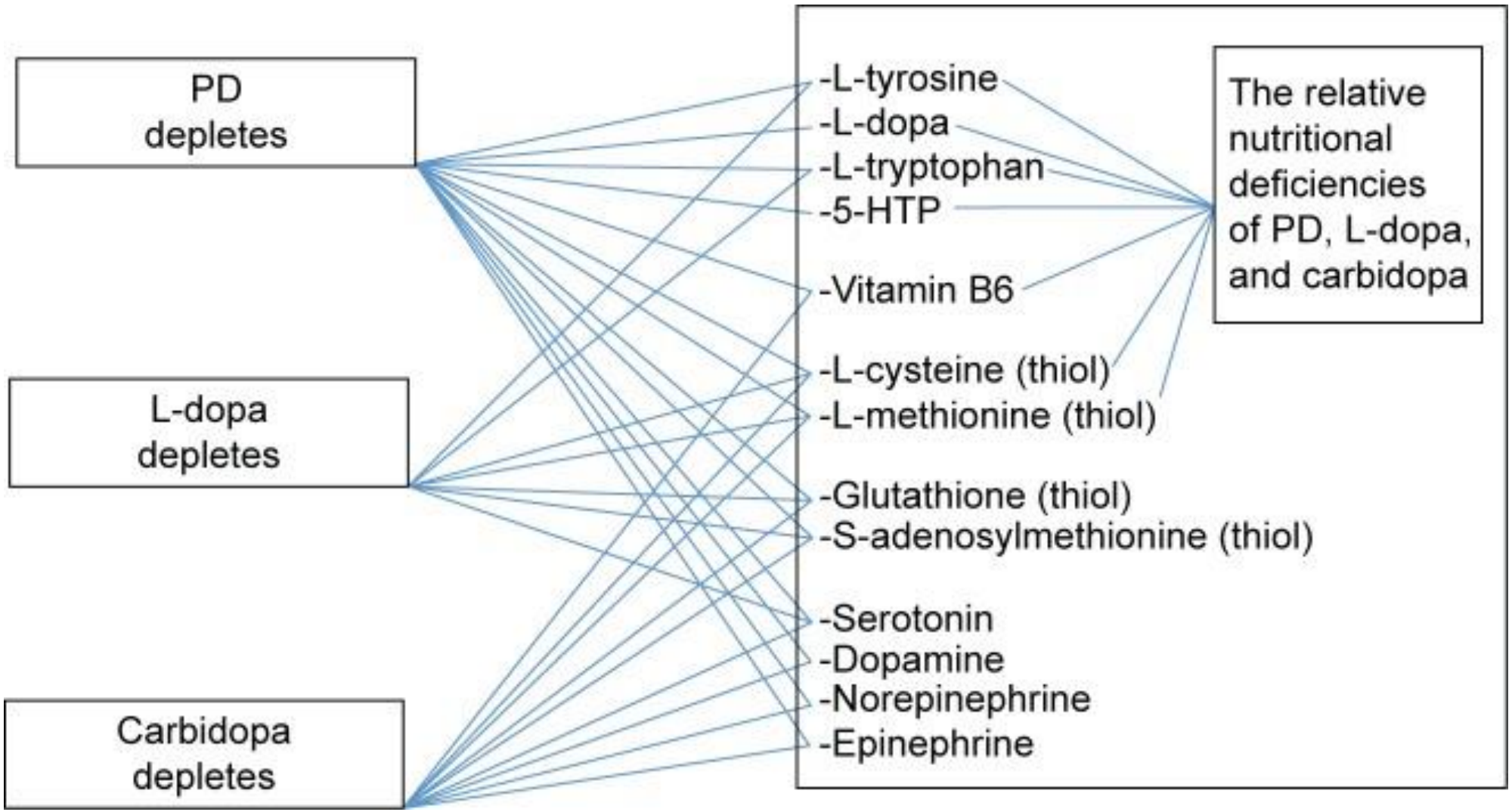
- The enteric nervous system not only contains a variety of functionally distinct enteric neurons but also harbors a prominent component of glial cells, the so-called enteric glial cells, which, like astrocytes of the central nervous system, contribute to support, protect, and maintain the neural network

- recently shown that enteric glial cell dysfunction occurs in PD.



