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REVIEW

Mild hyperbaric oxygen: mechanisms and effects

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Abstract
Adequate oxygen supply by exposure to mild hyperbaric oxygen at appropriately high atmospheric pressure (1266–1317 hPa) and increased oxygen concentration (35–40% oxygen) has a possibility of improving the oxidative metabolism in cells and tissues without barotrauma and excessive production of reactive oxygen species. Therefore, metabolic syndrome and lifestyle-related diseases, including type 2 diabetes and hypertension, in rats were inhibited and/or improved by exposure to mild hyperbaric oxygen. It accelerated the growth-induced increase in oxidative capacity of the skeletal muscle in rats and inhibited the age-related decrease in oxidative capacity of the skeletal muscle in mice. A decrease in dopaminergic neurons in the substantia nigra of mice with Parkinson's disease was inhibited by exposure to mild hyperbaric oxygen. This review describes the beneficial effects of exposure to mild hyperbaric oxygen on some metabolic diseases and their perspectives.

Keywords Dissolved oxygen · Mild hyperbaric oxygen · Oxidative metabolism

Introduction

Oxygen is essential for energy production in most cells and is carried by red blood cells that flow in blood vessels. The oxygen bound to hemoglobin in red blood cells is referred to as the 'oxygen bound to hemoglobin.' The oxygen dissolved in blood plasma is referred to as the 'dissolved oxygen.' Although the quantity of dissolved oxygen is less than that of oxygen bound to hemoglobin, it can flow to peripheral cells, especially those in the brain, heart, and eyes, even if capillaries are very narrow, since it is dissolved directly in blood plasma (Fig. 1a).

Enhanced atmospheric pressure and/or increased oxygen concentration can increase the oxygen content, especially the dissolved oxygen content in blood plasma [1, 2] (Fig. 1b). Exposure to mild hyperbaric oxygen at 1266–1317 hPa with 35–40% oxygen inhibited metabolic syndrome [3] and lifestyle-related diseases, including type 2 diabetes [4] and hypertension [5], in experimental animals since it improved oxidative metabolism, which was lower than that in controls [6].

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However, side effects associated with enhanced atmospheric pressure and/or increased oxygen concentration, including barotrauma and excessive production of reactive oxygen species in tissues and organs, are thought to occur. Hyperbaric oxygen therapy at 2026–3039 hPa with 100% oxygen for medical treatment is associated with the risk of inducing myopia and cataracts [7–9]. A previous study [7] reported that exposure to hyperbaric oxygen at 2534 hPa with 100% oxygen for 2–2.5 h, twice a week, up to 100 sessions, induces cataracts in guinea pigs. Similarly, myopia and cataracts developed in human lenses after exposure to prolonged hyperbaric conditions of 2026–2534 hPa with 100% oxygen for 90 min, once a day, from 150 to 850 sessions [8]; however, it was rarely seen to occur after only 48 sessions of hyperbaric oxygen conditions at 2534 hPa for 90 min [9]. Hyperbaric oxygen therapy increases the number of invasive inflammatory cells in mice [10] and causes excessive production of reactive oxygen species in rats [11, 12], rabbits [13], and humans [14]. Excessive production of reactive oxygen species plays a key role in the pathogenesis of many diseases and their complications; generation of free radicals and increased levels of oxidative stress are associated with atherosclerosis, cataracts, retinopathy, myocardial infarction, hypertension, diabetes, renal failure, and uremia [15–17]. In addition, regardless of pressure, oxygen treatments involving > 40% oxygen have shown adverse effects, e.g., damage of erythrocytes due to reactive oxygen species

