RESEARCH ARTICLE

Beneficial Effects of Novel Non-invasive therapeutic Acute Intermittent Hypoxia (AIH) to treat spinal cord injury

Atiq Hassan, Nazim Nasir, Khursheed Muzammil, Mohammad Suhail Khan, Mohammad Rehan Asad, Shadma Wahab

Department of Basic Medical Sciences. Department of Public Health, College of Applied Medical Sciences, Khamis Mushait Campus, King Khalid University (KKU), Abha, Kingdom of Saudi Arabia (KSA).
Department of Basic Sciences, College of Medicine, Majmaah University, Kingdom of SaudiArabia (KSA).
Department of Pharmacognosy, College of Pharmacy, King Khalid University, Abha 61421, Saudi Arabia

Abstract

Spinal cord injury (SCI) damage the axonal pathways and disrupts synaptic communications between the brain and spinal cord, ultimately affecting multiple body functions and causing lifelong deficits, limiting functional independence. Functional recovery, especially arm function, is the highest priority of the persons living with an SCI. Most of the SCI is incomplete and left some spared axonal pathways. Spontaneous plasticity underlies some functional recovery, but it is slow, variable, and frustratingly limited. However, available therapies to overcome persistent motor deficits after an SCI are very limited. Recently, brief exposures to reduced oxygen (O2) levels alternating with normal O2 levels known as acute intermittent hypoxia (AIH) have emerged as a novel noninvasive therapy. AIH has shown tremendous potential to induce spinal plasticity in respiratory and non-respiratory motor neurons and ultimately enhance locomotor function in animals and human subjects with an SCI. The application of AIH alone or in combination with rehabilitation training has demonstrated success as a therapeutic tool in improving critical physiological functions following an SCI in animals and humans. The present review aims to provide an overview of the therapeutic use of AIH to induce spinal plasticity in the neural network of the spinal cord to improve functional recovery in spinal injured animals and humans. *ASEAN Journal of Psychiatry, Vol. 23: August – September 2022: 01- 07.*

Keywords: Acute Intermittent Hypoxia, Spinal Cord Injury, Spinal Plasticity.

Introduction

Spinal Cord Injury (SCI) is a serious, devastating global problem that damages axonal pathways between the brain and the spinal cord. It is estimated that approximately 300,000 persons living with chronic SCI in the United States of America [1]. The most common cause of spinal cord injuries is motor vehicle accidents, which account for 39% of reported SCI. The second most common cause of SCIs falls accounted for 32% of SCI reported. The remaining

causes include gunshot wounds 14%, sports-related injuries 8%, and non-traumatic injuries, including spinal stenosis and spinal tumors, 8% of total SCI [1]. SCI disrupts neuronal communication and ultimately affects the sensory, motor, and autonomic function below the level of the injury [2]. SCI affects multiple body functions: respiration, muscle movement, limb movement, sensations, autonomic functions, cardiovascular functions, sexual function, and bowel and bladder movements [3]. Persons living with SCIs thus experience devastating physical, psychological, emotional, and social consequences and compromises with functional independence and quality of life. Restoring motor functions of limb movement has become a top priority in increasing quality of life and independence [4]. While most SCIs are incomplete and leave some uninjured axonal pathways between the brain and spinal cord. Spontaneous functional recovery resulting from neural plasticity occurs; this neural plasticity is extremely slow and inadequate to restore complete function following SCI [5-7]. Even though extensive research has been done in regenerative medicine to restore normal function after SCI, unfortunately, there is no single effective therapy available for the treatment of SCI patients. Various strategies have been investigated to treat SCI and improve functional recovery in animals and humans with SCI. Exposure to low Oxygen (O2) for a brief period (i.e., a few minutes) alternating with periods of exposure to normal levels of oxygen known as Intermittent Hypoxia (IH) is one of the therapeutic approaches that has been shown to enhance endogenous mechanism to induce plasticity and improvement in functional recovery in the respiratory, non-respiratory and autonomic function of lower urinary tract following incomplete SCI in rodents and humans. AIH treatment produces persistent functional improvements that may last one week or more. In addition, Intermittent hypoxia has been used to train competitive athletes [8], enhance the ventilatory output in healthy humans [9, 10], and improve high altitude adaptation [11]. Intermittent hypoxia has also been applied to the treatment and prevention of human diseases, including to combat bronchial asthma [9], ischemic coronary artery disease [12], Parkinson's disease [13], and leukemia [14].

