Review Article ISSN 2641-4333

Neurology - Research & Surgery

Why Hypoestoxide is the Ideal Candidate Drug for Disease Modifying Treatment of Parkinson's Disease

Emmanuel A. Ojo-Amaize* and Howard B. Cottam

[1]*Immune Modulation, INC., P.O. BOX 998, Bloomington, CA 92316-0998, USA.*

***Correspondence:**
Emmanuel A. Ojo-Amaize, Immune Modulation, Inc., P.O. Box 998, Bloomington, CA 92316-0998, USA, Tel: 951-733-6787.

Received: 25 Jan 2023; **Accepted:** 28 Feb 2023; **Published:** 04 Mar 2023

Citation: Emmanuel A. Ojo-Amaize, Howard B. Cottam. Why Hypoestoxide is the Ideal Candidate Drug for Disease Modifying Treatment of Parkinson's Disease. Neurol Res Surg. 2023; 6(1): 1-3.

ABSTRACT

Parkinson's disease (PD) is an idiopathic, relentlessly progressive neurodegenerative and chronic inflammatory disease caused by the accumulation of pathologic α-synuclein leading to neuronal death by apoptosis/mitophagy, chronic inflammation, abnormal calcium transport into cells and oxidative damage. Hypoestoxide (HE), is a natural diterpene extracted and purified from the Nigerian shrub Hypoestes rosea (Acanthaceae). HE has been shown to induce apoptosis, inhibit nuclear factor kappa B (NF-κB) activation leading to the inhibition of the production of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6), inhibit oxidative damage via the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway which is a transcription factor that induces anti-oxidant response genes, activate Peroxisome proliferator-activated receptor- γ (PPAR-γ) leading to enhanced apoptosis and autophagy/mitophagy and inhibit α-synuclein accumulation. The accumulation of pathologic α-synuclein is said to be the eventual cause of neuronal death. These various molecular targets make HE an ideal candidate drug for eliminating the underlying cause and pathological features of PD.

Keywords

Parkinson's disease, Hypoestoxide, Alzheimer's disease.

Introduction

In the elderly population, PD is the second most common progressive neurodegenerative, chronic inflammatory incurable disorder after Alzheimer's disease. While the underlying mechanisms of PD are still poorly understood, it is believed that the progressive nature of PD is driven by chronic inflammation-induced neurodegeneration of dopamine producing neurons within the substantia nigra (SN) and striatum [1-3].

Hypoestoxide (HE) is a novel, natural, non-synthesizable, non-toxic, and potent non-steroidal anti-inflammatory drug (NSAID). While HE is primarily a NSAID [4], it has other biological activities such as anti-cancer [5], anti-parasitic [6] and anti-viral [7]. HE is the major active pharmaceutical ingredient (API) of the Nigerian shrub Hypoestes rosea (Acanthaceae) [4]. Interestingly, the consumption of the dried leaf powder of this shrub as a daily dietary supplement [sold as "Peko-D": NAFDAC REG. NO. A7-1913L] immensely improves the quality of life of PD patients in Nigeria.

HE has several molecular targets, which include but not limited to the following: NF-κB, Nrf2/ARE, PPAR-γ, α-synuclein. Each one of these targets will be discussed in relation to PD respectively.

Discussion

NF-κB, PD and HE

PD is a neurodegenerative condition, which is primarily driven by chronic inflammation. NF-κ B is a family of inducible transcription factors that are expressed in a wide variety of cells and tissues, including microglia, astrocytes and neurons. This pathway plays an important role in the activation and regulation of pro- inflammatory cytokines' production during the process of inflammation.

Evidence supporting the view that NF-κB plays a central role as a regulatory target for PD therapy comes from studies using specific NF-κB inhibitors such as pioglitazone (a PPAR-gamma agonist) or curcumin in murine models of PD to show that the administration of these inhibitors could halt the progression of neurodegeneration induced by the neurotoxin, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [8] or by activation of CNS inflammation by the intracranial injection of LPS [9]. Our studies with HE have also clearly demonstrated that administration of HE to α-syn-transgenic mice, significantly decreased the elevated levels of phosphorylated NF-κB in the neocortex of these mice to the low levels observed in the non- transgenic mice [10]. The inhibition of NF- κB activation by HE led to significant inhibition of the production by microglia cells, of the pro-inflammatory cytokines, TNF-α, IL-1β and IL-6, as well as improvement in their locomotor function compared with untreated transgenic control mice [10]. Elevated levels of all of these pro-inflammatory cytokines have been found in the brains, CSF and plasma of PD patients [11].

Nrf2/ARE, PD and HE

Nuclear factor E2-related factor 2 (Nrf2) is a master regulator that induces a battery of cytoprotective genes including antioxidative enzymes, anti-inflammatory mediators, the proteasome, and several transcription factors involved in mitochondrial biogenesis [12].

