Hyperbaric Oxygen Therapy Effect on "Kinesia Paradoxa" Brain Circuits

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Abstract

This article aims to determine the effectiveness of hyperbaric oxygen therapy (HBOT) for treating symptoms of Parkinson's disease. We present a brief review of the relevant literature and general information about HBOT. This paper describes evidence that HBOT has crucial effects to the three specific brain circuits possibly involved in "Kinesia Paradoxa" (noradrenergic system, basal ganglia, and the cerebellum circuit). Moreover, we are presenting clues supporting "Norepinephrine Hypothesis" according to which HBOT increases norepinephrine levels and restores motor deficits in Parkinson's disease patients.

Keywords

Hyperbaric oxygen therapy (HBOT) · Parkinson's disease (PD) · Noradrenergic system (NA) · Norepinephrine (NE) · Kinesia paradoxa (KP)

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1 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is characterized often as a movement disorder because of the motor symptoms (bradykinesia, tremor, freezing, postural instability) most patients develop. Hyperbaric oxygen therapy (HBOT) is already indicated in various diseases and several studies have shown that HBOT could be used as a treatment for PD patients. After providing a brief review about the effectiveness of HBOT in PD patients, we tried to identify its possible effects on the three brain circuits involved in the "Kinesia Paradoxa" phenomenon. There are strong indications that HBOT has an effect on all three circuits. We tried to identify possible connection pathways, and we propose that "Norepinephrine Hypothesis" is the responsible mechanism behind neurochemical abnormalities' restoration after HBOT.

1.1 HBOT: Definition, History, Indications, and Mechanisms of Action

Hyperbaric oxygen therapy (HBOT) consists of intermittently administering 100% oxygen at pressures greater than one atmosphere absolute (ATA) in a pressure vessel [1]. HBO_2 treatment is carried out in chambers either individually (single patient) or collectively (typically 2–14

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patients, multi-place chamber). In 1662 (oxygen was discovered nearly a century later), Nathaniel Henshaw, a British physician and clergyman, put his mark on history for pioneering the use of the first hyperbaric chamber [2, 3] by increasing the pressure in a sealed room connected by bellows, through special valves which he called "domicilium." The simplistic principle behind its use was that patients suffering from acute conditions could benefit more from increased air pressure, while those suffering from chronic conditions would benefit from reduced air pressure. Nearly 200 years later, the interest in hyperbaric oxygen revived in France (1832: Emile Tabarie chamber; 1837: Pravaz chamber in Lyon; 1877: Fontaine explored the surgical application of hyperbaric therapy [3]). In the USA Orval J. Cunningham used HBOT for treatment of the Spanish influenza epidemic that swept North America after World War I. Heinrich Drager in 1917 was the first to explore the use of pressurized oxygen in decompression sickness, and his protocols were put into practice by Behnke and Shaw in the late 1930s [4]. The HBOT chamber which was considered the most important and received the most publicity in history was that of Dr. Cunningham who was a professor of anesthesiology at the University of Kansas and built the largest chamber ever, consisting of five floors and a diameter of 64 meters. Each floor had 12 rooms with all the amenities of a good hotel. This chamber was used in the treatment of various diseases such as syphilis, diabetes, hypertension, cancer, etc.

In 1962, Smith and Sharp reported the enormous benefits of HBOT in carbon monoxide poisoning which aroused international interest. Since then, HBOT has been utilized in the treatment of numerous medical conditions and research continues to prove its effectiveness in several others [5]. In the USA, the Undersea and Hyperbaric Medical Society (UHMS) formulated indications for HBOT use that include 17 diseases [6]. The European Committee for Hyperbaric Medicine (ECHM) divided their recommended indications into four types: (a) strongly indicated, (b) suggested, (c) possible/optional, and (d) negative/not indicated [7]. Compared to the USA and Europe, the number of hyperbaric oxygen indications approved in China [8] and Russia [9] is relatively high. However, there is a general consensus about its use for air or gas embolism, carbon monoxide poisoning, sudden deafness, and decompression illness (DCI). It should be mentioned that HBOT is inappropriate due to contraindications if a patient has untreated pneumothorax, active hemorrhage, pulmonary bulla, severe emphysema, high blood pressure [8], etc. Also, there are side effects associated with HBOT such as middle ear barotrauma (MEB), dental barotrauma, hyperoxic myopia, and hypoglycemia in diabetics [10], but in general HBOT remains among the safest therapies used today.

