Hypoxia therapy--a new hope for the treatment of mitochondrial dysfunctions

Jun-long Huang[1, 2], Anatol Manaenko[3], Zhou-heng Ye[2], Xue-jun Sun[2], Qin Hu[1, *]

1 Discipline of Neuroscience, Department of Anatomy, Histology and Embryology, Shanghai Jiao Tong University School of Medicine, Shanghai, China

2 Department of Naval Aviation, the Second Military Medical University, Shanghai, China

3 Departments of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany

*Correspondence to: Qin Hu, M.D., Ph.D., huqinle20010709@126.com.

orcid: 0000-0002-2270-8822

Abstract

Mitochondrial dysfunctions are characteristic features of numerous diseases and play a critical role in disease pathogenesis. Despite intensive research in this area, there are no approved therapies that directly target mitochondria. Recently a study by Jain et al. from Massachusetts General Hospital, USA reported the effectiveness of hypoxia for treatment of mitochondrial disease in mice. In this commentary, we summarized the potential mechanisms underlying the therapeutic effects of hypoxia on mitochondrial dysfunction, and clinical limitations of hypoxia as a therapy for human patients. We hope that our concerns will be helpful for further clinical studies addressing moderate hypoxia in mitochondrial dysfunction.

Key words: mitochondrial dysfunction; hypoxia; hypoxia-inducible factor-1α; Von Hippel-Lindau factor; respiratory chain; neuroprotective; Leigh syndrome; oxygen toxicity

doi: 10.4103/2045-9912.191365

How to cite this article: Huang JL, Manaenko A, Ye ZH, Sun XJ, Hu Q (2016) Hypoxia therapy--a new hope for the treatment of mitochondrial dysfunctions. Med Gas Res 6(3):174-176.

Mitochondria are essential for regulation of cellular function and metabolism, and mitochondrial dysfunctions are hallmark of pathogenesis of numerous disease and aging process. Mitochondrial dysfunctions originate either from primary defects of the genes encoding mitochondria-localized proteins or are induced by environmental stresses (Koopman et al., 2016). The current mainstay of mitochondrial disease therapies involves administration of antioxidants and modulators of metabolism. However the efficacy of these approaches needs to be further investigated (Wang et al., 2016). Recently, using a clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR associated protein 9 (Cas9) mediated genome-wide screen in a model of mitochondrial disease on human cell culture, Jain et al. (2016) identified the inhibition of Von Hippel-Lindau (VHL) factor (the key regulator of the hypoxic pathways) as the undoubted effective genetic suppressor of mitochondrial disease. Jain et al. (2016) postulated that triggering hypoxia innate responses is protective in mitochondrial disease. The authors mimicked mitochondrial dysfunction by adding respiratory chain (RC) inhibitors (complex I inhibitor Piericidin, complex III inhibitor Antimycin, or complex V inhibitor Oligomycin) to the cultured HT-29s, HEK 293Ts, or K562s cell lines, and administering FG-4592 (prolyl-hydroxylase inhibitor) rescued the growth defects in a dose-dependent manner. Furthermore, VHL KO or FG-4592 treatment activated the hypoxia inducible factor (HIF) response in zebrafish embryos and alleviated death caused by RC inhibition. The results were also confirmed using a mouse model of Leigh syndrome by knocking out Ndufs4 gene, in which continuously breathing 11% O_2 improved survival and locomotor activity, and alleviated circulating biomarkers as well as neuropathology (Jain et al., 2016).

Jain et al. (2016) suggested that hypoxia activates evolutionarily conserved adaptive programs and that the

activation represents the promising therapeutic strategy with a vital clinic significance. Indeed, there are only few therapeutic options for mitochondrial disease caused by devastating and often fatal inborn mutations. The hypoxia exposure may be a fast-track attempt for this sort of mitochondrial disease.