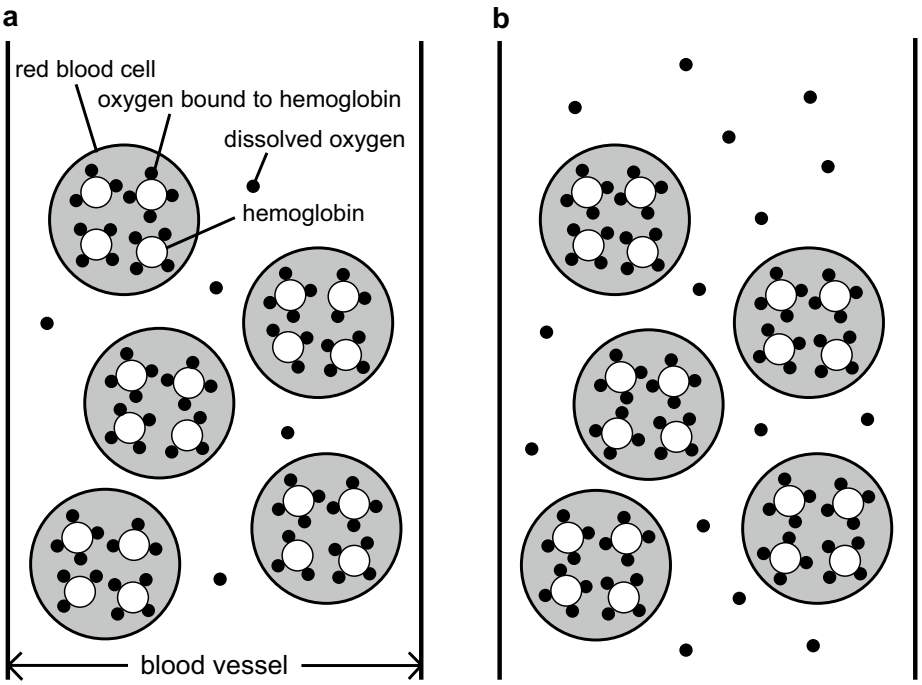

Fig. 1 Schematic diagram depicting the distribution of oxygen bound to hemoglobin and dissolved oxygen in blood vessels under normobaric (**a**) and mild hyperbaric oxygen (**b**) conditions. Abundant hemoglobin is distributed in red blood cells, and up to four oxygen molecules can bind to one hemoglobin (oxygen bound to hemoglobin). The other kind of oxygen is dissolved in blood plasma (dissolved oxygen). The quantity of dissolved oxygen is less than that of oxygen bound to hemoglobin. Enhanced atmospheric pressure and/or oxygen concentration can increase oxygen in the body, especially dissolved oxygen in blood plasma. In addition, dissolved oxygen is able to flow to the peripheral cells, especially those in the brain, heart, and eyes, even if capillaries are very narrow, since it is dissolved directly in blood plasma

and reduced quantity of oxygen bound to hemoglobin in rats [18].

Exposure to mild hyperbaric oxygen at a low oxygen concentration (35–40% oxygen) does not result in enhanced levels of oxidative stress in rats [5, 19] and humans [20]. Based on previous findings from experimental animal and human clinical studies, the effects of exposure to mild hyperbaric oxygen at 1266–1317 hPa with 35–40% oxygen are summarized in Table 1. It is noteworthy that these findings were obtained in the first step of exposure to mild hyperbaric oxygen. Therefore, it is expected to define a suitable recommendation regarding a generally applicable protocol for exposure to mild hyperbaric oxygen in the subsequent step. This review describes the beneficial effects of exposure to mild hyperbaric oxygen on some metabolic diseases and related perspectives.

Metabolic syndrome

Metabolic syndrome, linked to chronic physical inactivity and consumption of a high-fat and high-calorie diet, is characterized by obesity, high blood pressure, and increased blood glucose, low density lipoprotein-cholesterol, and triglyceride levels [21, 22]. Experimental animals with metabolic syndrome have a nonsense mutation in the leptin receptor [23, 24]. Rats with metabolic syndrome have a low oxidative capacity in the skeletal muscle compared to normal rats [6, 25]. Reduced oxidative capacity in the skeletal muscle is suggested to impair glucose metabolism and increase the risk of development of metabolic syndrome [6, 21, 22, 25]. Rats with metabolic syndrome exposed to mild hyperbaric oxygen had lower blood pressure, blood glucose, total cholesterol, triglyceride, and insulin levels, but higher adiponectin levels than those not exposed to mild hyperbaric oxygen [3]. In addition, rats with metabolic syndrome exposed to mild hyperbaric oxygen had high oxidative capacity and increased levels of peroxisome proliferator-activated receptor γ coactivator-1α (*Pgc-1α*) mRNA, which plays an important role in oxidative metabolism by regulating mitochondrial biogenesis in the skeletal muscle [26, 27].

Exposure to mild hyperbaric oxygen is thus considered to inhibit the growth-related increase in blood glucose levels and decrease the muscle oxidative capacity of rats with metabolic syndrome owing to the improved oxidative metabolism [3].