Mechanisms of action of HBOT mainly have been reported to be increased oxygen delivery, reduction of gas bubble size, and antagonism of carbon monoxide [11].

1.2 HBOT and Parkinson: Literature Review and Application in Medical Centers

The effectiveness of HBOT in Parkinsonism treatment was first investigated in Russia (Neurological Department of the Moscow Oblast M. F. Vladimirsky Scientific Research Clinical Institute) by Neretin Vla et al. in 1989 [12]. They had 64 Parkinson's disease (PD) patients from 37 to 78 years old under observation. The course of treatment included 8–12 procedures with an exposure of 40–60 to a single-seater HBOT chamber. The therapeutic effect was considered as "Good" in 18 patients, "Satisfactory" in 26 patients, and "Insignificant" in 11 patients, while five patients presented a medium improvement of their tremor which lasted 1–3 h after HBOT treatment. Also, four patients abandoned the research due to claustrophobia. Thirty-six patients maintained therapeutic effects up to 6 months after HBOT. As a result, the authors suggested that HBOT, either independent or in combination with antiparkinsonian agents, is effective for PD treatment. Interestingly enough, they assumed that HBOT has positive influence on the brain

neurotransmitter's systems. Based on the research of Borromei et al. in 1996 [13], other researchers from Chico Hyperbaric Center [14] presented a case study of a 72-year-old male PD patient who after 25 HBO therapy treatments showed improvement of speech and hand movements. Another interesting case [15] reported about a 45-year-old male PD patient with severe motor (tremor, bradykinesia) and non-motor symptoms (depression and anxiety "including a loss of interest in daily life, unwilling to communicate with others, and often having suicidal thoughts"). The patient refused treatment with drugs, he lost weight – about 20 kilos – and he was only sleeping 2 or 3 h per day. He did HBOT and after 4 days his sleep improved in 5 h and his overall mood recuperated. He continued to do HBO for a month. There were no complications. After the treatment, his sleep returned to normal – about 10 h per day – and his weight increased by 10 kg. The tremor and bradykinesia improved significantly. Experiments have also been performed on rodents (animal models of PD) which have shown that HBOT resulted in significant protection against the loss of neurons [16] and leads to motor function improvement [17]. These researchers [16, 17] believe that this beneficial effect is due to HBOT anti-apoptotic function and/or oxidative metabolism activation that HBOT triggers in dopaminergic neurons, theories that are also emphasized by very recent findings [18]. It is important to note that nowadays many medical centers and clinics worldwide, mainly in the USA but also in EU (i.e., the UK, Switzerland), use HBOT for Parkinson's disease treatment. Although FDA (US Food and Drug Administration) has not approved HBOT for PD and European Committee for Hyperbaric Medicine (ECHM) has not made a clear statement, the aforementioned clinics submit the following arguments:

1. Anecdotal evidence support use: "PD patients treated with HBOT for other conditions e.g. for diabetic foot, got up from the wheelchair and walked across the room after a series of HBOT."
2. Hyperbaric oxygen dramatically lowers inflammation and decreases oxidative stress.
3. HBOT promotes neurogenesis.
4. HBOT reduces pain, accelerates healing, and decreases inflammation.
5. "Hyperbaric oxygen is able to effectively oxidize and remove harmful toxins, heavy metals, bacteria, and viruses, which are all often present with Parkinson's. The bacteria that are associated with Parkinson's thrive in low oxygen. But these bacteria are poisoned and killed by high levels of pressurized oxygen."

1.2.1 HBOT and Traumatic Brain Injury (TBI)

A possible explanation for the beneficial function of HBOT is the neuroplasticity activation. At first, experimental research focused on animal models of TBI. Experiments on dog models [19, 20], rat models [21], and rabbit models [22] demonstrated the neuroprotective effects of hyperoxia: reduced mortality, less brain edema, and cognitive improvements. One of the first clinical trials for human TBI [23] showed also reduced mortality. A clinical trial for post-stroke patients [24] showed for the first time convincing results that HBOT activates neuroplasticity which brought beneficial effects for almost all treated patients. Furthermore, other researchers [25] supported that HBOT led to reactivation of neuronal activity: They conducted a clinical trial with 56 patients with prolonged post-concussion syndrome (PCS) who after 40 HBOT sessions presented significant improvement in brain perfusion and changes in brain activity resulting in better quality of life. The results of a recent study [26] were equally impressive and confirmed the neuroplasticity theory: Dr. Shai Efrati and his fellow researchers demonstrated for the first time in humans, that HBOT can induce brain microstructure recovery in TBI patients.