For mitochondrial disease induced by environmental stresses (acquired mitochondrial dysfunctions), hypoxia has drawn an attention to the administration of supplemental oxygen as a conventional therapy. Acquired mitochondrial dysfunctions are implicated in numerous diseases and conditions, such as cardiovascular disease; neurodegenerative diseases, including Alzheimer's and Parkinson's; metabolic disorders (diabetes and obesity); cancer; and in normal aging (Pieczenik and Neustadt, 2007). Mitochondrial dysfunctions can be also induced as consequence by such diseases conditions as ischemia and hypoxia (Khan et al., 2015; Lioutas et al., 2015; Qi et al., 2015). All these cases represent a mismatch between normal oxygen delivery and impairment, due to the mitochondrial dysfunction, oxygen utilization (Etminan, 2015; Lapchak, 2015). Clinically a supplemental oxygen exposure is one of the routine treatments (Stoller, 2015; Yan et al., 2015). The toxic effects of the superfluous oxygen are, however, not always taken into consideration by this strategy. In Ndufs4 KO mice, breathing normobaric hyperoxia (55% O_2) markedly reduced the survival, indicating that hyperoxia is toxic to patients with mitochondrial dysfunction (Jain et al., 2016). Without toxic side effects, hypoxia triggers innate adaptive programs, preventing the advance of mitochondrial dysfunctions, and has a great therapeutic potential. Repetive hypoxic exposures have been reported to show protective effects against ischemic attack in animal models (Dong et al., 2003; Stowe et al., 2011; Tsai et al., 2011). These programs are primarily dependent on HIF-1α activation, which leads to reprograming of metabolism, promoting of cell survival and inducing angiogenesis (Stowe et al., 2011; Cho et al., 2015; Gonzalez-Rothi et al., 2015).

Although hypoxia might have a considerable therapeutic potential as a simple and effective treatment of mitochondrial dysfunctions, there are several challenges in translating hypoxia, as a treatment option, into the clinical settings. First, the prolonged hypoxia can lead to a range of severe pathophysiological reactions. Therefore, the intensity, duration and frequency of hypoxic episodes should be carefully monitored and adjusted, according to the patient's response (Navarrete-Opazo and Mitchell, 2014). The chronic hypoxic expose (11% oxygen), which turned out as a promising approach in the study by Jain et al. (2016) and delivered positive results in a mouse model of Leigh syndrome, might not be well tolerated by patients. Consequently, Jain et al. (2016) proposed moderate and intermittent hypoxia paradigm as more translatable approach. They suggested the application of an intermediate hypoxia (oxygen levels between 11% and 20%), during nighttime with facemasks or sleeping tents for patients as a clinical applicable option. Second, one of challenging hurdles is the attitudes of clinicians and patients towards the breathing low levels of O_2 (Dempsey and Morgan, 2015). Despite observed beneficial effects, long term expose to the hypoxia can cause adverse physiologic effects. The pharmacological activation of the hypoxic pathway under normoxic conditions might be a better option for treatment of mitochondrial dysfunctions (Agani and Jiang, 2013; Lioutas et al., 2015; Wang et al., 2015). Today small molecule HIF-prolyl hydroxylase inhibitors are most advanced. Some of these inhibitors (such as FG-4592) have entered clinical trials (phase Ⅲ) evaluating their effectivity for treatment of anemia. Third, despite safety, lack of negative side effects and other advantages of hypoxia, as mentioned above, no clinic trials have been conducted in human patients with diseases associated with mitochondrial dysfunctions. Further preclinical studies are required to understand whether hypoxia or HIF-prolyl hydroxylase inhibitors can be developed into a safe and effective treatment for patients with impaired mitochondrial function.

Author contributions

JLH write the paper; XJS and ZHY gave suggestions; AM and QH modified the language. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

References

Agani F, Jiang BH (2013) Oxygen-independent regulation of HIF-1: novel involvement of PI3K/AKT/mTOR pathway in cancer. Curr Cancer Drug Targets 13:245-251.

Cho Y, Shin JE, Ewan EE, Oh YM, Pita-Thomas W, Cavalli V (2015) Activating injury-responsive genes with hypoxia enhances axon regeneration through neuronal HIF-1alpha. Neuron 88:720-734.