Table 1 Effects of exposure to mild hyperbaric oxygen reported in previous studies

	Species	Effects	References
Metabolic syndrome	SHR/NDmcr-cp rat	Inhibition of metabolic syndrome	[3]
Type 2 diabetes	GK rat	Inhibition of type 2 diabetes	[4, 36, 37]
	OLETF rat	Inhibition of type 2 diabetes	[38]
	GK rat	Improvement of type 2 diabetes	[39]
Diabetes-induced cataracts	Repeated inbreeding of diabetic mouse	Inhibition of cataracts	[46]
Hypertension	SHR	Inhibition of hypertension	[5]
Arthritis	Collagen-induced DA rat	Inhibition of arthritis	[19]
Parkinson's disease	MTPT-injected C57BL/6JJmsSlc mouse	Inhibition of decrease in dopaminergic neuron	[86]
Pigmentation	Male subject irradiated with UVB	Melanin pigmentation turns light	[62]
	Female subject	Senile spot size becomes small	[62]
Proliferation	Aged hairless (Hos, HR-1) mouse	Improvement of proliferative activity of epidermal basal cell	[60]
Metabolism	Human	Decrease in SpO2, increase in resting HR and energy expenditure	[20]
Skeletal muscle fiber	Wistar rat	Increase in oxidative capacity	[63, 64]
	Wistar rat	Inhibition of atrophy	[83]
	Aged ICR mouse	Improvement of oxidative capacity	[69]
Spinal motoneuron	Wistar rat	Increase in oxidative capacity	[63, 64]
	GK rat	Improvement of oxidative capacity	[44]
Infertility	Woman with intractable infertility	Improvement of the outcome of in vitro fertilization	[96]

SHR spontaneously hypertensive rat, *GK* Goto-Kakizaki, *OLETF* Otsuka Long-Evans Tokushima Fatty, *DA* dark Agouti, *UVB* ultraviolet B, *ICR* Institute of Cancer Research, *MPTP* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride, *SpO2* peripheral oxygen saturation, *HR* heart rate

Type 2 diabetes

In general, blood glucose, hemoglobin A1c (HbA1c), and triglyceride levels are higher in patients with diabetes than in healthy lean people. Hyperglycemia worsens vascular disorders including a stroke, myocardial infarction, retinopathy, nephropathy, and peripheral neuropathy. Patients with type 2 diabetes have decreased oxidative capacity in the skeletal muscle, similar to those with metabolic syndrome [28]. Decreased oxidative capacity in the skeletal muscle of patients with diabetes is suggested to be related to insulin resistance and impaired glucose metabolism. Both non-obese and obese rats with diabetes, which were developed as Goto-Kakizaki [29, 30] and Otsuka Long-Evans Tokushima Fatty [31] models, respectively, have lower oxidative capacity in the skeletal muscle than that of normal rats [32–34]. Zucker diabetic fatty rats show similar muscle properties as obese rats with diabetes [35]. Blood glucose, HbA1c, and triglyceride levels were higher in non-obese and obese rats with diabetes than in normal rats [33, 34], and those levels improved by exposure to mild hyperbaric oxygen [4, 36]. In the skeletal muscle, *Pgc-1α*, myogenin, and myogenic factor 5 mRNA levels and oxidative capacity were higher in rats with diabetes exposed to mild hyperbaric oxygen than in those not exposed to mild hyperbaric oxygen [37, 38].

The growth-related increase in blood glucose levels in rats with type 2 diabetes was inhibited by exposure to mild hyperbaric oxygen [4, 36–38]. The decreased blood glucose levels induced by exposure to mild hyperbaric oxygen in rats with type 2 diabetes were maintained even after these rats were subsequently returned to breeding under normobaric conditions [39]. The increased blood glucose levels of adult rats with type 2 diabetes not exposed to mild hyperbaric oxygen were lowered even if they were exposed to mild hyperbaric oxygen afterward [39]. These results indicate that low blood glucose levels in rats with type 2 diabetes can be maintained by exposure to mild hyperbaric oxygen compared to those not exposed to mild hyperbaric oxygen, both when blood glucose levels are increasing during growth [36–38] and after blood glucose levels are high in adulthood [39].

Exposure to mild hyperbaric oxygen, therefore, seems to prevent the decrease in oxidative capacity of the skeletal muscle of rats with type 2 diabetes, irrespective of their age [36–38]. In addition, exposure to mild hyperbaric oxygen is effective for the inhibition [4, 36–38] as well as improvement [39] of hyperglycemia in rats with type 2 diabetes.

The morphological and histochemical properties of fibers in the skeletal muscle correspond well with those of spinal motoneurons that innervate muscle fibers [40–43]. A previous study [44] had shown decreased oxidative capacity of spinal motoneurons in rats with type 2 diabetes. In addition, this study [44] had examined the effects of exposure to mild hyperbaric oxygen on oxidative capacity

of spinal motoneurons. The inhibition of growth-related decrease in oxidative capacity of spinal motoneurons by exposure to mild hyperbaric oxygen corresponds well with that observed in muscle fibers innervated by spinal motoneurons, thereby implying that the properties and responses of spinal motoneurons and their innervating muscle fibers are closely related under diabetic, as well as normal conditions [44].