AIH is a novel non-invasive therapy that has demonstrated success as a therapeutic tool in improving critical physiological functions after an SCI in humans and rodents [15-19]. AIH combined with task-specific training has improved forelimb function in rats and humans with SCI [19-21]. Recent studies demonstrate the effectiveness of AIH to enhance hand and leg function in persons with chronic, incomplete spinal injuries. Specifically, AIH combined with hand opening practice for five days improved hand dexterity and maximum hand opening in persons with chronic incomplete SCI [17, 18, 21]. AIH combined with task-specific training for seven days has also improved upper limb function in rats with SCI [17, 18]. Another study demonstrated the AIH combined with overground walking training for five days increased the walking speed and endurance in persons with incomplete chronic SCI; these functional benefits lasted up to one-week post-treatment. A well-established mechanism underlying the beneficial effects of AIH treatment is an increased serotonin release in the vicinity of spinal motoneurons to activate the post-synaptic serotonin receptors on motor neurons. This, in turn, stimulates the new synthesis of Brain-Derived Neurotrophic Factor (BDNF) and activation of its high-affinity receptor, Tyrosine Kinase B (TrkB) [22-24]. These cascades of signaling events are purported to eventually increase the strength of synaptic input onto spinal motoneurons and promote functional motor recovery. Intermittent Hypoxia (IH) treatment has been a focus of research in spinal plasticity for several decades [25]. Various IH protocols, from chronic IH to acute IH, have been used to examine the effect of IH on physiological systems [25, 26]. AIH treatment has received considerable attention in recent years in spinal plasticity [25]. AIH is a novel non-invasive protocol involving fewer hypoxic episodes than chronic IH protocols. AIH can induce spinal plasticity by augmenting spared synaptic pathways in intact and spinal-injured animal models [27-32]. In this review, we have provided information about recent advancements in the clinical application of AIH to improve functional recovery in patients living with chronic SCI. In the last couple of decades, AIH has emerged as a novel non-invasive strategy to enhance respiratory and non-respiratory motor function in persons living with chronic SCI. In addition, this review will discuss the various paradigm and protocols of Intermittent Hypoxia (IH), from bad Chronic Intermittent Hypoxia (CIH) to good

intermittent hypoxia, AIH. This review enhances our knowledge of the possible cellular and molecular mechanisms to induce neural plasticity in response to IH.

Chronic intermittent hypoxia (CIH)

In sleep apnea, airway obstruction repeatedly occurs throughout the sleep, resulting in intermittent reductions in blood oxygen levels. Chronic Intermittent Hypoxia (CIH) is an experimental protocol that aims to reproduce many of the pathophysiological consequences of obstructive sleep apnea. Severe protocols of CIH in animal models have deleterious side effects, including systemic hypertension [33-37], impaired baroreflex control of the heart [38], metabolic syndrome [39], cognitive impairment [40-42], neuronal death in the hippocampus, and neurobehavioral dysfunction [43], synaptic transmission in the nucleus of the solitary tract [44], neurodegeneration, oxidative stress and inflammatory responses [45].