1.3 HBOT Effect on "Kinesia Paradoxa" Brain Circuits

In our previous articles [27, 28] we studied the phenomenon of "Kinesia Paradoxa" (KP) pre-

sented in Parkinson's disease patients, who generally cannot move but under certain circumstances they exhibit a sudden, brief period of mobility (walking or even running). We identified three brain circuits possibly involved [27] as well as the interconnections between them [28]. We summarize in brief the following:

(A) The brain circuits involved are the *noradrenergic (NA) system*, the *basal ganglia,* and the *cerebellum circuit.*
(B) About their interconnections:
  (a) There is no connection between NA system and basal ganglia
  (b) In the brain, the cellular bodies of the noradrenergic neurons mainly exist in the locus coeruleus where they project to various brain regions, including the cerebellum. There is a spectrum of noradrenergic neurotransmitter operations at the level of Purkinje neurons, and Purkinje cells are target cells for the NA glands. So, a *coerulocerebellar pathway* is formed [29].
  (c) Cerebellum-basal ganglia: Cerebellum and basal ganglia have a two-way communication with each other and are linked together to form a complete functional network.

As a next step to our previous work, we thought that it would be an interesting research challenge for us to try to find out if HBOT has an effect on these circuits.

1.3.1 HBOT and Noradrenergic System-Noradrenaline (NE)

Noradrenergic system is the neuronal system responsible for the synthesis, storage, and release of noradrenaline also known as norepinephrine (NE). The effect that the HBOT has on the noradrenergic system was already being investigated in the 1960s with contradictory results. In some articles, it is mentioned [30] that "exposure of mice to oxygen at pressures of 4 and 5 atm decreases the concentrations of brain NE."

Other researchers report [31] that "increased oxygen pressures were not found to alter the rate of NE turnover in rats." Certainly, however, the noradrenergic system plays an important role in HBOT [32]. In general, the effect of hyperbaric oxygenation on the levels of monoamines and free amino acids in whole mouse brain was found to vary with time of exposure and the pressure system used [30]. The approaches of HBOT as an alternative method for antidepressant therapy [33] and for posttraumatic stress disorder (PSTD) treatment [34] highlighted the importance of NE action. These experiments showed that HBOT had an antidepressant effect, improved immobility, and reduced the symptoms of anxiety and fear. The results demonstrated that HBOT partially restored neurochemical abnormalities, and authors proposed that at least part of the mechanism behind these HBOT effects may be related with noradrenaline [33, 34].

1.3.2 HBOT and Basal Ganglia

Experiments in 74 patients who suffered from stroke and had at least one motor dysfunction [24] indicate that HBOT can induce significant neurological improvement in post-stroke patients. Among others, results showed significant basal ganglia perfusion improvement (Fig. 1). Other studies about HBOT's neuroprotective effect against hemorrhagic brain injuries [35] reported that in rats, brain edema in the basal ganglia was reduced by 22% after five HBOT sessions. This is very important for intracerebral hemorrhage (ICH) because the ICH refers to bleeding within the tissue of the brain, most often the basal ganglia. In any case, high efficacy of HBOT for brain hemorrhage has been noted and it is clear that HBOT has an effect on basal ganglia.

1.3.3 HBOT and Cerebellum Circuit

A first approach to connect the HBOT and the cerebellum was made in 1968 in which Rucci [36] indented to investigate the role of the cerebellum in the mechanism of the onset and development of hyperoxic seizures in unanesthetized rats and eventually showed several ways of connection between them.