Diabetes-induced cataracts

Cataracts are characterized by an accumulation of sorbitol, mediated by aldose reductase activity. The polyol pathway is the major contributor to diabetes-induced cataracts, i.e., the denaturation of lens protein, since an increased flux of glucose via this pathway leads to diabetic lesions in the lens, and large quantities of glucose are reduced to sorbitol, which is not metabolized any further [45]. The increased availability of oxygen by exposure to mild hyperbaric oxygen inhibited the growth-related increase in blood glucose levels in rats with type 2 diabetes, thereby delaying cataract formation induced by the accumulation of sorbitol in the lens [46].

Hypertension

Spontaneously hypertensive rats (SHRs) were developed by repeated inbreeding of normal Wistar–Kyoto rats, which exhibited high blood pressure levels [47]. SHRs exposed to mild hyperbaric oxygen showed lower systolic and diastolic blood pressure levels than those of age-matched SHRs not exposed to mild hyperbaric oxygen [5]. Furthermore, SHRs exposed to mild hyperbaric oxygen had lower oxidative stress and higher antioxidant levels than age-matched SHRs not exposed to mild hyperbaric oxygen [5]. Abnormalities of central neural mechanisms regulating the peripheral sympathetic outflow, i.e., an enhanced sympathetic activation and catecholamine metabolism following neurotransmitter release from nerve endings, have been associated with hypertension [48, 49]. An enhanced sympathetic activation in rats with hypertension is mediated by the overproduction of highly reactive oxygen species, which induces sympathoexcitation and thus hypertension [50, 51], whereas exposure to mild hyperbaric oxygen has been suggested to eliminate reactive oxygen species and maintain normal blood pressure levels [5]. An enhancement of oxidative metabolism in cells and tissues increases the carbon dioxide concentration in the surrounding region, which in turn, facilitates blood flow in blood vessels [52, 53].

Arthritis

Exposure to mild hyperbaric oxygen is effective in decreasing levels of reactive oxygen species overproduced in arthritis [19]. Oxidative stress and C-reactive protein levels are high in rats with arthritis [54], whereas the levels shifted to those in normal rats by exposure to mild hyperbaric oxygen [19]. Arthritic joints are characterized by hypoxia caused by an increased oxygen demand and decreased blood flow triggered by the increased intraarticular pressure [55–57]. Therefore, exposure to mild hyperbaric oxygen is effective in reducing reactive oxygen species levels overproduced during arthritis [19].

Pigmentation and proliferation

The skin undergoes age-related degenerative changes, including tissue dehydration and transepidermal water loss [58]. Proliferation of epidermal basal cells decreases with age [59]. Exposure to mild hyperbaric oxygen has been reported to accelerate the proliferative activity of epidermal basal cells in aged mouse skin [60]. An adequate oxygen supply from exposure to mild hyperbaric oxygen may accelerate the turnover rate of aged skin by enhancing the proliferative activity of epidermal basal cells. Therefore, the dissolved oxygen, which is increased by exposure to mild hyperbaric oxygen, is considered to diffuse from the dermis to the epidermis through blood microcirculation, thus accelerating proliferation of epidermal basal cells and inhibiting epidermal aging [60].

Suppression of ultraviolet B irradiation-induced pigmentation is due, at least in part, to the reduction in prostaglandin synthesis via the inhibition of cyclooxygenase by indomethacin, and to the induction of annexin or lipocortin by corticosteroids [61]. Exposure to mild hyperbaric oxygen was found to accelerate the fading of ultraviolet B irradiation-induced melanin pigmentation of the skin [62]. Furthermore, senile spot sizes on faces became smaller after exposure to mild hyperbaric oxygen [62]. Keratinocyte proliferation and epidermal cell regeneration are considered to be activated by enhanced oxidative metabolism induced by exposure to mild hyperbaric oxygen, which may be effective for damage repair in the epidermis.

Adaptation of the neuromuscular system

Exposure to mild hyperbaric oxygen facilitates oxidative metabolism, particularly in pathways such as the mitochondrial tricarboxylic acid cycle, thus enhancing the oxidative

capacity of skeletal muscle fibers and the spinal motoneurons innervating them [63, 64]. Growing rats exposed to mild hyperbaric oxygen exhibited greater voluntary running activities compared to those maintained under normobaric conditions (without exposure to mild hyperbaric oxygen); the oxidative capacity of muscle fibers and the innervating spinal motoneurons in rats increased after exposure to mild hyperbaric oxygen [64].