In pathology of neurodegenerative disorders such as PD, the generation of reactive oxygen species (ROS) may be harmful affecting proteins, lipids and nucleic acids [13].

The Nrf2 pathway is one of the pathways that respond to ROS by activating the transcription of phase II detoxification enzymes [14]. When redox balance is tipped toward the oxidative side, Nrf2 trans-locates into the nucleus and activates the transcription of anti-oxidant response element (ARE)-dependent genes [15]. In regard to PD, one line of evidence suggests the involvement of the Nrf2/ARE pathway in PD's pathogenesis and that is the localization of Nrf2 in susceptible neuron populations in PD brain tissues from a postmortem study [16]. It was shown that in neurodegenerative diseases, Nrf2 expression is altered in neurons and astrocytes. Nrf2 was activated in SN in PD brains even though the response appeared insufficient to protect neurons from degeneration. However, in Nrf2-knockout mice, dopaminergic neurodegeneration and microglial activation induced by chronic injection of MPTP were more severe than in wild-type mice [17]. Studies demonstrating the Nrf2-activating effects of PD drugs such as apomorphine (Apo) support the link between the Nrf2/ARE pathway and PD. Apo is a drug used for clinical therapy of PD. Apo is a dopamine receptor agonist and has scavenger and protective effects in ROS-induced cell death. Thus, Apo acts by producing intracellular ROS and activating the Nrf2 pathway to promote neuroprotective effects [18].

In studies unrelated to PD, HE was shown to be a potent activator of the Nrf2 signaling pathway, and even 5 times more potent than curcumin in activating Nrf2 target genes [19]. It was demonstrated that the α-β unsaturated carbonyl functional group on HE was essential for Nrf2 activation [19]. Thus, the ability of HE to activate Nrf2 signaling pathway would help promote its scavenger effects in ROS-induced cell death and neuroprotective effects in PD.

PPAR-γ, PD and HE

Peroxisome proliferator-activated receptor-gamma (PPAR-γ) is a nuclear receptor and ligand-dependent transcription factor, which regulates pathways of inflammation, lipid and carbohydrate metabolism, antioxidant defenses and mitochondrial biogenesis. PD has since been associated with impaired mitochondrial complex I (CI) activity, while several gene defects associated with familial PD involve defects in mitochondrial function, causing an imbalance between mitochondrial biogenesis and removal of dysfunctional mitochondria by autophagy [20]. The inhibitors of CI, MPTP and 1-Methyl-4-phenylpyridinium (MPP+), have widely been used in vivo and in vitro to model PD due to their capacity to produce neurochemical, neurological and pathological changes similar to those observed in PD [21,22]. All of these changes were reversed by pre-treatment with the PPAR-γ agonist, rosiglitazone that increased mitochondrial biogenesis, increased oxygen consumption and suppressed free radical generation and autophagy. Thus, rosiglitazone is neuroprotective in PD through a direct effect on mitochondrial function.

Similar to rosiglitazone, HE has also been reported to be a PPAR-γ agonist [23]. Thus, we theorized that the activation of PPAR-γ would lead to multiple levels of protection (increased autophagy, oxygen consumption, mitochondrial biogenesis, SOD, and catalase) [23].

α-Synuclein, PD and HE

PD is characterized by the loss of dopaminergic neurons in the SN and the formation of intraneuronal inclusions called Lewy bodies, which are composed mainly of α-synuclein. Studies have convincingly demonstrated that abnormal deposition of α-synuclein is not only pathological but also critical to the onset and progression of PD [24].

The involvement of α-synuclein in neurodegenerative processes also raises the prospect of new therapeutic strategies that, by counteracting protein accumulation and toxicity, would slow down or halt disease progression. Indeed, administration of HE was shown in α-syn transgenic mice to inhibit the aggregation and reduce the accumulation/deposition of α-synuclein in neurons and the neuropil, which were correlated with the behavioral improvements observed in the mice [10].

Conclusion

Our on-going research and development of Hypoestoxide as a therapeutic agent for PD is primarily based on the four molecular targets described here. For any potential anti-PD drug to be highly effective, it must be able to target these four molecules (NF-κB, Nrf2/ARE, PPAR-γ and α-Synuclein) and of course, most importantly, to cross the blood-brain-barrier and be safe for chronic use. Preliminary toxicology studies in rats and dogs showed that HE was very safe and orally bioavailable.