Combining HBOT with other treatment modalities

- Nutrition: Ketogenic Diet?
- Optimizing gut microbiome
- Tailored supplements, vitamins and minerals
- Cannabidiol
- Low dose naltrexone
- Near infrared light therapy
- Repetitive transcranial magnetic stimulation
- Pulsed electromagnetic field therapy
- Exercise


PD
depletes
L-dopa
depletes
Carbidopa
depletes
-L-tyrosine
-L-dopa
-L-tryptophan
-5-HTP
-Vitamin B6
-L-cysteine (thiol)
-L-methionine (thiol)
-Glutathione (thiol)
-S-adenosylmethionine (thiol)
-Serotonin
-Dopamine
-Norepinephrine
-Epinephrine
The relative nutritional deficiencies of PD, L-dopa, and carbidopa

Cannabidiol

- Two studies presented at the 21st International Congress of Parkinson's Disease and Movement Disorders further explored this possibility and assessed the effects of oral cannabidiol (CBD) and inhaled cannabis in patients with Parkinson's disease.
- Maureen A. Leehey, MD, Professor of Neurology and Chief of the Movement Disorders Division at the University of Colorado in Aurora, and colleagues conducted a phase II, open-label, dose-escalation study to evaluate the safety and tolerability of CBD (Epidiolex) in Parkinson's disease
- Over a 31-day treatment period, patients received 5-, 7.5-, 10-, 15-, and 20-mg/kg/day doses of CBD.
- 13 patients, mean total UPDRS score significantly decreased from 45.9 at baseline to 36.4 at the final visit. UPDRS motor score decreased from 27.3 to 20.3. Mean rigidity from 9.14 to 6.29
- Laurie K. Mischley, ND, PhD, MPH, Associate Clinical Investigator at Bastyr University Research Institute in Kenmore, Washington, and colleagues evaluated the effect of inhaled cannabis on Parkinson's disease tremor using motion sensors and qualitative interviews.

LDN

- low-dose naltrexone blocks opioid receptors in the brain for few hours and creates a “rebound effect,” resulting in up-regulated production of the endogenous opioids beta-endorphin and met-enkephalin, as well as increased expression of opioid receptors

- both endogenous and exogenous opioids immune modulators

- suppress microglial activation via its antagonistic effect on toll-like receptor 4 (TLR4), a non-opioid receptor that is found on macrophages such as microglia

Neuron Photomodulation-light therapy

Front Neurosci. 2015; 9: 500.
Published online 2016 Jan 11. doi: 10.3389/fnins.2015.00500
PMCID: PMC4707222
PMID: 26793049

Turning On Lights to Stop Neurodegeneration: The Potential of Near Infrared Light Therapy in Alzheimer's and Parkinson's Disease

Daniel M. Johnstone,[1] Cécile Moro,[2] Jonathan Stone,[1] Alim-Louis Benabid,[2] and John Mitrofanis[2,*]

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Abstract

Go to:

Alzheimer's and Parkinson's disease are the two most common neurodegenerative disorders. They develop after a progressive death of many neurons in the brain. Although therapies are available to treat the signs and symptoms of both diseases, the progression of neuronal death remains relentless, and it has proved difficult to slow or stop. Hence, there is a need to develop neuroprotective or disease-modifying treatments that stabilize this degeneration. Red to infrared light therapy ($\lambda = 600–1070$ nm), and in particular light in the near infrared (NIr) range, is emerging as a safe and effective therapy that is capable of arresting neuronal death. Previous studies have used NIr to treat tissue stressed by hypoxia, toxic insult, genetic mutation and mitochondrial dysfunction with much success. Here we propose NIr therapy as a neuroprotective or disease-modifying treatment for Alzheimer's and Parkinson's patients.

Monitoring the progress of PD patients before, during and after HBOT

Unified Parkinson's Disease Rating Scale

PD workbook
THE WEMOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

I. Mentation, Behavior and Mood

1. Intellectual Impairment

0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.

4. Motivation/Initiative

0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. Activities of Daily Living

(for both "on" and "off")

5. Speech

0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

Thank you