CIH protocols induce robust plasticity in the spinal cord alongside these pernicious side effects. Chronic intermittent hypoxia elicits plasticity at multiple sites of the respiratory control system, including carotid body chemosensitivity [46, 47], increased synaptic strength in the nucleus tractus solitarious [44], and increased synaptic strength in spinal pathways to phrenic motor neurons [29, 48]. CIH gave for seven days (alternating 11% O2 and air; 5 min periods; 12 hr per night; 7 nights) following C2 hemisection has been demonstrated to enhance spontaneous plasticity and improve phrenic motor output [29]. This CIH-mediated enhancement in spontaneous plasticity is serotonin-dependent [49, 50]. Pre-treatment with CIH increases the sensitivity and phrenic response during hypoxia and augments the effect of acute intermittent hypoxia [30]. Nevertheless, the deleterious side effects of CIH make it inappropriate to use as a therapeutic regime for spinal cord injury. Recent studies have demonstrated more acute IH protocols that elicit plasticity in the spinal cord without pernicious side effects [32].

Acute intermittent hypoxia (AIH)

Acute Intermittent Hypoxia (AIH) protocols involve exposure to fewer hypoxic episodes than chronic protocols. Daily Acute Intermittent Hypoxia (dAIH), for example, is a paradigm in which the animal is exposed to 10 hypoxic episodes per day for seven days (a total of 70 episodes of hypoxia in one week) when in comparison, a CIH protocol might consist of 504 episodes of hypoxia during the same period [31, 51]. Many acute intermittent hypoxia paradigms can induce spinal plasticity by augmenting spared synaptic pathways in intact and spinally injured animal models [27-32]. A single acute protocol composed of 3, 5-min episodes of AIH (35–45 mmHg arterial PO2, 25–30 mmHg arterial PO2) in rats can induce spinal plasticity in respiratory motoneurons in the spinal cord for a short period (30-90 minutes) [48, 52, 53]. The duration of AIH-induced plasticity can be prolonged and enhanced by repetitive use of AIH, such as daily exposure (dAIH; 10 episodes per day, 7 d) for one week (dAIH) [32] or exposure to AIH three times per week for 3-10 weeks (3xwAIH) [54, 55]. dAIH elicits comparable effects to CIH, such as increases in the expression of BDNF within the phrenic motor nucleus [22] without deleterious side effects such as systemic hypertension and hippocampal cell death [30, 56].

The most thoroughly studied model of AIH-induced plasticity is Long-Term Facilitation (LTF), the strengthening of synapses onto respiratory motor neurons [57-59]. Long-term facilitation is manifested as a progressive increase in phrenic or hypoglossal motoneurons output in response to 10 alternating exposures to 5-minute episodes of moderate hypoxia (e.g., 11% inspired oxygen) alternating with 5 minutes of normoxic exposure [27-30]. This increase in motoneuron output is sustained for at least 2 hours following the end of AIH exposure. LTF can be evoked in both anesthetized [31, 60] and unanaesthetized [50, 61, 62] rats and in humans during sleep [51, 63]. It is important that sustained exposure to hypoxia for the same duration, i.e., without alternation with normoxia, cannot induce LTF [64]. Therefore, episodic exposure to hypoxia is necessary to evoke the response. It has been demonstrated that at least three episodes of alternating exposures to low oxygen are required to evoke LTF in the respiratory motor system [48, 52]. Physiologically, long-term facilitation may serve as a compensatory mechanism to stabilize the respiratory output following periods of hypoxia [31].

In addition to effects in intact animals, AIH elicits respiratory and forelimb function recovery in rodent models of incomplete cervical SCI [18, 19, 23]. In separate experiments, rats exposed to 10 episodes of 5 min 11% oxygen alternating with 5 min normoxia for seven days at 4 wks post-SCI showed a sustained improvement in respiratory output or skilled forelimb function during a ladder walking task [18].

AIH induces plasticity and improves functional recovery in SCI rats

AIH-induced spinal plasticity was initially investigated in the context of respiratory plasticity in spinal motor neurons. The most thoroughly studied model of AIH-induced plasticity is Long-Term Facilitation (LTF), the strengthening of synapses onto respiratory motor neurons [26, 57-59]. In a well-established animal model, brief (5 min) exposures to reduced oxygen levels (10.5% inspired O2) in rats, alternating with exposures to normal levels (20% O2), results in a sustained increase in phrenic motor neuron output that outlasts the stimulus [65]. The mechanism of action is complex, but it is known to involve episodic increases in spinal serotonin, triggered by AIH-induced activation of carotid afferents. Spinal serotonin, in turn, stimulates the new synthesis of Brain-Derived Neurotrophic Factor (BDNF) and activation of trkB receptors in spinal motor nuclei, resulting in strengthened synaptic input onto spinal motoneurons [65].