The cerebellum plays crucial role in balance [37, 38], and one of the most characteristic signs of cerebellar damage is walking ataxia or gait

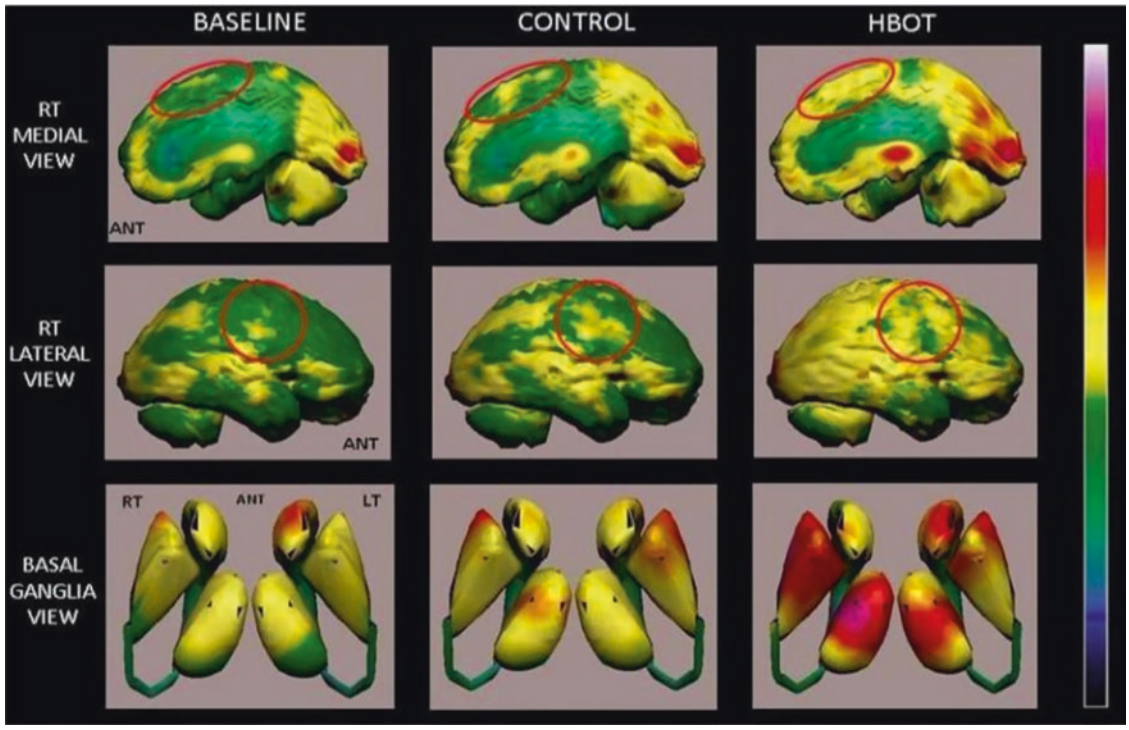

Fig. 1 HBOT SPECT scan done at the end of HBOT treatments shows significant basal ganglia perfusion improvement. (Source: From [24] Efrati et al. (2013))

ataxia, which is often described as a "drunken gait," with distinctive features including variable foot placement, irregular foot trajectories, a widened base of support, a veering path of movement, and abnormal interjoint coordination patterns [38].

Many conditions can cause ataxia, including alcohol intoxication, certain medication, stroke, tumor, cerebral palsy, brain degeneration, and multiple sclerosis [39, 40]. The word ataxia comes from the Greek and means "without order." It is obvious that gait ataxia with its characteristic disorganized, clumsy movements affects autonomy and quality of life.

We hypothesize that HBOT affects the cerebellum via the *coerulocerebellar tract* that we are describing below.

2 Coerulocerebellar Pathway and Norepinephrine Hypothesis

2.1 Locus Coeruleus (LC)

The locus coeruleus (LC) is the major noradrenergic nucleus of the brain [29] found in the pons. The LC ("blue spot" in Latin) was first described by French anatomist Félix Vicq d'Azyr in 1700. LC is the sole source of cortical noradrenaline. The LC projects to areas throughout the cerebellum and in particular to the cerebellar cortex. LC innervates most structures of the neuraxis and plays a crucial role through these structures for the regulation of arousal and autonomic function.

Changes in LC activity result in complex patterns of neuronal activity throughout the brain [29].

2.2 Coerulocerebellar Pathway

As mentioned above, LC projects to areas throughout the cerebellum and in particular to the cerebellar cortex. Depletion of noradrenaline from the cerebellum has been found to result in impaired motor performance [29, 41].

The locus coeruleus (LC) (A6 in Fig. 2) and the coerulocerebellar tract (from A6, A4, A5, and A7 noradrenergic neurons) pass to the cerebellum [43].