Dempsey JA, Morgan BJ (2015) Humans in hypoxia: a conspiracy of maladaptation?! Physiology (Bethesda) 30:304-316.

Dong JW, Zhu HF, Zhu WZ, Ding HL, Ma TM, Zhou ZN (2003) Intermittent hypoxia attenuates ischemia/reperfusion induced apoptosis in cardiac myocytes via regulating Bcl-2/Bax expression. Cell Res 13:385-391.

Etminan N (2015) Aneurysmal subarachnoid hemorrhage--status quo and perspective. Transl Stroke Res 6:167-170.

Gonzalez-Rothi EJ, Lee KZ, Dale EA, Reier PJ, Mitchell GS, Fuller DD (2015) Intermittent hypoxia and neurorehabilitation. J Appl Physiol 119:1455-1465.

Jain IH, Zazzeron L, Goli R, Alexa K, Schatzman-Bone S, Dhillon H, Goldberger O, Peng J, Shalem O, Sanjana NE, Zhang F, Goessling W, Zapol WM, Mootha VK (2016) Hypoxia as a therapy for mitochondrial disease. Science 352:54-61.

Khan MB, Hoda MN, Vaibhav K, Giri S, Wang P, Waller JL, Ergul A, Dhandapani KM, Fagan SC, Hess DC (2015) Remote ischemic postconditioning: harnessing endogenous protection in a murine model of vascular cognitive impairment. Transl Stroke Res 6:69-77.

Koopman WJ, Beyrath J, Fung CW, Koene S, Rodenburg RJ, Willems PH, Smeitink JA (2016) Mitochondrial disorders in children: toward development of small-molecule treatment strategies. EMBO Mol Med 8:311-327.

Lapchak PA (2015) Critical early thrombolytic and endovascular reperfusion therapy for acute ischemic stroke victims: a call for adjunct neuroprotection. Translational stroke research 6:345-354.

Lioutas VA, Alfaro-Martinez F, Bedoya F, Chung CC, Pimentel DA, Novak V (2015) Intranasal insulin and insulin-like growth factor 1 as neuroprotectants in acute ischemic stroke. Translational stroke research 6:264-275.

Navarrete-Opazo A, Mitchell GS (2014) Therapeutic potential of intermittent hypoxia: a matter of dose. Am J Physiol Regul Integr Comp Physiol 307:R1181-1197.

Pieczenik SR, Neustadt J (2007) Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol 83:84-92.

Qi Z, Dong W, Shi W, Wang R, Zhang C, Zhao Y, Ji X, Liu KJ, Luo Y (2015) Bcl-2 phosphorylation triggers autophagy switch and reduces mitochondrial damage in limb remote ischemic conditioned rats after ischemic stroke. Transl Stroke Res 6:198-206.

Stoller KP (2015) All the right moves: the need for the timely use of hyperbaric oxygen therapy for treating TBI/CTE/PTSD. Med Gas Res 5:7.

Stowe AM, Altay T, Freie AB, Gidday JM (2011) Repetitive hypoxia extends endogenous neurovascular protection for stroke. Ann Neurol 69:975-985.

Tsai YW, Yang YR, Wang PS, Wang RY (2011) Intermittent hypoxia after transient focal ischemia induces hippocampal neurogenesis and c-Fos expression and reverses spatial memory deficits in rats. PLoS One 6:e24001.

Wang L, Wang X, Su H, Han Z, Yu H, Wang D, Jiang R, Liu Z, Zhang J (2015) Recombinant human erythropoietin improves the neurofunctional recovery of rats following traumatic brain injury via an increase in circulating endothelial progenitor cells. Transl Stroke Res 6:50-59.

Wang W, Karamanlidis G, Tian R (2016) Novel targets for mitochondrial medicine. Sci Transl Med 8:326rv323.

Yan L, Liang T, Cheng O (2015) Hyperbaric oxygen therapy in China. Med Gas Res 5:3.