Physiologically, long-term facilitation may serve as a compensatory mechanism to stabilize the respiratory output following AIH [31]. Previous studies have examined the impact of AIH on forelimb functional recovery in SCI rats by assessing performance on multiple behavior tests in response to AIH alone or in combination with motor training, i.e., ladder training and reaching tasks. These studies have demonstrated that AIH treatment for seven days initiated 4 wks after incomplete cervical experimental SCI in laboratory rats produces sustained improvement in forelimb performance on a ladder walking task when combined with daily ladder task training [23].

In cervical SCI rats, AIH treatment combined with task-specific training for seven days failed to significantly improve skilled movement in reach-to-grasp task performance in single pellet retrieval and staircase pellet retrieval tasks. However, the AIH-treated rats demonstrated a trend towards improvement in performance on the reach-to-grasp task up to 4 wks of post-treatment. The lack of recovery of reach-to-grasp performance after seven days of AIH and task training does not necessarily mean that AIH cannot facilitate recovery on these tasks. Prolonged protocol of AIH treatment (12 weeks of AIH: 10, 5 min episodes of 11% inspired O2; 5 min intervals of 21% O2) combined with task-specific training has demonstrated improved reach to grasp forelimb functions in rats with a chronic hemisection at the 3rd cervical spinal segment [19]. Therefore, the findings of these studies strongly suggest that AIH, as a modest form of intermittent hypoxia, can elicit beneficial effects when combined with task-specific motor training.

AIH improves motor functions in human patients with incomplete chronic SCI

Various strategies have been used to treat experimental SCI, either alone or in combination [7, 66, 67]. Unfortunately, these experimental strategies have not been translated into the clinic. AIH is a novel non-invasive treatment strategy advancing towards clinical application due to its therapeutic potential [68]. The first study to use AIH as a therapy for SCI reported that a single AIH exposure increased ankle strength and plantar flexor torque in human patients with incomplete chronic spinal cord injury [15]. More recently, AIH treatment improved over-ground walking and endurance in persons with chronic incomplete SCI. The impact of AIH treatment was enhanced when combined with walking practice [16]. Walking distance was increased by more than 37% with combined AIH + walking practice [16].

The current study's findings that foot slip performance on a ladder walking task significantly improved with combined AIH treatment and ladder training in cervical SCI rats is consistent with the clinical study conducted with human subjects with chronic incomplete SCI [16]. The treatment paradigm used in the current research on rats with cervical SCI is slightly different from the clinical study. Human patients with SCI received AIH treatment for five days, each day consisting of 15 AIH episodes of 9% O2 for 90 seconds alternating with 60 seconds of 21% O2, and training occurred 1 hour after treatment. The

paradigm used in the present study consist of AIH treatment for seven days, consisting of 10 episodes of 11% O2 for 5 minutes alternating with 5 minutes of 21% O2, with locomotor training in the form of a ladder task also carried out 1 hour following AIH treatment. Altogether, the evidence shows that AIH is a moderate form of intermittent hypoxia that has therapeutic potential to induce spinal plasticity and improve functional recovery in persons living with chronic SCI, suggesting that AIH treatment with combinatorial therapies may promote greater functional recovery following SCI.

Potential cellular and molecular mechanisms of AIH-induced plasticity

Cellular adaptation to changes in oxygen level is essential for the maintenance and survival of cells in physiological and pathological states. Hypoxia is known to change cellular functions by altering the expression of hypoxia-associated proteins and their mRNAs, including HIF-1α and VEGF [23, 54, 55, 69]. The findings of previous studies have demonstrated that AIH enhanced the spinal expression of key molecules known to play an important role in spinal plasticity, including HIF-1α, VEGF, BDNF, trkB, and ptrkB, consistent with earlier findings [23, 54, 55, 70, 71].