2.3 HBOT Norepinephrine Hypothesis

Articles presented cases that under life-threatening events (e.g., fire or earthquake) PD patients who couldn't walk managed to run out and this may be due to noradrenergic activation [42]. The major neurotransmitter localized in noradrenergic neurons is norepinephrine (noradrenaline). We described above in this article a few instances, from articles and clinical cases, that indicate the beneficial effect of HBOT on PD patients. Some of these results demonstrated that HBOT partially restored neurochemical abnormalities, and authors proposed that at least part of the mechanism behind these HBOT effects may be related with norepinephrine [33, 34].

As known, PD patients present decreased noradrenergic cell bodies which leads to significant depletion of NA concentration [44]. Therefore, a possible explanation for the beneficial effects of HBOT on PD patients could be the increased norepinephrine. Due to HBO therapy, norepinephrine is increased, and balance is restored in PD patients. That is through the connection between the noradrenergic system and the cerebellum in which LC neurons innervate the cerebellum and increase the levels of norepinephrine to be transported through the coerulocerebellar pathway. This hypothesis agrees with the "Adrenergic Hypothesis" [45] which formu-

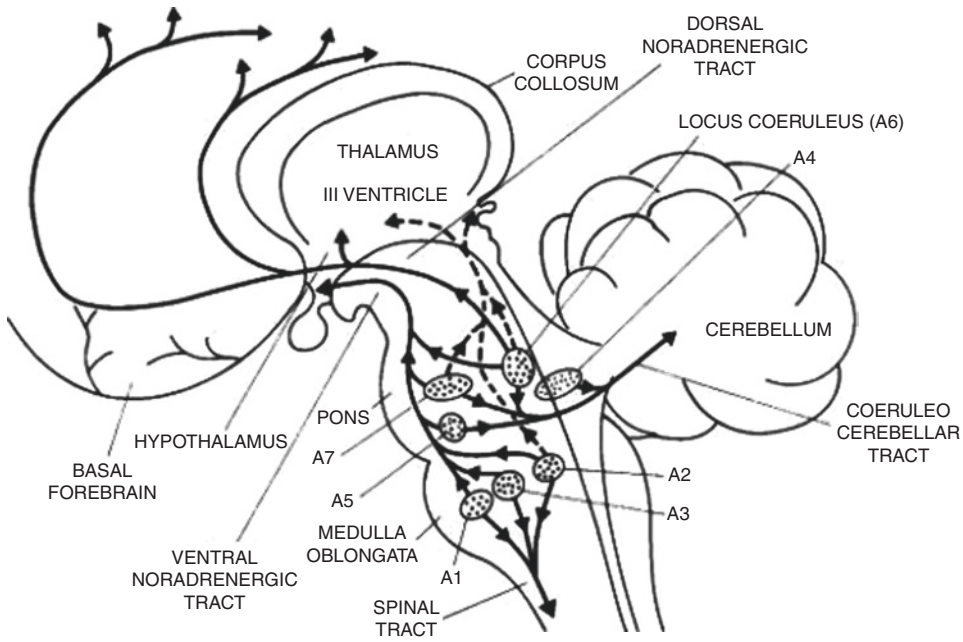

Fig. 2 Coerulocerebellar tract A1, A2…A7 noradrenergic neurons. The coerulocerebellar tract (from A6, A4, A5, and A7 noradrenergic neurons) passes to the cerebellum. (Source: From [42])

lates that therapeutic correction of the central norepinephrine deficit might reduce postural disturbances in neurodegenerative disorders, including PD.

3 Discussion

Nowadays, growing interest in HBOT's possible use to treat neurodegenerative diseases such as PD is noticed, and many medical centers and clinics worldwide use HBOT as a treatment for PD patients. Several findings support the beneficial effect of HBOT on parkinsonism symptoms. The data that we described above provide us strong indications that HBOT has an effect on these three circuits possibly involved in "Kinesia Paradoxa" (noradrenergic system, basal ganglia, and the cerebellum circuit). In particular, the influence of HBOT on the noradrenergic system is of great interest because it could be a possible therapeutic method for restoring PD neurochemical abnormalities. Further studies and clinical trials are needed to improve our understanding of the mechanisms underlying the effects of HBOT and clarify its effect in the coerulocerebellar tract.

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