Reduction in skeletal muscle mass is one of the most striking features of the aging process [65]. Atrophy and reduced oxidative capacity of the skeletal muscle have been observed with age [66, 67]. Muscle atrophy in aged rats is associated with reduced activity levels of certain enzymes involved in oxidative metabolism [68]. An age-related decrease in oxidative capacity of the skeletal muscle in mice was reported to be reversed by exposure to mild hyperbaric oxygen [69] as much as by exercise in aged rats [70]. Exposure to mild hyperbaric oxygen has an advantage over exercise since it can increase the dissolved oxygen content owing to the enhanced atmospheric pressure and/or increased oxygen concentration, which does not occur in exercise. Therefore, it is concluded that exposure to mild hyperbaric oxygen reduces the age-related decrease in oxidative capacity of the skeletal muscle due to the improvement in oxidative metabolism [69].

Chronic inactivity, as in hind limb unloading and microgravity exposure, induces atrophy and degenerative changes in the skeletal muscle and its fibers [71–75], as well as in spinal motoneurons that innervate the muscle fibers [76–82]. Muscle atrophy and decreased oxidative capacity were shown to be unaffected by either pre- or post-conditioning with exposure to mild hyperbaric oxygen [83]. In contrast, the degenerative changes were almost restored to normal levels after reloading, when pre- and post-conditionings with exposure to mild hyperbaric oxygen were combined [83]. Only a combination of pre- and post-conditionings is considered to activate the signaling cascades required for the recovery from atrophy and decreased oxidative capacity of the skeletal muscle.

Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disorder in the elderly that is characterized by typical motor symptoms such as resting tremors, rigidity, bradykinesia, and gait disturbances [84]. Parkinson's disease results from the progressive decrease in dopaminergic neurons in the substantia nigra [85]. Exposure to mild hyperbaric oxygen was shown to inhibit the decrease in dopaminergic neurons in the substantia nigra of a neurotoxic experimental animal with Parkinson's disease [86]. The number of times the feet of the mouse slid off the stick in a balance beam test was fewer in mice with Parkinson's disease exposed to mild hyperbaric oxygen than in those not exposed to mild hyperbaric oxygen [86]. PGC-1α, a transcriptional co-activator, may be one of the factors that contribute to the improvement in oxidative metabolism of dopaminergic neurons in Parkinson's disease [87], since oxidative metabolism, mitochondrial biogenesis, oxidative stress, and gene expression are regulated by PGC-1α [88, 89].

It is concluded that exposure to mild hyperbaric oxygen activates oxidative metabolism in the dopaminergic neurons in the substantia nigra and inhibits the reduction in dopaminergic neurons, thereby resulting in the inhibition of Parkinson's disease [86].

Infertility

Hyperbaric oxygen therapy, an established medical treatment usually conducted under conditions of 2026–3039 hPa with 100% oxygen, has been investigated for improving female [90–93] and male [94, 95] infertility. However, several side effects, including barotrauma and excessive production of reactive oxygen species, associated with hyperbaric oxygen therapy, have been reported [7–12, 14]. Low metabolism in the uterus and ovaries may be a factor responsible for infertility since the former reduces the ability of fertilized eggs to remain in the uterus. Exposure to mild hyperbaric oxygen has been suggested to enhance oxygen supply to cells and tissues, thus improving oxidative metabolism, without barotrauma and excessive production of reactive oxygen species. In a recent study [96], 37 women with intractable infertility, who had previously received over 5 embryo transfers with a low clinical pregnancy rate (4.9%) and without birth, were exposed to mild hyperbaric oxygen before receiving any further embryo transfer. As a result, 13 women achieved clinical pregnancy with a rate of 13.8%; 5 women gave birth after in vitro fertilization treatment. Two women achieved natural conception and gave birth. However, 1 woman had an extra-uterine pregnancy, and 5 women had miscarriages.

Perspectives on exposure to mild hyperbaric oxygen

Exposure to mild hyperbaric oxygen is effective for elderly people, those with physical disability, as well as injured athletes, since no special movement needs to be performed under mild hyperbaric oxygen conditions. In future, exposure to mild hyperbaric oxygen may be investigated for: (1) prevention and improvement of dementia, (2) improvement of functional imbalances of autonomic (sympathetic and parasympathetic) nerves, e.g., menopausal disorders and emotional instability, (3) maintenance and improvement of

immunity, health, and physical fitness, and (4) early recovery from an injury. Further studies are required to solve these problems and define a useful protocol for exposure to mild hyperbaric oxygen.

Compliance with ethical standards

Ethical approval This article does not contain any studies with animals or human participants performed by the author.

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