Cellular and molecular mechanisms of AIH-induced plasticity in respiratory motor neurons are well documented [26, 72]. Ongoing studies have revealed that multiple converging cellular pathways, named the Q, S, V, and E pathways, induce spinal plasticity in response to AIH [26, 72-74]. Several of these pathways require BDNF synthesis and/or activation of its high-affinity receptor trkB [26, 48, 51].

The first and most thoroughly studied pathway, known as the Q pathway, is serotonin-dependent. The term Q pathway refers to Gq protein-coupled metabotropic 5-HT2a receptors [26, 48, 51]. AIH treatment triggers the episodic release of serotonin in the vicinity of phrenic motor neurons in the spinal cord, thereby activating the serotonin receptor 5-HT2a, which, via a PKC pathway, results in increased synthesis of new BDNF. This BDNF, through its high-affinity receptor trkB on the same or adjacent neurons, initiates a cascade of signaling through ERK and MAP kinase pathways [53, 75]. A result is a form of plasticity known as pLTF, the increase in the output of phrenic motoneurons [31, 51, 72].

A second cellular pathway, known as the "S Pathway," induces serotonin-independent respiratory plasticity. This pathway does not require the synthesis of a new BDNF protein but requires the synthesis of a new immature trkB receptor isoform and Phosphoinositide 3 (PI3) kinase/protein kinase B signaling [53, 76]. Activation of either Q or S pathways can induce respiratory spinal plasticity resulting in LTF [48, 54, 73, 74]. The BDNF and/or trkB signaling system is the center of both pathways and also plays a critical role in multiple forms of spinal plasticity [72, 77]. Previous studies have found that AIH treatment and training enhance the expression of BDNF, trkB, ptrkB, in motor neurons at multiple spinal segments, so activation of the Q or S pathway might be activated underlie improvements in motor performance in AIH-treated SCI rats.

Previous studies have also demonstrated that AIH treatment altered the expression of hypoxia-related proteins, HIF-1α and VEGF. Hypoxia-Inducible Factor-1α (HIF-1α) is a master transcriptional regulator of genes. HIF-1α controls the various adaptive responses to low oxygen tension to maintain oxygen homeostasis in mammalian cells. The HIF-1 protein is a heterodimer and composed of the HIF-1α subunit and the constitutively expressed HIF-1β subunit [78]. HIF-1α is oxygen-sensitive and is stabilized and activated under hypoxia conditions and degraded in normoxia conditions by proteasomes [71, 79]. In hypoxia conditions, HIF-1α translocates from the cytoplasm to the nucleus and dimerizes with the HIF-1β subunit to form the active HIF heterodimer complex [80]. This dimer complex binds with Hypoxia Response Elements (HRE) in target genes to induce gene expression [80]. HIF-1 binds to promoter/enhancer elements and regulates the transcription of hypoxia-inducible target genes expression of several dozen target genes, including VEGF, EPO, Inducible Nitric Oxide Synthase (iNOS), heme oxygenase-1 [70, 71, 81-86].

Vascular Endothelial Growth Factor (VEGF) is a 45 Da dimeric glycoprotein and a fundamental regulator

of pathological and physiological angiogenesis [79]. HIF-1α regulates the expression of VEGF. VEGF promotes endothelial cell formation and proliferation in several organ systems during embryonic development and after injury in various tissues, including the central nervous system [87]. VEGF is critical for blood vessel growth in developing and adult nervous systems [88]. Apart from its role in angiogenesis, VEGF appears to play neurotrophic and neuroprotective roles in the spinal cord and brain injury [89-91].