References

1. Block ML, Hong JS. Microglia and inflammation mediated neurodegeneration Multiple triggers with a common mechanism. Progress in Neurology. 2005; 76: 77-98.
2. Bartels AL, Leenders KL. Neuroinflammation in the pathophysiology of Parkinson's disease evidence from animal models to human in vivo studies with [C]-PK 11195 PET. Movement Disorders. 2007; 22: 1852-1856.
3. Dauer W, Przedborski S. Parkinson's disease mechanisms and models. Neuron. 2003; 39: 889-909.
4. Ojo-Amaize EA, Kapahi P, Kakkanaiah VN, et al. Hypoestoxide a novel anti-inflammatory natural diterpene inhibits the activity of IkappaB kinase. Cell Immunol. 2001; 209: 149-157.
5. Ojo-Amaize EA, Nchekwube EJ, Cottam HB, et al. Hypoestoxide a natural non-mutagenic diterpenoid with antiangiogenic and antitumor activity Possible mechanisms of action. Cancer Research. 2002; 62: 4007-4014.
6. Ojo-Amaize EA, Nchekwube EJ, Cottam HB, et al. Plasmodium berghei Antiparasitic effects of orally administered Hypoestoxide in mice. Exp Parasitol. 2007; 117: 218-221.
7. Ojo-Amaize EA, Okogun JI. Hypoestoxide derivatives and agonists thereof for use as antiviral agents. Immune Modulation Inc. 1999.
8. Zhang E, Qian PM, Flood JS, et al. Inhibition of IκB kinase β protects dopamine neurons against lipopolysaccharide induced neurotoxicity. J Pharmacol Exp Therapeutics. 2010; 333: 822-833.
9. Andersson PB, Perry VH, Gordon S. The acute inflammatory response to lipopolysaccharide in cns parenchyma differs from that in other body tissues. Neuroscience. 1992; 48: 169-186.
10. Changyoun K, Ojo Amaize EA, Spencer B, et al. Hypoestoxide reduces neuroinflammation and α-synuclein accumulation in a mouse model of Parkinson's disease. J Neuroinflammation. 2015; 12: 236.
11. Starhof C, Winge K, Heegaard NHH, et al. Ceresbrospinal fluid pro-inflammatory cytokines differenciate parkinsonian syndromes. J Inflammation. 2018; 15: 305.
12. Beal MF. Therapeutic approaches to mitochondrial dysfunction in Parkinson's disease. Parkinsonism Related Disorders. 2009; 15: 5189-5194.
13. Valko M, Rhodes CJ, Moncol J, et al. Free radicals metals and antioxidants in oxidative stress-induced cancer. Chemico-Biological Interactions. 2006; 160: 1-40.
14. Kobayashi A, Ohta T, Yamamoto M. Unique function of the NrF2-Keap 1 pathway in the inducible expression of antioxidant and detoxifying enzymes. Methods in Enzymology. 2004; 378: 273-286.
15. Dhakshinamoorthy S, Jaiswal AK. Functional characterization and role of Nrf2 in antioxidant response element mediated expression and antioxidant induction of NAD(P)H quinone oxidoreductase 1 gene. Oncogene. 2001; 20: 3906-3917.
16. Johnson DA, Johnson JA. Nrf2- a therapeutic target for the treatment of neurodegenerative diseases. Free Radic Biol Med. 2015; 88: 253-267.
17. Chen PC, Vargas MR, Pani AK et al. Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease Critical role for the astrocyte. PNAS. 2009: 106: 2933-2938.
18. Hara H, Ohta M, Adachi T. Apomorhine protects against 6-hydroxydopamine-induced neuronal cell death through activation of the Nrf2-ARE pathway. J Neuroscience Research. 2006; 84: 860-866.
19. Wu RP, Hayashi T, Cottam HB, et al. Nrf2 responses and the therapeutic selectivity of electrophilic compounds in chronic lymphocytic leukemia. PNAS. 2010; 107: 7479-7484.
20. Schapira AH, Cooper JM, Dexter D, et al. Mitochondrial complex1 deficiency in Parkinson's disease. J Neurochem. 1990; 54: 823-827.
21. Meredith GE, Rademacher DJ. MPTP mouse models of Parkinson's disease: An update. J Parkinson's Dis. 2011; 1: 19-33.
22. Zeng X, Chen J, Deng X, et al. In vitro model of human dopaminergic neurons derived from embryonic stem cells MPP toxicity and GDNF neuroprotection. Neuropharmacology. 2006; 31: 2708-2715.
23. Ojo-Amaize EA, Cottam HB. Short review of current research on the development of hypoestoxide as a therapeutic agent for Parkinson's disease. J Neurol Neurophysiol. 2016; 7: 385.
24. McCormack AL, Di Monte DA. Enhanced α-synuclein expression in human neurodegenerative diseases Pathogenetic and Therapeutic Implications. Current Protein and Peptide Science. 2009; 10: 476-482.