VEGF and its high-affinity receptors VEGFR-2 are expressed in phrenic motor neurons [55, 74]. AIH can also increase VEGF expression and mediate respiratory spinal plasticity through activation of the VEGF receptors VEGFR-2. The intracellular signaling pathways ERK and Akt are involved in this "V" pathway, activation of which will induce spinal plasticity [55, 74, 92].

In addition to VEGF, HIF-1α also regulates the expression of the Erythropoietin Factor (EPO) [78, 93]. EPO and its receptors (EPO-R) are expressed in the brain and spinal motor neurons [26, 94-96]. AIH increases the expression of EPO and its receptors EPO-R in phrenic motor neurons [73]. EPO initiates a signaling cascade via ERK and Akt activation through its receptor EPO-R and induces a form of respiratory plasticity similar to BDNF / trkB and VEGF [26, 73]. This last pathway is also known as the "E Pathway."

The outcome of all of these cellular pathways, Q, S, V, and E pathways, is hypothesized to be the phosphorylation and/or insertion of glutamate receptors at the synaptic sites between premotor and motor neurons [48, 97-99]. AIH could change the excitability of motor neurons by increasing the strength of the synaptic connections between motoneurons and premotor neuron inputs. In this manner, all 4 cellular pathways which can produce pLTF have the potential to induce functional recovery following SCI [48, 54, 73, 74].

Summary and Conclusion

Spinal Cord Injury (SCI) interrupts the brain and spinal cord synaptic connections, causing lifelong mobility and functional independence deficits. Spontaneous plasticity underlies some functional recovery, but it is slow, variable, and frustratingly limited. Many promising therapeutic approaches have been investigated to promote the endogenous mechanism to improve functional recovery in SCI [100-103]. Unfortunately, the majority of the pre-clinical therapies that have shown some success in a particular animal model have not proven robust enough to be replicated in other animal models, much less translated to the clinic. This is maybe due to the time of application of therapies [104, 105]. The present review provides an overview of IH and its possible cellular and molecular mechanism. AIH emerges as a novel non-invasive therapy with tremendous potential to enhance functional recovery in rodents and humans with incomplete SCI [106, 107]. AIH triggers plasticity in spare neural pathways to respiratory and non-respiratory motor neurons, restoring lost motor functions.

Even though extensive research has been done in rehabilitation medicine to restore normal function after SCI, unfortunately, there is no single effective therapy available for the treatment of SCI patients [105]. Two therapies - brief exposures to reduced oxygen (O2) levels alternating with normal O2 levels (known as acute intermittent hypoxia, AIH) and Electrical Stimulation (ES) of the spinal cord have independently emerged as promising strategies to enhance motor function in both animal and human subjects with an SCI [15, 16, 107-109].

Electrical Stimulation (ES) of the spinal cord has been shown to activate spared neural networks and facilitate the physiological effects of activity-based motor training to result in volitional control of leg movements after a functionally complete SCI in humans [110-112]. Interestingly, the impact of spinal electrical stimulation in activating a dormant spinal neural circuitry to facilitate movement after an SCI is shown to be drastically enhanced when administered with serotonin or serotonin receptor agonists [113, 114]. Since AIH enhances the endogenous release of serotonin and BDNF [22, 23]and previous studies have established the additive effects of serotonin agonist and ES in regaining lower limb motor function after a severe SCI [113, 114]. ES and AIH therapies' early success as individual therapies is encouraging, but

restoring complete function after an SCI may require a combination of treatments that target distinct yet complementary mechanisms.

The combinatorial use of AIH and ES therapies will significantly improve the quality of life for persons with cervical spinal cord injuries. Combining therapies may be more effective and enhance the effect of treatment which will ultimately help develop an effective treatment to improve functional recovery for persons living with SCI [105].

Conflict of interest

The authors declare that they do not have any conflicts of interest.

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Correspondence author: ***Atiq Hassan, Department of Basic Medical Sciences College of Applied Medical Sciences, Khamis Mushait Campus, King Khalid University (KKU), Abha, Kingdom of Saudi Arabia (KSA)***

Email: atiqhassan@gmail.com

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